Identifying Knee Osteoarthritis

Classification, early recognition and imaging

Dieuwke Schiphof

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Classificatie, eerste herkenning en imaging

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CONTENT

Chapter 1

General introduction

GENERAL INTRODUCTION

Osteoarthritis (OA) is a progressive and disabling joint disease. It is one of the most frequently occurring health problems for middle-aged and older people.[1-2] OA can occur in every synovial joint, but is most common in hip, knee, hand, foot and spine.[3] It is characterized by joint pain and limited function of the joint. In a synovial joint several structures can cause these clinical symptoms. Bone, cartilage, synovial fluid, ligaments and also the muscles around the joint are tissues that change with OA and affect the function of the joint.[4] Several tissues might be a starting point for pathways that lead to OA. Cartilage might be tissue in which the pathophysiological process of OA starts, but biochemical and imaging studies have shown that synovium and bone can also be starting points. However, it remains unclear which of these three types of tissue, or some combination thereof, might serve as the key tissue for OA.[5]

A diagnosis of OA is mainly based on symptoms. A patient that has reached a certain age and has joint pain, limitation of movement, crepitus and, sometimes, effusion in the joint might get the diagnosis of OA. Recommendations for the diagnosis of knee OA were published in 2010.[6] They include three main symptoms: knee pain, short-lived morning stiffness, and functional limitation in combination with three signs on physical examination (crepitus, restricted movement and bony enlargement). The treatment of OA is symptom driven (mainly pain and anti-inflammatory medication in combination with exercise treatment and lifestyle changes) but, unfortunately, such treatment cannot prevent or cure OA. The symptomatic treatment often fails to provide satisfactory pain relief.[2-3] Joint replacement may be possible in developed countries for patients with severe OA and significant disability.[2] Research efforts during the past decades have focused on the search for disease-modifying treatments.[7] Most of these disease-modifying treatments were directed towards regeneration of the cartilage and were tested in patients with evident OA. However, so far, these efforts have not been very successful and have not had a significant influence on the symptoms of OA.

In all joints, the prevalence of OA increases with age. In addition, the elderly population continues to increase, resulting in an even higher clinical and economic burden of OA.[8] At present, musculoskeletal disorders, of which OA is the most common, is the fourth leading cause of the economic healthcare burden. OA is more common in women than in men, with differences in both symptomatic and radiographic prevalence between the genders. Worldwide estimates are that 9.6% of men and 18.0% of women aged 60 years and over have symptomatic OA. For radiological knee OA these estimates are somewhat higher, even at a younger age (45 years and over):14.1% for men and 22.8% for women.[2] OA of the knee and hip are the major cause of disability in the general population, causing more trouble with walking and climbing stairs at population level than any other disease. Furthermore, in many cases hip and knee OA often leads to total joint replacement surgery. Knee OA is twice as prevalent as hip OA.[2] The work in this thesis focuses on knee OA. Figure 1 shows the prevalence of OA of the knee per age group and gender at the year 2000 (based on a publication of the World Health Organization).[2]

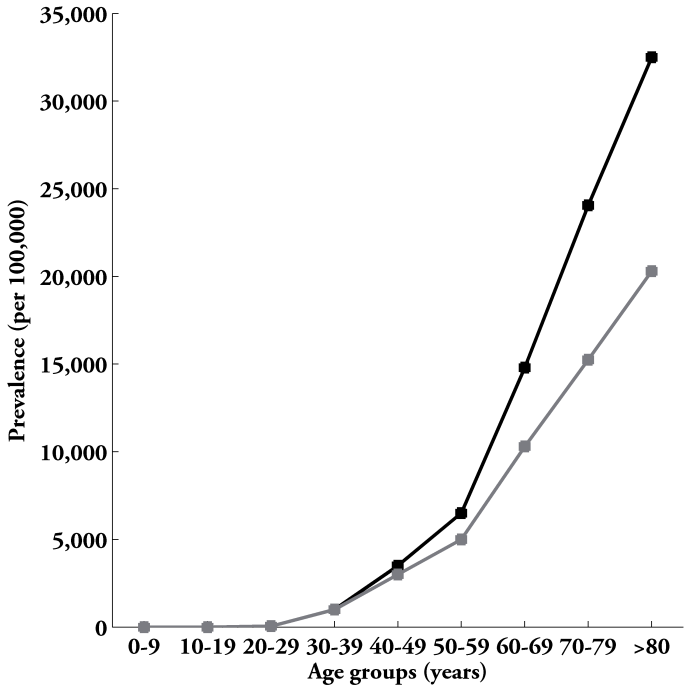

Figure 1: Prevalence rates of symptomatic radiological knee OA per age group at the year 2000 for the European population. Black line is the prevalence rate for women, grey line for men (based on data of a publication of the World Health Organization[2]).

In the knee, the proportion of radiographic OA ranges from 15-76% in patients who have knee pain, whereas the proportion of knee pain in people with radiographic knee OA ranges from 15-81%.[9] This illustrates the lack of agreement between the clinical definition and the radiographic definition of knee OA. When a patient presents in healthcare with symptoms of OA, it is likely that there is already pathological damage in the knee, perhaps for a long period. Symptomatic treatment (e.g. exercise and mechanical interventions, like insoles) might be more effective at an earlier clinical stage; the same probably applies to disease-modifying treatment. In a pre-clinical stage with early pathological damage of the knee joint, such disease-modifying treatment might be even more promising. However, it is not yet possible to define a study population at this pre-clinical or early clinical stage - for example, a population with an extremely high risk for developing OA or a population with early OA signs or symptoms. Therefore, to study the effect of treatment in an early or pre-clinical stage, first the early predictive signs for evident (clinical) knee OA need to be identified. It is probably easiest to study these early predictive signs in a population with known risk factors for knee OA. In a cross-sectional study, possible early features and signs of OA should be identified before we can explore their predictive ability.

Classification criteria

To define early knee OA, including pre-clinical OA, the definition of evident knee OA needs to be clear. However, as mentioned above, there is discordance between pathological evidence of OA and the presence and severity of clinical symptoms.[10-11] Partly because of this lack of agreement, and due to the lack of a gold standard definition, many different classification criteria for knee OA exist. This makes it difficult to establish a uniform definition of knee OA. A systematic overview of the different classification criteria for knee OA, and their reliability and validity, would be very useful.

The Kellgren and Lawrence (K&L) classification criteria are the most widely used radiographic classification criteria to identify and grade OA. The World Health Organization (WHO) adopted these criteria as the standard for epidemiological studies of OA.[12] In the first publications on the K&L grades, the radiographs did not contain any description of the grades.[13] The first descriptions were published in the WHO Atlas in 1963.[12] After this, several studies used the original K&L criteria, but the descriptions often differed from those published in the WHO Atlas. Moreover, an overview of these different descriptions and their impact on the classification and distribution of severity of knee OA on radiographs of the knees is lacking. Also, the association between clinical knee complaints and the different descriptions remains largely unknown.

It is suggested that the well-known discordance between the pathological evidence of OA and the presence and severity of clinical symptoms and signs is particularly true for the less severe grades of OA. Pain is more common in the more severe grades of OA.[11,16] However, there are people with moderate to severe OA (K&L grade 3 or 4) in the knee, without any knee pain. It is unknown why these people experience no pain whilst they have such well-recognized joint pathology. Therefore, it is important to investigate the differences in the determinants associated with pain in people with different grades of knee OA.

Identification of early knee OA

Radiographs have for long been the most frequently used and the standard images for visualizing OA. MRI has the advantage of direct assessment of the cartilage, which is still thought to be an important tissue in OA, as well as the advantage of visualizing all the other important tissues of the joint. Therefore, MRI is increasingly used to visualize OA features. MRI has another important potential advantage compared to radiographs: it can show structural damage or lesions earlier than can be seen clinically or on radiographs. Therefore, identifying OA features at a pre-clinical stage seems possible with MRI.

Identification of pre-clinical OA features with MRI might best be achieved in a population without knee OA but with established risk factors for knee OA, such as female gender, overweight, knee malalignment, and history of knee injury;[14] then, they can be followed-up over time to observe development of more evident OA. In addition, it would be interesting to see how these risk factors lead to initial damage of the joint structures and if there are differences between these risk factors in initial location and/or type of OA-related damage. Evidence for associations between risk factors and differences in location and/or type of OA-related damage of semi-quantitatively measured OA features

on MRI is lacking. This type of knowledge could be a starting point for investigating treatment or disease-modifying drugs specific for that risk factor or that type of damage. In addition, a recent review showed that we need more knowledge on how pain in the knee is associated with the semi-quantitative MRI features; this might help in our search for tissue-specific treatment.

