Knee joint instability and exercise therapy in patients with osteoarthritis of the knee

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Chapter 1

General introduction

Epidemiology

Osteoarthritis (OA) is a common and complex joint disorder that is among the ten most disabling conditions in developed countries (1). Together with the hand, the knee is the most commonly affected joint in OA (2;3). The lifetime risk of symptomatic OA in at least one knee is 45% on average (4). Knee OA studies have traditionally focused on the tibiofemoral (TF) compartment only, thereby ignoring the patellofemoral (PF) joint. However, PF OA is commonly observed, in isolation (11%) or combined with TF OA (41%) (5). Knee OA should therefore be considered a multi-compartmental disease, in which disease processes across compartments are closely linked to each other (6).

Worldwide, OA involves over 150 million people (1); in the Netherlands over 650.000 people have OA in one or more joints (2). These numbers are likely to be underestimations, as many patients do not seek medical care. Nevertheless, OA is still the third most common diagnosis made by general practitioners in older patients (7). The economic burden of OA is high, with annual costs per patient estimated at 8,000 US dollars (8).

OA is considered to be a heterogeneous disease, as patients differ in underlying clinical symptoms (type and course over time), pathogenesis, and treatment response. To reduce this heterogeneity, it is suggested that the patient population needs to be classified into clinically relevant subgroups or so called phenotypes. Such a phenotype could represent one specific OA subtype that should be treated differently from the others (9;10).

Risk factors

An overview of risk factors for the onset and progression of knee OA, and for functional decline (i.e., progression of activity limitations) in patients with knee OA is shown in Table 1. The most important risk factors for the onset of knee OA are age and obesity. Due to the aging population and an increased incidence of obesity, the prevalence of knee OA will only increase further (11). However, it should be noted that the idea of OA as an aging process is not helpful, as approximately two-thirds of patients with OA are under 65 years (3).

Clinical symptoms

The major symptom of OA is pain, which is usually usage-related and often worsens towards the end of the day, with more persistent rest and night pain that can occur in advanced OA (12). Other symptoms are short-lasting and inactivity-related joint stiffness, cracking of joints (crepitus), and reduced range of joint motion, while joint inflammation can also occur (9). Patients with knee OA are limited in their daily functioning, as activities like walking, stair climbing, and transfers like rising from a chair can become problematic. More recently,

Table 1. Risk factors for onset and progression of OA disease, and functional decline in patients with knee OA

	onset knee OA	**progression knee OA**	**functional decline**
Mechanical:			
age	x	x	x
overweight/obesity	x	x	x
history of knee trauma or surgery	x		
repetitive use of joint	x		
certain intense/competitive sports	x	x	
malalignment	x	x	
quadriceps weakness	x		x
proprioceptive inaccuracy			x
laxity			x
Systemic:			
female sex	X		
generalized OA	X		
genetic factors	X		
race/ethnicity	X		x
nutritional factors (e.g., vitamin D depletion)	X	x	
bone density	X		
hormone replacement therapy (protective)	X	x	
comorbidities			x
psychosocial factors			x

Based on review studies from Felson et al (7), Bijlsma et al (9), Zhang et al (11), and Dekker et al (14).

instability of the knee joint has been recognized as an important and frequently reported symptom in knee OA patients (13).

Pathogenesis

The underlying pathway of knee OA is not fully understood, presumably due to the complex, multifactorial nature of the disease process, but may be best described as resulting from excessive mechanical stress applied in the context of systemic susceptibility (3). Knee OA has long been considered to be mainly cartilage driven, but recent evidence revealed an additional and integrated role of bone, synovial tissue, and peri-articular tissues like ligaments and muscles (9) (Fig. 1).