Traditionally, research on knee OA has primarily focused on the tibiofemoral joint, although awareness of the importance of the patellofemoral joint has recently increased.[15] Little is known about the relationship between findings on specific physical examination of the patellofemoral joint and MRI OA features of this joint. It is worthwhile to establish whether there is a relationship between clinical findings of the patellofemoral joint and prevalent MRI OA features of the patellofemoral joint.

A fourth advantage of MRI over radiography is the three-dimensional view. In addition, more objective than the relatively subjective semi-quantitative scoring of MRI and radiographs, is the quantitative assessment of the cartilage in OA. Until recently, most studies quantified the cartilage with semi-automatic methods.[16] In 2007 a novel fully-automatic method was developed for quantification of the cartilage.[17] This novel morphometric framework has been tested in a population with healthy people, and people with varying degrees of OA symptoms on low-field MRI. It showed promising results in its ability to differentiate the healthy from OA patients, and even to differentiate between borderline OA cases and healthy cases. The framework has now been tested in our open population on a high-field MRI. First explorative analysis can elucidate whether there is an association between the cartilage volume (assessed with this novel software) and radiographic severity (K&L, osteophytes and joint space narrowing), semi-quantitative scoring of MRI features (cartilage defects, osteophytes, bone marrow lesions and cysts), and pain of the knee.

Another feature that can be quantified and might be helpful in the diagnosis of early knee OA is bone morphology. Although quantification of the trabecular bone is not outlined in this thesis, the shape of the bone is and might contribute to an earlier diagnosis of OA. Changes in the bone occur in the knee joint.[18] One difficulty in analyzing the involvement of the shape of the joint in OA, is that shape can play a role in the initiation of OA and also be changed by the OA process itself. For this reason, it is interesting to determine which aspects of bone shape in the knee associate to OA, and then assess which aspects of the shape are different in OA defined knees versus healthy knees, and whether the presence of these aspects depends on the severity of OA determined by radiographic and MRI features.

Study population

The Rotterdam Study

To address some of the gaps in the available knowledge regarding the criteria for early knee OA, and for evident knee OA, we make use of the Rotterdam Study. The Rotterdam Study is a prospective cohort study among persons living in the Ommoord district in the city of Rotterdam (the Netherlands). This study is ongoing since 1990, and investigates the incidence of, and the risk factors for, a variety of invalidating diseases. These diseases are: coronary heart diseases, heart failure and stroke, Parkinson disease, Alzheimer

disease and other dementias, depression and anxiety disorders, macular degeneration and glaucoma, diabetes mellitus and osteoporosis. From January 1990 onwards inhabitants of Ommoord aged 55 years and over were invited to participate in the Rotterdam Study. At that time, 7,983 (78% of the invited people) participants were included (RS-I-1).[19] In 1999, 3,011 participants (out of 4,472 invitees) who had reached 55 years of age or had moved into the district were also included in the cohort (RS-II-1). In 2006, 3,932 participants aged 45-54 years, living in Ommoord, were added to the total cohort (RS-III-1). By the end of 2008, 14,926 subjects aged 45 years and over were participating in the Rotterdam Study.[20] All participants were interviewed at home. A large amount of demographic data, and data on all kinds of diseases, have been collected. All participants had an extensive set of examinations in a research centre in Ommoord. Among other examinations, radiographs of the joints were taken at the research center. Follow-up was carried out every 3-4 years.

A nested cohort in the Rotterdam Study

To study early signs of knee OA, we make use of a nested cohort in the Rotterdam Study. The main aim of the nested study is to identify early predictive signs of pre-clinical knee OA and identify a population at extremely high-risk of developing knee OA. Women aged 45-60 years from the RS-III-1 cohort were invited to join the study. We included 891 women with a variable distribution of risk factors, and a small number of women who already had knee OA in at least one knee. Figure 2 shows the overlap of the risk factors in this female population without radiographic knee OA.

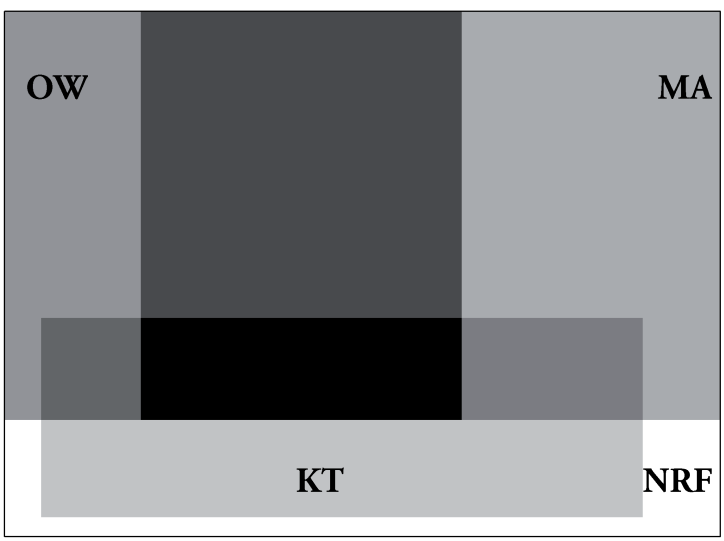

Figure 2: Overlap of risk factors in the female population of the nested cohort in the Rotterdam Study without radiographic knee OA. The largest rectangle represents the whole female population without radiographic knee OA. OW, overweight (BMI≥25); MA, knee malalignment; KT, history of knee trauma/injury; NRF, no risk factors. The darker grey rectangles represent the overlap with the risk factors, with the darkest rectangle representing the overlap of all three risk factors.

The data of the included women were extended with a knee-specific questionnaire, a knee-specific physical examination, and MRI of both knees. After two years all women of the nested cohort filled in another knee-specific questionnaire. It is planned to perform the follow-up of all baseline measures, including the knee-specific assessments, of this population five years post-baseline.
All the studies presented in this thesis are conducted using baseline data: Chapter 4 on baseline data of the RS-III-1, Chapter 5 on baseline data of the RS-I-1, and Chapters 6-9 are based on data from the nested cohort study.

STUDY AIMS AND OUTLINE OF THIS THESIS

The aim of **Chapter 2** is to evaluate the reliability and validity of the different classification criteria for knee OA used in epidemiological studies. **Chapter 3** provides information on how many different descriptions of one of these classification criteria for knee OA, the Kellgren and Lawrence classification criteria, are used in epidemiological studies, and **Chapter 4** identifies the impact of these different descriptions and assesses the association between knee complaints and the different descriptions. **Chapter 5** describes differences in the determinants of pain which are associated with different grades of knee OA. In **Chapter 6** we assess how different risk factors are associated with early MRI OA features in women without radiographic knee OA, evaluate whether these risk factors differ in their initial location and type of OA-related damage, and finally explore how these features are associated with knee pain. In **Chapter 7** the aim is to examine the relationship between the clinical findings and prevalent MRI OA features of the patellofemoral joint in women with and without knee OA. **Chapter 8** has the aim to investigate if quantitatively measured cartilage volume differs with radiographic severity, semi-quantitative scoring of MRI features, and pain of the knee. **Chapter 9** describes which aspects of the shape of radiographically-defined OA knees are different from control knees, and whether the presence of these shape aspects depend on the severity of OA as determined from radiographs and MRI. Finally, in **Chapter 10** the main results of the previous chapters are discussed, together with the study limitations and their implications for further OA research.

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Chapter 2

Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal

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ABSTRACT

Objectives: Despite extensive epidemiological and clinical research, there is no consensus on classification criteria to define knee osteoarthritis (OA). No gold standard is available and many different definitions are used. For future research and interpretation of epidemiological studies, we aimed to evaluate reliability and validity of commonly used classification criteria.

Methods: Systematic searches were performed in Medline/Pubmed and Embase for articles evaluating reliability, construct validity, and content validity of knee OA classification criteria.

Results: In 18 articles, 25 classification criteria were found that could be summarized in three categories (radiological clinical and radiological combined classification criteria, and clinical classification criteria). No classification criteria based on magnetic resonance imaging could be included. In general, intra-and interrater reliabilities were good. Construct validity was low when radiological criteria were compared with clinical classification criteria. Associations between classification criteria and symptoms and risk factors like pain and obesity were moderate.

Conclusion: More research is needed to investigate the impact of different classification criteria in epidemiological research and to reach consensus about which criteria should be used to define knee OA. Meanwhile, to create uniformity in epidemiological research we recommend separate lesion scoring, overall scoring, and pain registration to define knee OA.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and one of the most frequently occurring health problems for middle-aged and older people.[1-4] OA affects the knee more often than the hip and can have a significant impact on the functional ability in daily life.[2] OA can be defined in many ways, but epidemiological studies most commonly use pathological (imaging and laboratory tests) and clinical signs and symptoms as the basis for classifying knee OA. Pathological changes that occur with OA are loss of cartilage, osteophytes (OPs), subchondral sclerosis and cysts, and deformation of the bone. Soft tissue, such as ligaments, can be affected. Most pathological changes can be seen on radiographs, although cartilage is only seen by absence (i.e., space between the bones), and soft tissue and fluid cannot be seen at all. On magnetic resonance imaging (MRI), however, these structures are visible. Some pathological changes can be seen with laboratory findings (e.g., elevated CTX-II marker [C-telopeptide of type II collagen], and a low degree of inflammation markers in synovial fluid and serum).[5,6] Clinical symptoms and signs that occur with OA are joint pain, tenderness, stiffness, limitation of movement, occasional effusion, and crepitus.[1-4] Clinical symptoms and signs can be ascertained by history and physical examination and by self-completed questionnaire.
Discordance between pathological evidence of OA and the presence and severity of clinical symptoms and signs is well documented.[7-9] Despite extensive clinical and epidemiological research on knee OA, there is no gold standard to define knee OA.[10-13] The Kellgren and Lawrence (K&L) classification system and the American College of Rheumatology criteria (ACR criteria) are most frequently used in, respectively, epidemiological (descriptive) studies and clinical trials.[1,14] Criticisms of the K&L system, however, include the weak relationship with clinical symptoms and signs, the different descriptions used for the grades, and the focus on OPs.[13,15] Clinical criteria have hardly been used in epidemiological studies because of lack of validation.[16] Because of these criticisms, other radiological and clinical criteria for defining knee OA have been developed and all these criteria are made with assumptions about the biology of the disease.[17] However, all these different classification criteria make it difficult to uniformly define knee OA and to compare the results of different epidemiological studies.[17,18] The use of various classification criteria also makes it difficult to investigate (potential) risk factors for knee OA and to cross-validate them in different epidemiological studies or for use in meta-analysis. Therefore, the aim of this systematic appraisal was to evaluate the validity and reliability of the different classification criteria of knee OA available for epidemiological studies, and to discuss how uniformity in use of the classification criteria of knee OA in epidemiological research can best be reached.

METHODS

Literature search

Searches were performed in the following databases: Medline/Pubmed (1966 - March 2006) and Embase (1990-March 2006). The search terms included: (knee AND OA) AND (classification OR comparison OR criteria OR definition) AND ([MRI OR magnetic resonance imaging] OR [radiography OR x-ray OR radiologic OR radio-

logical] OR [clinical OR symptomatic OR symptoms OR signs]). Two independent reviewers (D.S. and B.M.d.K.) read all abstracts. Full-text articles were read of all included abstracts and checked for the inclusion criteria by the two reviewers. Disagreement regarding the inclusion of articles was resolved by discussion with each other or with a third reviewer (S.B.-Z.) until consensus was reached. Studies were included if they fulfilled the following inclusion criteria: (1) the study population contained persons with and without knee OA, (2) it was an original article, (3) the study population contained more than 20 participants, (4) the article investigated classification criteria of knee OA based on clinical, radiological, laboratory, or MRI criteria or a combination of these, (5a) the study described the design, reliability, or validity of one classification criteria or (5b) the study investigated risk factors or determinants of knee OA and used at least two classification criteria, and (6) the article was written in English, Dutch, German, Norwegian, Swedish, or Danish. Screening the reference lists of all relevant articles extended the search.

Assessment of methodological quality

Two reviewers (D.S. and B.M.d.K.) assessed (independently of each other) the methodological quality of the included articles. A kappa value was calculated to assess the interrater variation of the initial assessment of both reviewers. A final score was made by agreement. Table of Appendix A lists the criteria.[19,20] All criteria were used to define quality, except for the description of the selection of the study population, which was for information only. For acceptable methodological quality, the article needed a score above 60%.

Criteria for reliability and validity of the classification criteria

Three other items (reliability, construct validity, and content validity) for classification criteria were assessed. Criteria for these items were formulated with information from the criteria of Buchbinder et al. (1996),[19] Felson and Anderson (1995),[21] and Reijman et al. (2004).[22] Two reviewers extracted the data (D.S. and B.M.d.K.). Criteria for this assessment are described below. Reliability is expressed in terms of inter-and intrarater agreements, by kappa statistics, percentage agreement, or correlation coefficient. In general, kappa above 0.8 is very good, between 0.6 and 0.8 is good, and between 0.4 and 0.6 is moderate.[23,24]

Construct validity is evaluated by considering two questions: (1) Do the classification criteria discriminate between two entities (i.e., those with or without OA) and (2) do the classification criteria show a relationship with known risk factors such as obesity (body mass index [BMI]≥30)), symptoms (knee pain), or signs (pathological changes such as joint space narrowing [JSN] and OPs)? Results to the first question were summarized as sensitivity and specificity of the classification criteria compared with the comparator used in the original article, because no gold standard is available. The expert opinion was judged to be an acceptable comparator, as was subsequent total knee replacement. Results of the second question were summarized as odds ratios (ORs) and relative risks, both with 95% confidence intervals (95% CIs).

Content validity refers to the extent to which classification criteria represent all facets of knee OA as symptoms, physical signs, radiological signs, and laboratory findings (e.g., pain, stiffness, and loss of function of the knee, loss of articular cartilage, OP formation, and a low degree of inflammation markers).[1,16] To evaluate the content validity of the classification criteria, the following question should be considered: Are elements of each of the facets that occur with knee OA included in the classification criteria?[19,21]

RESULTS

Identification and selection of literature

The searches resulted in 1,321 abstracts, 1,258 hits in Medline/Pubmed, and 63 hits in Embase. There were 15 articles that fulfilled the predefined inclusion criteria. Main reason for exclusion (84%) was the first inclusion criterion (the study population contained persons with and without knee OA). After screening the reference lists of the included articles, another three articles were included. Table 1 presents the characteristics of the 18 included studies.

Critical assessment of methodological quality

The initial agreement on methodological quality between the two reviewers (D.S. and B.M.d.K.) was good with a κ-value of 0.87 (actual agreement of 95%). After consensus was reached, 16 articles[5,23,25-38] showed acceptable methodological quality. The quality scores are presented in the table of Appendix B.

Classification criteria

In the included articles, we found 25 classification criteria which could be summarized in three categories: (1) Radiological classification criteria (ROA) based on pathological changes such as JSN, OP, cysts, sclerosis, bone deformity, including the K&L radiological classification criteria in 11 studies,[23,25,28,29,31,32,34-39] Ahlback radiological classification criteria in two studies,[25,40] and other radiological classification criteria in six studies,[23,27,29,30,33,37] (2) clinical criteria such as ACR clinical in three studies,[5,26,31] ACR clinical + laboratory criteria in two studies,[5,31] and other clinical classification criteria in four studies,[5,29,33,34] and (3) clinical and ROA combined (clinical + radiological), such as ACR clinical + radiological classification criteria in one[5] and other clinical + radiological classification criteria in two studies.[33,34,38] Further description and multiple cutoffs of the different classification criteria are described in Table 2. MRI-based classification criteria with cutoffs for knee OA or grade of knee OA were not found in this search.

Reliability

Twelve articles described the reliability of classification criteria for knee OA.[23,25-27,29,30,32-35,37,39] Table 3 shows the reliability of these classification criteria by category with their different cutoffs. Summarizing, the majority of the radiological classification criteria showed good to very good reliability (κ between 0.6 and 0.8 and above 0.8). For the clinical OA and combined classification criteria, the interrater reliability was slightly lower.