The OA disease process may be initiated by a shifted equilibrium between cartilage formation and breakdown, often in a situation where the mechanical loads applied exceed those that can be tolerated by the joint tissues (3). Consequently, the tissue enters a vicious cycle in which cartilage breakdown dominates over synthesis. As cartilage is a-neural, these changes will not result in clinical signs until other, neural tissues become involved. The progressive loss of cartilage can result in changes in surrounding tissues, for instance osteophyte formation. Inversely, cartilage integrity also depends on the mechanical properties of its underlying bone (15). In this pathway, persistent overloading of the joint

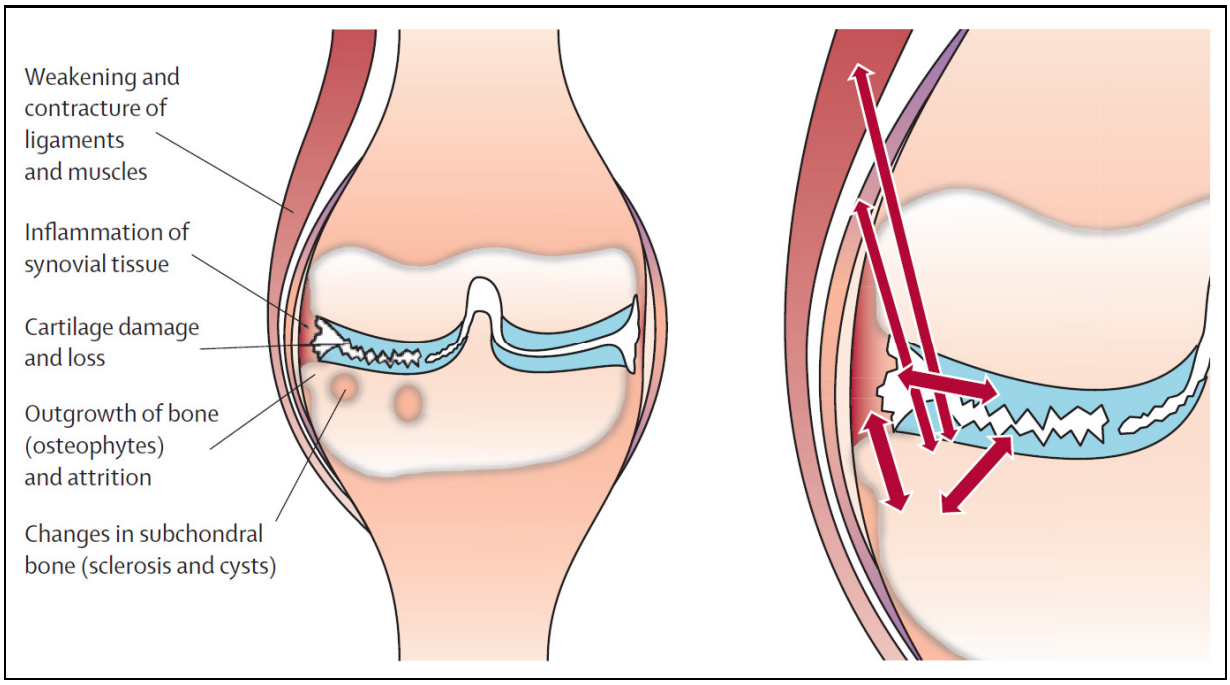

Fig. 1. Integrated role of different tissues in pathogenesis of knee OA (from Bijlsma et al (9), printed with permission)

may result in microfractures and stiffening of the subchondral bone, thereby reducing the absorption capacity of the bone and affecting the cartilage's overlay integrity. Knee OA can also be accompanied by synovial inflammation (synovitis), clinically expressed as pain and joint swelling. This may occur as a consequence of posttraumatic joint injury or secondary to the chemical process of OA. Inflammatory mediators from synovial tissues may also act on cartilage degeneration, thereby resulting in a vicious circle of progressive joint degeneration (16).

Imaging techniques

Plain radiography (X-ray) is widely used for diagnosis and assessment of disease severity. X-rays are relatively cheap and widely available, but only detects bony changes and joint space width, in a two-dimensional view. Magnetic resonance imaging (MRI) can be considered golden standard for OA imaging, as this technique offers a three-dimensional view of all structures in the joint, also including important soft tissues as cartilage, synovial membrane, and menisci. Furthermore, MRI can detect abnormalities already in an early stage of OA, in contrast to conventional X-rays, but is on the other hand more expensive, time-consuming, and not widely available.

Interestingly, a discrepancy between the symptomatic and structural expression of knee OA is typical for OA, with nearly half of the persons with radiographic evidence of OA not having pain, whereas many persons with knee pain do not have any sign of structural

damage (17). It should also be noted that, although imaging techniques are frequently used by medical practitioners, they are often unnecessary for diagnosis, as the American College of Rheumatology (ACR) criteria (18), based on history taking and physical examination only, can be sufficient. According to these criteria, knee OA can be diagnosed in the presence of knee pain and at least 3 of the following: age over 50 years, morning stiffness less than 30 minutes, crepitus on active motion, bony tenderness, bony enlargement, or absence of palpable warmth of synovium.