Table 1: Characteristics of the included studies (N=18)

Reference	Study-design	X-ray method	Classification used in study	Com-parator	Study population				Prevalence of knee OA according to classification (%)		Prevalence of knee OA according to reference standard (%)	
					Setting	Size	Male (%)	Mean age (range in years)				
Felson (1997)[29]	CS	AP, lateral, weightbearing	ROA-K&L (modified) 3 alternatives	Clinical	Open population, Framingham OA study	1000	34.7	79.4	-		ROA-TFJ ROA-TFJ+PFJ	15 24.5
LaValley (2001a)[37]	PCS	AP, weightbearing	ROA	ROA-K&L (Modified)	Open population, Framingham OA study	843	36.1	71.1 (61-91)	-		-	
LaValley (2001b)[38]	CS	AP, lateral, weightbearing,	Clinical	Clin+ROA	Open population, Framingham OA study	1921	43.9	61.2 (±12.5)	-		ROA Clin+ROA	19.6 10.4
Claessens (1990)[28]	CS	AP, weightbearing	-	ROA-K&L	Open population Zoetermeer	2865	46.1	≥45	-		ROA-K&L (right knee) ROA-K&L & pain	19.7 4.7
Kellgren (1957)[39]	CS	AP	ROA-K&L	-	Open population	85	-	55-64	-		-	
Lanyon (1998)[30]	CC	AP, weightbearing extended knees	ROA	-	Open population General practice	452	35	62 (40-80)	ROA (OP≥2) ROA (JSN≥2)	19 20	-	
Petersson (1997)[25]	CS	AP, Extended knees, weightbearing	ROA-Ahlback	ROA-K&L	Open population	2000	-	35-54	ROA(≥1) with pain *	1.1	ROA-K&L ≥ 2 + pain ROA-K&L ≥ 3 + pain	1.5 0.9
Schouten (1995)[31]	PCS	-	Clinical	ROA-K&L	Open population Zoetermeer	-	-	-	-		-	

Table 1 (continued)

Reference	Study-design	X-ray method	Classification used in study	Com-parator	Study population				Prevalence of knee OA according to classification (%)		Prevalence of knee OA according to reference standard (%)	
					Setting	Size	Male (%)	Mean age (range in years)				
Hart (1993)[34]	CS	AP, weightbearing	Clin+ROA	ROA-K&L	Open population, Chingford study	985	0	54.3	Clin+ROA	5,8	ROA-K&L>2	12
Hart (2003)[35]	PCS	AP, weightbearing	ROA-K&L	-	Open population, Chingford study	169 (180 knees)	0	57.1	Baseline >2 After 5 yr After 10 yr	0 22.8 42.2	-	
Hart (1991)[36]	CS	AP, weightbearing	-	ROA-K&L	Open population, Chingford study	541	0	54 (45-65)	-		ROA-K&L (with symptoms)	19 56
Spector (1993)[23]	CS	AP, weightbearing	ROA	ROA-K&L	Open population, Chingford study	1003	0	45-65	-		-	
Bellamy (1999a)[26]	CC	-	Clinical (ACR-clin)	-	Australian Twin Register	159	28.9	58.37	-		-	
Bellamy (1999b)[27]	CC	-	ROA	-	Australian Twin Register	159	28.9	59	-		-	
Ahlback (1968)[40]	CS	AP, (non-) weightbearing,(semi) flexed,extended	ROA-Ahlback	-	St. Goran Hospital	298	20.3	40-89	-		-	
Altman (1986)[5]	CC	-	Clinical Clin+ROA	Clinical	Rheumatology centers	237	27	42-63 OA 62 C: 47	Clinical Clin+ROA	54.4 57	Clinical	54.9
Englund (2003)[33]	RS	AP, semi-flexed	Clin+ROA	ROA	Lund Univ. hosp. &Nat. Pop. Record	223	80	Pt: 54.3 C: 56.3 55.3	Clin+ROA	25	ROA	18

Table 1 (continued)

Reference	Study-design	X-ray method	Classification used in study	Com-parator	Study population				Prevalence of knee OA according to classification (%)	Prevalence of knee OA according to reference standard (%)
					Setting	Size	Male (%)	Mean age (range in years)		
Vilalta (2004)[32]	CS	AP, weightbearing	ROA-K&L modified	-	Consecutive patients	95	28	71	-	-

CC, Case-control study; CS, Cross-sectional study; RS, Retrospective study; PCS, Prospective cohort study; AP, Anterior-Posterior direction of x-ray; ROA, Radiological classification criteria; clin, Clinical classification criteria; TFJ, Tibiofemoral joint,;PFJ, Patellofemoral joint; C, Controls; Pt, Patients

* prevalence over 1853 participants which responded to the questionnaire

Table 2: Classification criteria

Radiological classification criteria: Scoring of features (joint space narrowing (JSN), osteophyte (OP), cysts, sclerosis, bone deformity)

A. Kellgren and Lawrence classification system (K&L) (≥ grade 2) Grade 0: normal, Grade 1: possible osteophytic lipping, unimpaired JSN, Grade 2: definite OP(s) and possible JSN, Grade 3: definite multiple OPs, and definite JSN, Grade 4: marked JSN, large OPs, sclerosis and deformity[39]
B. Ahlback's classification system (≥ grade 1) Grade 1: JSN <3mm, grade 2: Joint space obliteration, grade 3: minor bone attrition (0-5mm), grade 4: moderate bone attrition (5-10 mm), grade 5 severe bone attrition (>10mm)[25,40]
C. In any of the two tibiofemoral compartments: JSN grade 2 or higher, sum OP compartment score >= 2 or grade 1 JSN in combination with grade 1 OP in the same compartment[33]
D. JSN and OP ≥ grade 2[37]
E. Any feature ≥ grade 2[37]
F. Either an OP ≥ grade 2 or JSN ≥ grade 2 with either sclerosis, cysts or an OP grade 1[29]
G. OP grade 1 and any sclerosis or JSN[29]
H. Sum of individual radiographic features ≥ grade 2[29]
I. JSN ≥ grade 1[27,30]
J. JSN ≥ grade 2[27,30,33,37]
K. JSN ≥ grade 3[23,30]
L. OP ≥ grade 1[23,27,30]
M. OP ≥ grade 2[27,30,33,37]
N. OP ≥ grade 3[30]
O. OP maximum whole knee (TFJ+PFJ) ≥ grade 1, 2 and 3[30]

Clinical classification criteria

A. ACR-Clinical list method: knee pain and at least 3 of 6: age >50, stiffness <30min, crepitus, bony tenderness, bony enlargement, no palpable warmth (for tree method see references)[5,26,31]
B. ACR-Clinical+Laboratory: knee pain and at least 5 of 9: age >50, stiffness <30min, crepitus, bony tenderness, bony enlargement, no palpable warmth, erythrocyte sedimentation rate <40mm/hour, rheumatoid factor ≤1:80, synovial fluid OA[5,31]
C. Frequent knee symptoms and presence of crepitus on physical exam (frequent knee symptoms are defined as pain in or around the knee on most days of the months during the year of the exam). Frequent knee pain is defined as positive answer on two questions: pain in or around the knee on most days of the month and on most days do you have pain, aching or stiffness in either of your knees?)[29]
D. Pain on movement or tenderness in the knee joint line at clinical exam[34]
E. Screening question 1): 'During the last month, did you have any knee pain or discomfort when walking 2-3 blocks (one-fourth of a mile)?'[38]
F. Screening question 2): Clin. E + 'Has a doctor ever told you that you have arthritis in your knees?'[38]
G. Screening question 3): Clin. E + 'How long does this stiffness take wear off? And 'Have you had knee pain on more than two occasions in the last year?'[38]

Radiological+clinical (combined) classification criteria

A. ACR-Clinical+Radiological: list method: knee pain and OP and at least 1 of 3: age >50, stiffness <30min, crepitus (for tree method see references).[5,31]
B. JSN ≥1 with OP ≥1 in same compartment OR JSN ≥2 OR sum of OP score of both compartments ≥2 with symptomatic knee (subscale Knee Injury and Osteoarthritis Outcome Score, quality of life and 2 out of 4 additional subscale with cut-offs: QOL ≤87.5, pain ≤86.1, symptoms ≤85.7, activities of daily living ≤86.8 and sports and recreation ≤85.0).[33]
C. Presence of radiological changes (K&L ≥2) in addition to symptoms or clinical signs (reported pain present longer than 1 month in the last 10 year).[34]
D. K&L grade ≥2 for tibiofemoral compartment OR Grade ≥2 OP or Grade ≥2 JSN and grade ≥1 OP for patellofemoral compartment AND affirmative answer to the question: 'On most days, do you have pain, aching, or stiffness in either of your knees?'[38]