Management of knee OA

Knee OA management consists of conservative (pharmacological and non-pharmacological) treatment options, aiming to reduce pain and activity limitations (19-21). Surgery is preserved for end-stage OA. Interventions targeting the disease itself (i.e., disease modifiers) have to be approved yet.

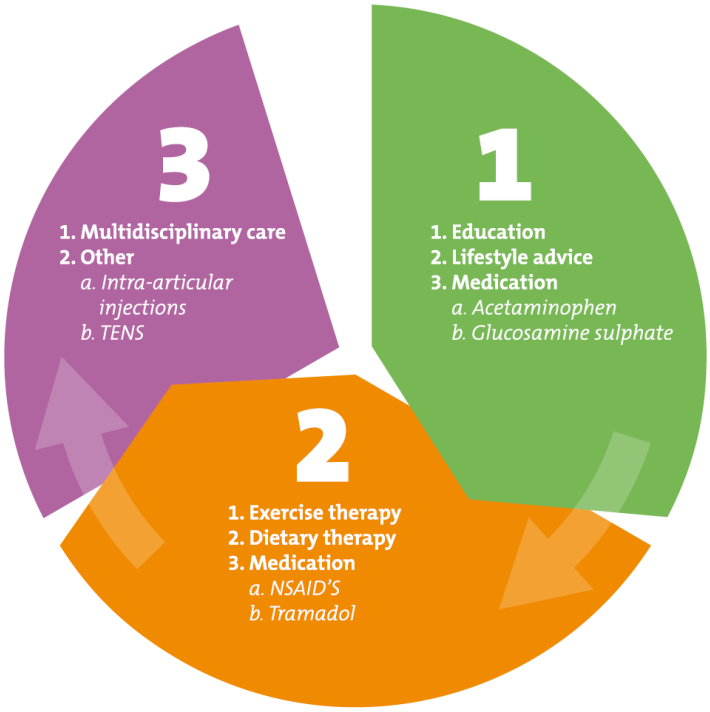

Fig. 2. BART stepped care model (AJ Smink. Zorgwijzer Artrose©. Bone & Joint Decade NL 2010. Printed with permission)

OA can be considered an 'undertreated' disease, as many patients do not receive any treatment at all (22), and simple conservative treatments are widely ignored before patients undergo total knee replacement or other secondary care (23). To optimize conservative OA management, the Beating Osteoarthritis (BART) strategy has recently been developed (24)

and implemented in the Netherlands (Fig. 2). BART is a stepped-care model, based on the most recent guideline recommendations for conservative interventions (19-21), to guide health professionals and patients through different treatment phases. In the first step of this BART strategy, treatment should consist of education, lifestyle advices, and simple analgesics (especially acetaminophen, also known as paracetamol). If these treatments are ineffective, interventions in step 2 are needed, which includes referral to a physical therapist/exercise therapist, to a dietician, and/or stronger medications (i.e., non-steroidal anti-inflammatory drugs [NSAIDs], tramadol). For patients with sustained symptoms after step 1 and 2, interventions from step 3 are recommended, including multidisciplinary care.

Exercise therapy

Exercise therapy can be considered a cornerstone treatment in knee OA. Exercise consists of planned, structured, and repetitive bodily movement designed to improve or maintain one or more components of physical fitness (10;25). In knee OA, regular exercise programs consist of strength training, aerobic training, range of motion exercises, and training of problematic daily activities, which can be performed under supervision (individually or group-based) or unsupervised at home.

The usage of exercise therapy is strongly recommended in both national (26) and international guidelines (19-21). The evidence for the effectiveness of exercise therapy on pain and activity limitations is overwhelming (27). Compared to pain medication, exercise therapy is equally effective in reducing pain and superior in reducing activity limitations (without causing side-effects or having contra-indications). On the other hand, effect sizes of exercise therapy are still only moderate at best, and not all patients seem to benefit from exercising (27). No specific type of exercises has yet been found to be superior over the others. Furthermore, the optimal duration, frequency, and intensity of exercise programs are unknown, except for a superiority of programs over 12 sessions compared to programs with less than 12 sessions (27). Therefore, there is cause for further optimization of exercise therapy by improving the content of therapy and by adequate selection of patients in whom improvement can be expected. Because of the heterogeneity in the OA population, exercise programs may need to be tailored to specific subgroups of patients to optimize the outcome (28).

Although strongly recommended, exercise therapy is still ‘underused’ as a treatment strategy for OA. In a French study, less than 15% of general practitioners reported that they would prescribe exercise therapy as a first-line therapeutic approach (29). In Canada, only one-third of patients had been advised to use exercise for their condition (30). Even more concerning, Dutch GP’s were found to refer patients with OA 3 times more often to the orthopedic surgeon (65% of all referrals) compared to physical therapists (20%) (31).

Knee joint instability

Knee joint instability, or the inability of the knee to maintain a position or to control movements under different external loads (10;32), has become a focus of research. A large majority of knee OA patients (63%) experiences episodes of knee instability (33). This sudden loss of postural support across the knee at a time of weight bearing can be reported by patients as a feeling of buckling (i.e., abrupt and full giving way) or shifting (i.e., partial giving way) of the knee. The knee is presumed to be stabilized actively through dynamic neuromuscular control, provided by muscle actions and proprioceptive stimuli, and passively by passive restraint, provided by ligaments and capsule (32). Unfortunately, knee OA is characterized by muscle weakness, proprioceptive deficits, and an impaired passive restraint (i.e., laxity) (14).

Muscle weakness. Reduced muscle strength of the lower limb is considered one of the most important risk factors for functional decline in knee OA patients (14). In addition, evidence suggests that muscle weakness may precede the onset of knee OA (34-37) and plays a role in structural progression (38;39). The musculature around the knee, especially the quadriceps, is considered to be critical for maintaining dynamic stability by aiding in shock absorption and properly transferring forces across the joint (40). In research settings, muscle strength is mostly measured isokineticially (i.e., with constant motion velocity), while in clinical practice, hand-held dynamometers are mostly used to measure strength isometricially (i.e., resistance test) (10).

Knee joint proprioception. Proprioception can be defined as the conscious and/or unconscious perception of position and movement of an extremity or a joint in space (41). This perception partially derives from integrated afferent neural input arising from mechanoreceptors in different structures of the knee (i.e., joint capsule and ligaments, muscles, tendons, and associated tissue), but is also influenced by signals from outside the knee (e.g., vestibular organ, visual system, and cutaneous and proprioceptive receptors from other body parts) (42). Knee joint proprioception is presumed to be necessary to protect the knee against excessive and possible injurious movements via reflex responses, to stabilize the knee during static posture, and to coordinate complex movement systems and precise knee joint motions. Proprioception is mostly assessed by the detection of passive joint motion (motion sense) or by a repositioning task (position sense) (10).

Knee joint laxity. Knee joint laxity has been defined as the displacement or rotation of the tibia with respect to the femur in the varus–valgus direction after varus-valgus load. The inside and outside displacement of the tibia reflects the capsule-ligamentous stretch when load is applied to the knee joint (10;43). The total displacement depends on the resistance or stretch capability of the passive restraint system, i.e., ligaments, capsule, and other soft tissues. Increased laxity may destabilize the knee joint, and simultaneously increases the need for adequate muscle actions (32).

Knee joint stabilization process. Previous studies from our research group showed that the relationship between muscle weakness and activity limitations depends on knee joint proprioception, varus-valgus laxity of the knee joint, as well as varus-valgus knee motion during walking. It was found that in patients with poor proprioception, muscle weakness leads to more severe activity limitations than in patients with adequate proprioception (44). Likewise, high varus-valgus laxity (i.e., static laxity) (45) and high varus-valgus knee motion during walking (i.e., dynamic laxity) (46) resulted in a greater impact of muscle weakness on activity limitations. These findings can be explained through compensation mechanisms within the knee joint stabilization process. Muscle actions may compensate for poor proprioception or high laxity, as long as there is sufficient muscle strength available. However, weak muscles may be unable to perform the dual tasks of stabilizing the joint and providing the joint movements necessary for the performance of activities, resulting in activity limitations (Fig. 3).