JSN, Joint space narrowing; OP, Osteophyte; TFJ, Tibiofemoral joint; PFJ, Patellofemoral joint; ACR, American College of Rheumatology; OA, osteoarthritis; Clin. E, Clinical classification criteria E; QOL, Quality of life

Table 3: Reliability of classification criteria for knee OA

Classification criteria	Intrarater	Interrater	Cut-off	Statistics	Size	Prevalence (%)	Reference
ROA							
A	0.79 0.74	0.57	Grade ≥2	Kappa	40	-	Hart (1993)[34*]
	0.86 0.83	-	Grade ≥1 Grade ≥2	Kappa	40	-	Hart (2003)[35]
	0.83	0.83	Grade ≥2	Correlation coefficient	85	-	Kellgren (1957)[39]
	0.88	Not applicable	-	Kappa	185	1.5	Petersson (1997)[25]
	0.88 0.79 0.66	1-2**: 0.80 1-3: 0.64 2-3: 0.56	Grade ≥2	Kappa	100	-	Spector (1993)[23]
A (modified)	0.91 0.922	0.76 0.769	Grade ≥2	Kappa ICC	869	37.1	*** Felson (1997)[29], LaValley (2001)[37]
B	0.88	Not applicable	Grade ≥1	Kappa	185	1.1	Petersson (1997)[25]
I	0.79/0.97	0.79	Grade ≥1	Kappa	159	-	Bellamy (1999b)[27]
J	0.95/ 0.99	0.97	Grade ≥2	Kappa	159	-	Bellamy (1999b)[27]
J	-	0.66 (93%)	Grade ≥2	Kappa (% agreement	223	81	Englund (2003)[33]
K		> 0.7	-	Kappa	40	-	Lanyon (1998)[30]
I,J,K	-	1-2: 0.407 1-3: 0.305 2-3: 0.487	-	Kappa	95	-	Vilalta (2004)[32]
K	0.82/ 0.80/ 0.83	(1-2) 0.58 (1-3) 0.56 (2-3) 0.50	≥3	Kappa (using 10% cut-off)	100 knees	-	Spector (1993)[23]
L,M,N	-	1-2: 0.489 1-3: 0.552 2-3: 0.314	-	Kappa	95	-	Vilalta (2004)[32]
M	-	0.64 (92%)	Grade ≥2	Kappa (% agreement)	223	81	Englund (2003)[33]
L	0.88/ 0.94	0.91	Grade ≥1	Kappa	159	-	Bellamy (1999b)[27]
M	0.94/ 0.94	0.94	Grade ≥2	Kappa	159	-	Bellamy (1999b)[27]

Table 3 (continued)

Classification criteria	Intrarater	Interrater	Cut-off	Statistics	Size	Prevalence (%)	Reference
Clin-ROA							
A	-	0.91 0.52/ 0.68	Presence / absence	Obs agreem, Kappa	159	-	Bellamy (1999a)[26]
Clinical OA							
A	-	0.94 0.61/ 0.57	Presence / absence	Obs agreem, Kappa	159	-	Bellamy (1999a)[26]

Obs agreem, Observer agreement; * data in Spector et al. (1992)[50]; ** 1-2, interrater reliability between observer 1 and observer 2. *** Modified K&L definition description in Felson et al. (1995)[44]; ^ unadjusted for bias and prevalence, for adjusted kappa's see Bellamy 1999b[27]

Validity

Construct validity: discrimination

Table 4 presents the discriminative ability between two entities of the classification criteria. Only three articles conducted head-to-head comparisons of different classification criteria. The radiological classification criteria were compared with a clinical comparator, as defined in the original article and which can be found in Table 2.[29,30,33] Altman et al. (1986)[5] showed the sensitivity and specificity of the classification criteria compared with an expert opinion of the ACR. A definite knee OA several years later, as indicated by a total knee replacement, was not used as comparator.

Table 4: Discrimination of criteria (construct validity)

Classification criteria	Sensitivity (%) L / R	Specificity (%) L / R	Comparator	Reference
ROA				
A (TFJ)	53.8 / 64.3	77.9 / 75.3	Clinical: C	Felson (1997)[29]
F (TFJ&PFJ)	55.4 / 67.2	70.2 / 68.9		
G	63.9 / 72.3	50.1 / 45.4	Clinical: C	Felson (1997)[29]
H	76.5 / 78.2	41.1 / 33.1		
Clinical ROA				
A	91	86	Diagnosis by expert	Altman (19 86)[5]
A (+lab)	94	88		
Clinical OA				
A	95	69	Diagnosis by expert	Altman (19 86)[5]
A (+lab)	92	75		
E	56.6	85.1	Clinical+ROA: D	LaValley (2001b)[38]
F	46.2	94.1		
G	84.2	72.8		

L: left, R: right; TFJ, Tibiofemoral joint; PFJ, patellofemoral joint

In general, the sensitivity was moderate to low and the specificity was somewhat higher if radiological classification criteria are compared with clinical classification criteria. Only the ACR criteria showed good sensitivity and specificity with the expert opinion, but this is logical because the last step in the analytic method of construction of the ACR criteria was the selection of the combination of variables, which were most sensitive and specific to classify OA of the knee.

No clinical classification criteria were compared with radiological classification criteria alone as a comparator. One study compared their ROA with knee pain.[30] They found a sensitivity of 62% and specificity of 53% for the ROA based on JSN (cutoff ≥1). Other cutoffs (≥2 and ≥3) showed worse sensitivity (28% and 18%) and somewhat higher specificity (79% and 97%) compared to knee pain. For the ROA based on OP (cutoff ≥1) they found 62% and 58%, respectively. Other cutoffs (≥2 and ≥3) for this criterion also gave worse sensitivity (30% and 11%) and better specificity (93% and 98%).[30] Two other studies compared the presence of clinical symptoms with K&L radiological classification criteria (≥2); their sensitivity (and specificity) was even worse (1% and 6% sensitivity, respectively, and 99% both for specificity).[28,36]

Construct validity: associations

Obesity was the only risk factor that was investigated in more than one of the retrieved studies. As symptom, knee pain was investigated in the retrieved studies. None of the included studies investigated an association with signs as JSN or OP.

The associations between the classifications criteria (with the different cutoffs) and pain and obesity are presented in Table 5. All associations were presented as ORs with a 95% CI.

The association between the radiological classification criteria and pain ranged from OR 5 1.8 (1.3-2.7) to 6.6 (2.9-15.1). The majority of these associations were significant.[23,30,37] The differences between age ranges of the populations in these studies were large (see Table 1).

Only three articles reported the association between classification criteria and obesity.[23,31,33] The differences between age ranges in these populations were comparable (see Table 1). The ORs range from 1.01 (0.52-1.98) for a ROA based on JSN to 4.0 (1.3-12.8) for the combined criteria of Englund et al. (2003).[33]

For the separate classification criteria, the ORs for obesity were around 2 for ROA,[23,33] around 3 for combined classification criteria,[33] and around 2 for clinical OA.[31] All associations between the classification criteria and obesity were significant, except the association with the radiological classification criteria based on JSN.

Table 5: Associations of the classification criteria with pain and obesity (construct validity)

Classification criteria	OR pain (95% CI)	OR obesity (95% CI)	Reference
ROA			
A (incident)	3.61 (2.63-4.95)	3.28 (2.24-4.81)	Spector (1993)[23] (10th centile)
A (prevalent)	4.83 (2.15-10.87) 3.38 (1.63-6.96)		LaValley (2001a)[37]
C		1.3 (0.7-2.7)* 3.7 (1.2-11.2)	Englund (2003)[33]
D (incident) D (prevalent) E (incident) E (prevalent)	2.96 (1.58-5.53) 2.14 (0.95-4.83) 2.88 (1.53-5.41) 2.17 (0.96-4.95)		LaValley (2001a)[37]
I (TFJ+PFJ) I (max TFJ) J J K	1.8 (1.3-2.7) 1.9 (1.3-2.8) 3.1 (1.8-5.1) 4.4 (2.0-9.7) 6.6 (2.9-15.1)		Lanyon (1998)[30]
J (incident) J (prevalent)	4.38 (1.64-11.65) 5.96 (1.99-17.80)		LaValley (2001a)[37]
K	2.69 (1.82-4.01)	(0.52-1.98)	Spector (1993)[23] (10th centile)
L (incident) L (prevalent)	2.76 (1.52-5.02) 2.02 (0.90-4.55)		LaValley (2001a)[37]
M (medial) M (lateral)	3.73 (2.60-5.35) 3.16 (2.25-4.43)	3.22 (2.10-4.96) 4.63 (3.14-6.81)	Spector (1993)[23] (10th centile)
O (≥ 1) O (≥ 2) O (≥ 3) L (maxTFJ) M N	2.5 (1.6-3.4) 5.2 (2.9-9.3) 5.5 (2.1-14.6) 2.9 (1.9-4.5) 6.6 (3.1-14.3) 6.0 (1.8-3.4)		Lanyon (1998)[30]
Clinical+ROA			
C		2.4 (1.0-5.8)* 4.0 (1.3-12.8)	Englund (2003)[33]
Clinical OA			
ACR clinical tree A B		3.5 (1.9-6.4) 1.6 (1.1-2.3) 1.7 (1.1-2.4)	Schouten (1995)[31]

ROA, Radiological osteoarthritis; OR, Odds ratio; CI, Confidence interval; TFJ, Tibiofemoral joint; PFJ, Patellofemoral joint; ACR, American College of Rheumatology

* OR for overweight (BMI=25-29)

Content validity

None of the classification criteria contained elements of all facets of knee OA. The classification criteria that contained elements of almost all facets of knee OA are radiological + clinical classification criteria of Englund et al. (2003).[33] Beside the radiological element in the criteria, symptoms and physical signs are included, but no laboratory findings are included. The ACR criteria (consisting of three alternatives: clinical + laboratory, clinical + radiographic, and clinical)[5] with the three alternatives combined, does not contain anything about physical signs (e.g., loss of function of the knee).

DISCUSSION

Reviewing these 18 articles, the various classification criteria generally showed good reliability. Moderate-tolow sensitivity and somewhat higher specificity were reported for radiological classification criteria compared to clinical classification criteria. The associations for pain and obesity with the criteria were more or less comparable between the different classification criteria. None of the classification criteria was assessed with good content validity. We tried to make the search as comprehensive as possible. Nevertheless some articles may have been missed due to limiting the selection on languages, by the use of different keywords, to unclear abstracts or not being indexed in Medline/Pubmed or Embase. However, we believe that we included appropriate studies that give a good insight into the quality and variety of the classification criteria used for knee OA.

None of the included articles investigated a classification criteria based on MRI criteria. The last 5 years MRI classification systems have been developed, like for instance the Knee Osteoarthritis Scoring System[41] and the Whole Organ Magnetic Resonance Imaging System;[42] however, these definitions did not have clear cutoffs for knee OA and were not yet investigated in an open population with persons with and without knee OA. Therefore, they did not fulfill the inclusion criteria and were not included in this systematic appraisal. Although self-reported diagnosis of knee OA has been used to identify people in population studies,[43] we did not include self-reported knee OA as a classification criteria. This was because it was unclear where exactly this self-reported knee OA was based on. Applicability of the classification criteria is the description of how easy it is to get the criteria and define knee OA with it. This is not described in the present article, although it is common when describing classification criteria. In our opinion, the applicability of the included classification criteria was too obvious to give a useful addition to this systematic appraisal.

The Framingham population[29,37,38] and the Chingford population[23,34-36] are used in more than one study, although all these studies discussed different classification criteria and/or different kinds of validities and reliabilities over different sets of data. Therefore, all these studies are included in this appraisal. The reliability of the modified K&L system is the same for all studies in which the Framingham population participated.[44]

In general, the reliability was good for all radiological classification criteria. For the combined and clinical classification criteria, the reliability was somewhat lower. No intrarater reliability of the clinical definitions was provided. A reason for the low sensitivity and somewhat higher specificity of the ROA compared to the clinical criteria is that the clinical criteria are a poor test for the pathological changes.[13,36] This gap between the

ROA and clinical symptoms is also described by Hannan et al. (2000)[8] and McAlindon et al. (1999).[7] It has been suggested that patellofemoral OA plays a role in the discordance between radiological OA and clinical OA.[10,13,45,46]

Nowadays we know that OA involves the whole knee, the tibiofemoral joint (TFJ), and the patellofemoral joint (PFJ). Only three articles take the PFJ into account. Ahlback et al. (1968)[40] describes the PFJ in their design of radiological classification, and Felson et al. (1997)[29] and Lanyon et al. (1998)[30] compare the ROA containing PFJ with a clinical classification criterion and pain, respectively. Lanyon et al. (1998)[30] showed that the sensitivity increases from 38.1% to 62.3%, whereas specificity decreases from 82.7% to 58.7% for the presence of knee pain. Felson et al. (1997)[29] also concluded that adding the PFJ improves the correlation of clinical OA (based on clinical classification criteria) with OA based on radiological classification criteria.

Taking the PFJ into account in the radiological classification criteria could therefore narrow the gap between clinical classification criteria and radiological classification criteria, as is suggested in several articles.[10,13,29,30,45,46] The price to pay for this is taking more radiographs, which, in epidemiological research, is not always feasible.

The K&L system is the most commonly used, but also the most criticized definition of knee OA. A major point of criticism is the difference in descriptions used in the different articles.[13,15,23,46] Of the 11 articles that used the K&L criteria, five defined the K&L score grade 2 as having definite Ops.[23,25,28,36,39] The others did not describe grade 2[31,32,34,35] or used a slightly modified K&L grade 2.[29,37] It needs to be established whether these differences in descriptions make a difference in defining OA. Because of the criticisms of the K&L system and the variety of definitions available besides this system, Vignon et al. (1999) presented recommendations for the radiological assessment of knee OA.[47] They recommend the scoring of separate lesions; it is considered easier and more informative, but no cutoff for knee OA is given. Therefore, we think that the K&L criteria combined with the scoring of separate lesions can give a complete radiological definition for knee OA. This separate lesion scoring can be done with several atlases, for example, the OASRI atlas,[48] although they do not describe all features (e.g., subchondral bone cysts).

The heterogeneity of the included articles was great with respect to population selection, age, and gender; in addition, there were differences in the classification criteria used and almost as many different cutoffs. Due to all these differences, no direct comparison could be made between the studies. The association (ORs) of the classification criteria and symptoms and risk factors such as pain and obesity were not comparable between the studies because of the heterogeneity of the studies. No conclusions can be drawn about the differences in ORs due to different classification criteria. It would be preferable to compare the association between different classification criteria and symptoms or risk factors in the same study population.

A few studies did compare more than one classification criteria in the same study population,[23,25,29-31,37] such as the difference in estimates of prevalence for OA of the knee ranging from 32/1000 to 69/1000 as stated by Schouten and Valkenburg (1995).[31] Most of these studies provided some information about the impact of using different classification criteria in the same population, mainly for ROA.[23,29,30,37] All these studies concluded that OPs, compared to other radiological features, associate best with knee

pain; however, they state that OPs do not distinguish between people with and without clinical OA.[29]

Other studies that reviewed different classification criteria for knee OA were less extensive than the present appraisal.[13,22,49] Hart and Spector (1995) summarized classification criteria for OA at several joints divided in radiological and clinical criteria.[13] For radiological knee OA, they described K&L, Ahlback, and new criteria investigated by Spector et al. (1993).[23] They found that grading OPs is the best way of defining prevalent knee OA and they also concluded that the clinical criteria were a poor test for radiological definition.

Sun et al. (1997) reviewed the reliability of only radiological grading of knee and hip OA.[49] They cautiously concluded that the intra-and interrater reliabilities for the overall scores of the knee were satisfactory and also found that OPs were somewhat more reliable in the knee in most studies, which is supported by the present study.

Reijman et al. (2004) performed a similar review for definitions of the hip.[22] They showed that, in contrast to knee OA, JSN is an important feature for hip OA. There was no gold standard available and also no articles had investigated associations between risk factors and a definition of hip OA.