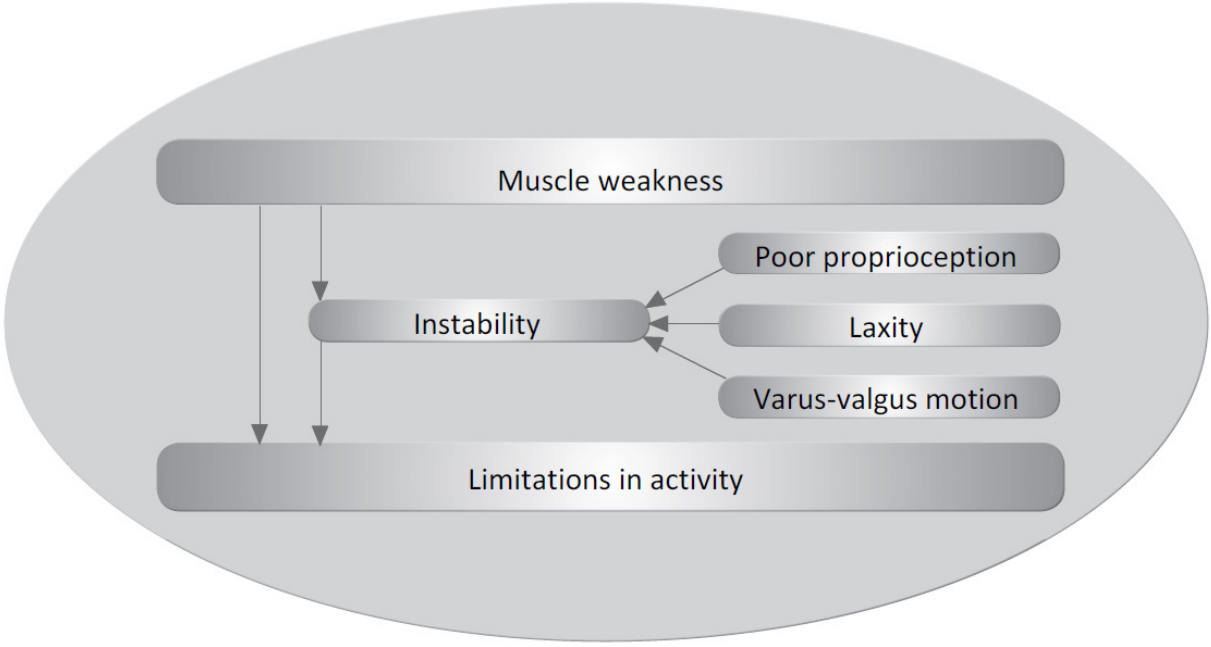

Fig. 3. Neuromuscular model (10) (printed with permission)

Knee joint stabilization training

Based on the above mentioned findings, we hypothesized that knee OA patients suffering from knee instability may not benefit optimally from standard exercise therapy that mainly targets muscle strengthening. An exercise program that additionally aims at knee joint stabilization is expected to be more beneficial for this subgroup. This training aims at improving proprioception, limiting the consequences of having an impaired passive restraint (i.e., laxity) and minimizing sideways movements of the knee. First, a patient needs to become aware of the position and movements of the knee during the exercises. For this

purpose, mirrors can be used to provide visual feedback on knee position and motion, whereas physical therapist provides verbal and tactile feedback on knee position and movement. Second, if awareness is improved, exercises can also target the ability to actively control movements of the joint, under increasingly difficult conditions. Adequate awareness and active control of the knee joint may act as compensating mechanisms to reduce the consequences of increased laxity. In lax knees, sudden unintended movements may occur. Since the structures involved in the passive restraint (i.e., ligaments and capsule) cannot be modified, compensating strategies are required. Third, instructions during exercises focus on the alignment of the knee, in an attempt to minimize sideways knee motion (i.e., hip-knee-ankle in a straight line), corresponding with a neutral loading pattern of the knee joint. Quality of exercise performance is critical in this modality. Exercise intensity and difficulty will only be increased, when quality of exercise performance can be sustained (10).

After the initial knee stabilization training, muscle strength training is provided. It is expected that patients suffering from knee instability are not able to perform high-intensity strengthening exercises safely and effectively. Therefore, the exercise program should start with knee joint stabilization training, prior to strength training. During the strengthening phase, training intensity will be further increased gradually each week. However, the quality of exercise performance remains critical and will be strictly monitored. Finally, in the last phase, training of problematic, daily activities will be added (i.e., functional training).