In summary, the reliability of the definitions is good, whereas the ROA shows higher reliability than the clinical and combined criteria. The validity of the classification criteria is low according to the association with the comparator, and is moderate according to the association between the classification criteria and pain. With 25 different classification criteria, there is no need to develop new radiological or clinical classification criteria. This would probably not close the gap between radiological and clinical aspects, but more research is needed to investigate the impact of the different classification criteria in epidemiological research within and between the different categories (radiological, clinical, and radiological þclinical). Beside the impact of the different classification criteria on knee OA, also the discriminative validity of these criteria and the associations with risk factors need more investigation. In the meantime, to reach uniformity and comparability in epidemiological research, we recommend for future knee OA studies a separate four-grade scoring of features, an overall scoring with K&L classification system of the whole knee (e.g., TFJ and PFJ), and at least a pain registration as important clinical aspect. More information about symptoms and physical signs should accomplish the information and could provide some extra information about the discordance between the radiological and clinical aspects of knee OA.

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Appendix A: Criteria for assessment of methodological quality

Study population

Selection

A. Classification criteria for epidemiological studies
   + Open population or randomly selected from open population (selection based on age(>45 years) or on gender (woman))
   - Selection of population based on any criterion, such as differential diagnosis, availability of MRI or radiographics, planned TKR, stages of disease.

B. Classification for clinical purposes
   + Selected population based on symptoms, consulters or prevalent cases (planned TKR, UKP or osteotomy, different interventions, new consultancies or known patients at clinic)
   - Differential diagnoses are excluded or stages of disease

Description of characteristics

+ at least 3 of the 5 features are clearly described (age, gender, BMI, working status, SES)

Classification criteria

Stages of disease

+ All stages of OA are in the population
- A selection of stages excluded

Classification

+ Reference standard and scoring system is clearly described and reliable for replication (radiographic: 2 of 3 features: AP/PA, weightbearing, flexed/extended; clinical exam: parts; MRI: 2 of 3 features: T, plane, sequentions)
+ Classification criteria are clearly described and reliable for replication (other)

Assessment

Observer

+ Trained or experienced observer

Blind

+ Reference standard and classification criteria assessed independently from each other and other relevant information

Measurement

+ Every measurement of reference standard and classification criteria is the same for each subject

Analysis

Inter- and intraobserver reliability

+ Inter- and/or intraobserver agreement is described (with kappas or ICC, coefficient of variation, correlation coefficient (Pearson, Spearman, or Kendall), intraclass correlation coefficient (Cronbach's alpha), Cohen's Kappa, or anovas)

Discrimination of criteria

+ Sensitivity and specificity are described (also when likelihood ratios, positive predictive values, negative predictive values are described), can be calculated or a relationship with risk factors or determinants is given (ORs or RRs)

Prevalence

+ Prevalence of OA, according to definitions used in study, is described or can be calculated.

+ Description of criterion for positive rating; - Description of criterion for negative rating; MRI, Magnetic resonance imaging; TKR, Total knee replacement; UKP, Unicompartmental knee protheses; SES, Socio-economic status; AP/PA, Anterior-posterior/posterior-anterior; T, Tesla; ICC, Intraclass correlation coefficient

Appendix B: Results of quality criteria

Reference	Study population		Definitions				Assessment			Analysis			Quality score (%)
	Selection*		Description of characteristics	Stages of disease	Classification		Observer	Blind	Measurement	Inter-& intra-observer reliability	Discrimi-nation of criteria	Prevalence	
	Epide-miolog-ical studies	Clinical purpose			Reference standard	Other definition							
Ahlback (1968)[40]	-	+	-	+	+	NA	?	?	+	-	-	-	40
Altman (1986)[5]	-	+	-	+	+	+	+	+	+	-	+	+	80
Bellamy (1999a)[26]	+	-	+	+	-	NA	+	+	+	+	-	-	60
Bellamy (1999b)[27]	+	-	+	+	-	NA	+	+	+	+	-	-	60
Claessens (1990)[28]	+	-	+	+	+	+	+	+	-	-	+	+	80
Englund (2003)[33]	-	+	+	+	+	+	+	+	+	+	+	+	100
Felson (1997)[29]	+	-	-	+	+	+	+	+	-	+	+	+	80
Hart (1993)[34]	+	-	+	+	+	+	+	+	+	+	-	+	90
Hart (2003)[35]	-	-	+	+	+	NA	+	+	+	+	+	+	90
Hart (1991)[36]	+	-	-	+	+	+	+	+	+	+	+	+	90
Kellgren (1957)[39]	+	-	-	+	NA	-	-	+	+	+	-	-	40
Lanyon (1998)[30]	+	-	-	+	+	+	-	+	+	+	+	+	80
LaValley (2001a)[37]	+	-	+	+	+	+	+	+	+	+	+	+	100
LaValley (2001b)[38]	+	-	+	+	+	+	+	+	+	_	+	+	90
Petersson (1997)[25]	+	-	-	+	+	+	+	+	+	+	-	+	80
Schouten (1995)[31]	+	-	+	+	+	+	?	+	+	-	+	+	80
Spector (1993)[23]	+	-	-	+	+	+	+	+	+	+	+	-	80
Vilalta (2004)[32]	-	+	-	?	+	NA	+	+	+	+	-	-	60

* Not included for the quality score; + Positive rating; - Negative rating; ? No information available; NA, Not applicable

Chapter 3

Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis

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ABSTRACT

Objective: Correct application of the Kellgren and Lawrence (K&L) classification system is difficult due to inexact wording of the descriptors. We summarised different descriptions and searched for evidence on the impact of such variations on classification of knee osteoarthritis (OA) in epidemiological studies.

Methods: We searched Medline/Pubmed (1966 to August 2006) for studies of epidemiological cohorts that professed use of the original K&L scale (grades 0–4, with 0 being normal and 4 severe OA), and recorded their descriptions of the five grades. The descriptions were compared with each other and with the original description.

Results: We identified five different descriptions. In grade 2, often used as a cut-off to classify OA, one description replaced "definite osteophytes and possible narrowing of joint space" (K&L) by "definite osteophyte, unimpaired joint space". Another description for grade 2 was "minimal osteophytes, possible narrowing, cysts, and sclerosis". In some cohort studies, descriptions changed during follow-up. None of the included articles studied the impact of the use of different descriptions.

Conclusion: Major OA cohort studies disagree between each other and even among themselves on the definition and grading of disease according to the original K&L system. The impact of this disagreement warrants further study, but consensus urgently needs to be reached on a single valid and feasible classification system.

INTRODUCTION

The classification for osteoarthritis (OA) described by Kellgren and Lawrence (K&L) is the most widely used radiological classification to identify and grade OA. Kellgren and Lawrence defined OA in five grades (0, normal to 4, severe). The radiological signs found to be evidence for OA were combined to define a grading scale for severity. For the knee, important changes are: (a) formation of osteophytes on the joint margins or in ligamentous attachments, as on the tibial spines, (b) narrowing of joint space associated with sclerosis of subchondral bone, (c) cystic areas with sclerotic walls situated in the subchondral bone, and (d) altered shape of the bone ends.

The World Health Organization (WHO) adopted these criteria for the radiological classification of OA as the standard for epidemiological studies of this pathology.[1] In the K&L article of 1957, no clarification was given as to how to interpret the grades;[2] this clarification was given with the radiographs in the WHO atlas,[1] in which the grades of eight joints, including the knee, were described.

Several published studies professed use of the original K&L criteria. However, the descriptions often differed from the descriptions published in the WHO atlas. Some studies have already pointed out the differences in written descriptions of the K&L criteria.[3] They also noted that even Lawrence[4] used other descriptions in a later article. Hart et al (1995) concluded that these different interpretations of the K&L criteria have led to problems in different classifications of OA in epidemiological studies.[3] There is no complete overview of the different descriptions of the K&L criteria of knee OA, and the real impact of the alternative descriptions is not yet known. This systematic appraisal provides information about how many different descriptions of the K&L criteria of knee OA are used, and what impact this might have on the classification of knee OA in epidemiological studies.