Such an exercise program has not yet been evaluated in the targeted subgroup of patients with knee OA suffering from knee instability.

Scope of this thesis

This thesis is subdivided into 3 parts:

Part I. Knee joint instability

Part II. Optimizing effectiveness of exercise therapy

Part III. Knee OA phenotypes

Part I. Knee joint instability

In the first part of this thesis, the focus is on patient-reported knee instability and biomechanical factors that may play a role in knee stabilization, namely upper leg muscle strength, knee joint proprioception, and varus-valgus laxity. In **Chapter 2**, the prevalence of patient-reported knee instability and its relationship with activity limitations will be evaluated in a clinical cohort of knee OA patients. In **Chapter 3**, the association between patient-reported knee instability and upper leg muscle strength, knee joint proprioception, and knee joint laxity will be determined. In **Chapter 4**, a literature study is performed to

provide a comprehensive overview of the existing literature on knee proprioception in knee OA. In **Chapter 5**, the association between reduced knee joint proprioception and a potential causal factor of this deficit, namely meniscal abnormalities on MRI, will be determined. Finally, **Chapter 6** is an explorative study to reveal possible associations between the 3 biomechanical factors and multiple knee joint abnormalities, as detected by MRI and/or radiography.

Part II. Optimizing effectiveness of exercise therapy

The second part of this thesis aims at further optimization of the effectiveness of exercise therapy in knee OA. In **Chapter 7**, the results from a randomized, controlled trial to determine the effectiveness of additional knee joint stabilization training in patients suffering from knee instability will be reported. The effectiveness will also be evaluated in specific subgroups of patients (i.e., those in whom knee instability is most severe) (**Chapter 8**). In Chapters 9 and 10, data from both exercise groups were used as a prospective 'exercise-cohort' to answer 2 additional study questions. In **Chapter 9**, the role of improvements in muscle strength and proprioception as potential underlying neuromuscular mechanisms of the beneficial effects of exercise therapy will be evaluated. Finally, the results from an explorative study on the role of baseline knee OA severity on MRI in the outcome of exercise therapy will be presented in **Chapter 10**.

Part III. Knee OA phenotypes

The third and final part of this thesis aims to identify clinically relevant, homogeneous phenotypes, which may need to be treated differently, from a large heterogeneous patient population (**Chapter 11**).

An overall discussion of the findings of this thesis, including recommendations for future research, is provided in **Chapter 12**. Finally, this thesis will be summarized in English and in Dutch.

In summary, the following research questions are established:

- What is the prevalence of patient-reported *knee instability* and the association with activity limitations in a clinical cohort of patients with knee OA? **(Chapter 2)**
- Is patient-reported *knee instability* associated with *biomechanical factors* of the knee joint (i.e., upper leg muscle strength, knee joint proprioception, and varus-valgus laxity) in patients with knee OA? **(Chapter 3)**
- What is the role of knee joint *proprioception* in knee OA, as described in the existing literature? **(Chapter 4)**
- Is reduced knee joint *proprioception* associated with *medial meniscal abnormalities* on MRI in knee OA? **(Chapter 5)**
- Are *biomechanical factors* of the knee joint (i.e., upper leg muscle strength, knee joint proprioception, and varus-valgus laxity) associated with *knee joint tissue abnormalities*, detected by MRI and/or radiography? **(Chapter 6)**
- What is the effectiveness of initial *knee joint stabilization training* prior to strength and functional training, compared to strength and functional training only, in knee OA patients suffering from knee instability? **(Chapter 7)**
- Is initial *knee joint stabilization training* only additionally effective in *subgroups* of patients in whom knee instability is most severe? **(Chapter 8)**
- Are *improvements in upper leg muscle strength and knee joint proprioception* longitudinally associated with reductions in pain and activity limitations following *exercise therapy*? **(Chapter 9)**
- Is the *severity of knee OA* on MRI associated with outcome of *exercise therapy*? **(Chapter 10)**
- Can a heterogeneous knee OA population be divided into homogeneous, clinically relevant *phenotypes*? **(Chapter 11)**

It should be noted that several studies in this thesis have been conducted with data from the Amsterdam Osteoarthritis (AMS-OA) cohort of Reade. This is an ongoing cohort, which explains the fluctuating sample sizes between studies.

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