METHOD

We were interested in epidemiological cohorts using the original K&L criteria. We performed a Medline/Pubmed (1966 to August 2006) search using the words: "Kellgren", "Lawrence", "knee" and "osteoarthritis" to find articles in English, German, Dutch, Danish, Swedish and Norwegian. We excluded articles that (1) did not use a epidemiological cohort, (2) explicitly mentioned the use of modified K&L criteria, (3) used the K&L criteria without referring to Kellgren[2] or the WHO atlas (Kellgren),[1] and (4) described less than five grades. The extracted descriptions and the original description of the K&L criteria[1] are listed in Table 1. When the (alternative) description remained the same we refer to the most recent publication of each epidemiological cohort. Finally, we summarise the results of the studies on the impact of using different descriptions if available.

RESULTS

The search resulted in 190 articles. A total of 44 articles gave a detailed description of the K&L criteria; of these, 18 studies used an epidemiological cohort. We found five different descriptions (Table 1). The Baltimore Longitudinal Study of Aging (BLSA),[5]

and the Southeast Michigan Cohort (SMC)[6] used the original criteria.[1] The Johnston County Osteoarthritis Project (JCOP, two articles),[7] one other epidemiological study,[8] and two out of three published studies of the Chingford Study (CS, two articles)[9] used description A, which was the same as the description Lawrence gave in 1977.[4] A third Chingford article[10] used a description that corresponded most with description B, which was used in the Beijing Study (BS, one acticle)[11] and the Framingham Osteoarthritis study.[11] Description C was used in the Clearwater Osteoarthritis Study (COS, three articles),[12] the Mechanical factors of Arthritis of the Knee study (MAK, three articles)[13] and also in another article of the Framingham Osteoarthritis Study (FOS, one article).[14] The last article,[15] described another alternative description (description D) of the K&L criteria.

Table 1: Different descriptions of the K&L criteria of knee OA

Original description[1,2,5,6]	**Alternative A**[7,9,10]	**Alternative B**[11]	**Alternative C**[12,13]	**Alternative D**[15]
Grade 1				
Doubtful narrowing of joint space and possible osteophytic lipping	Minute osteophyte, doubtful significance	Possible osteophytes only	Possible osteophyte lipping	Doubtful pathology
Grade 2				
Definite osteophytes and possible narrowing of joint space	Definite osteophyte, unimpaired joint space	Definite osteophytes and possible joint space narrowing	Definite osteophyte and possible joint space narrowing	Minimal osteophytes, possible narrowing, cysts, and sclerosis
Grade 3				
Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends	Moderate diminution of joint space (with osteophytes)	Moderate osteophytes and/or definite narrowing	Moderate multiple osteophytes, definite joint space narrowing, some sclerosis, and possible bone contour deformity (bony attrition)	Moderate, as in definite osteophytes with moderate joint space narrowing
Grade 4				
Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends	Joint space greatly impaired with sclerosis of subchondral bone	Large osteophytes, severe joint space narrowing and/or bony sclerosis	Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone contour deformity (bony attrition)	Severe, with large osteophytes and definite joint space narrowing

Between all descriptions, differences are seen; some descriptions are the same in one grade, but differ in the other grades. The most important grade in the K&L criteria is grade 2; this is the cut-off point for having definite OA according to K&L.[2] The original description and descriptions B and C are the same for grade 2. The description of grade 2 of the CS and the JCOP (description A) describe "unimpaired joint space", which is different from the original with possible joint space narrowing. Description D of grade 2 does not describe definite osteophytes. None of the included articles reported the impact of alternative descriptions of K&L criteria.

DISCUSSION

Despite 50 years of use of the K&L scale, OA investigators still disagree on the optimum format (in terms of validity and feasibility) to classify and grade OA. Despite the advent of newer imaging technologies such as MRI, radiological classification will probably remain the diagnostic gold standard for knee OA in large epidemiological studies for many years to come. Therefore, agreement on the descriptions is urgently needed. We limited ourselves to the five descriptions used in epidemiological cohorts. However, several other descriptions were found in studies other than epidemiological cohorts. All included articles referred to the original descriptions,[1,2] so we assume these K&L descriptions were not intended to be modified, yet they differed from the original descriptions. Also, we ignored the many mentioned revisions of K&L, as these incidences merit a separate study.

The use of different descriptions within one cohort, FOS and CS, is remarkable. However, it cannot be excluded that only the reported description in the article changed but not the actual reading.

Another important issue is the knee position in which the radiographs are obtained. Only the most recent studies mentioned semi-flexed knees, which can give a different K&L grading than straight knees. The K&L classification system is not tuned on the position of the knee.

The descriptions in the first article by Kellgren and Lawrence (1957)[2] described osteophytes on the tibial spines; this is only mentioned by Scott (1993)[5] although not for their K&L grading. It is unknown if this is taken into account by the other studies. There is low evidence that these osteophytes are important for osteoarthritis, but it is a point for further investigation.

One article excluded by our criteria because it only described the K&L grade 2 used in their study was, however, the only article reporting on the impact of the use of different descriptions.[16] Felson et al. (1995) investigated a modified scale that permits knees with isolated joint space narrowing as having possible OA (modified K&L grade 2) as well as the original description; definite osteophyte with possible joint space narrowing (K&L grade 2).[16] One radiologist scored 50 radiographs with both scales. The agreement using the different scales was good (κ=0.76, p,0.001), but no knees were graded as 2 with solely joint space narrowing. The study of Felson et al (1995) was performed from the perspective that the lack of focus on joint space narrowing in the K&L criteria is seen as a flaw;[3] however, they could not find support for this in their own study.[16] The lack of

focus on joint space narrowing in the K&L criteria might also be the reason why many different descriptions have been introduced.

Based on the latter study,[16] there is no evidence that alternative K&L descriptions change the diagnosis of knee OA. This is certainly not to be read as evidence that alternative K&L descriptions do not change the diagnosis. On the contrary, such alternatives might have major importance for our interpretation of study results. For instance, Schouten et al (1995) showed that the American College of Rheumatology (ACR) clinical criteria for knee OA in the traditional format (fulfilling three out of six criteria) yielded very different associations with age, obesity and meniscectomy than the same criteria in the decision tree format (the same criteria ordered to importance in an algorithm; odds ratios 1.4 vs 4.6, 1.6 vs 3.5, and 3.9 vs 6.6, respectively).[17]

To establish whether the alternative descriptions of the K&L criteria cause a change in prevalence and cause major differences in associations with known risk factors as reported above, all large cohort studies should score lesions of OA (eg, narrowing, osteophytes, sclerosis, cysts and deformity) as separate entities, as the guidelines recommend. Reliability and feasibility of the separate feature scores and the descriptions should be documented. Subsequently, investigators should correlate the separate lesions with the different descriptions of the K&L criteria and then compare the influence of the different descriptions on prevalence and associations with known risk factors. A consensus process is probably necessary to create one optimum classification score. This process should contain also points as an atlas to use for separate lesion scoring, position of the knee, taking into account osteophytes on tibial spines. Although mostly associated with outcome, the Outcome Measures In Rheumatology (OMERACT) initiative may be an appropriate place for such a process.

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Chapter 4

Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis

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ABSTRACT

Objectives: Although the Kellgren and Lawrence (K&L)-criteria for defining radiological OA are widely used in epidemiological and clinical studies, we previously documented the existence of five different versions of these criteria. This study identifies the impact of the use of alternative versions of the K&L-criteria and evaluates which description has the highest association with knee complaints.

Methods: Two readers scored most radiographs of the knees of participants of the Rotterdam Study with the original K&L-description (90%). In addition, each alternative description was used in a random part (20%) of the radiographs. We calculated reproducibility of all descriptions, and compared sensitivity and specificity of the alternative descriptions for three cut-off points with the original description as reference standard (K&L≥1, K&L≥2, and K&L≥3). We calculated kappa statistics to compare agreement between the original and alternative descriptions, and evaluated the association with knee complaints.

Results: The dataset comprises radiographs of knees of 3,071 people. For cut-off K&L≥1 all four alternatives classified more people as OA than the original description; the kappa was low, and sensitivity and specificity were moderate to good. For cut-offs K&L≥2 and K&L≥3 there was little difference in number of cases and the kappa, sensitivity and specificity were good to perfect. The original description and alternative 3 showed the strongest association with knee complaints.

Conclusion: The different descriptions of the K&L-criteria have impact on the classification of OA in the lowest grade (K&L≥1). All descriptions have strengths and weaknesses. It depends on the purpose which is the best description.

INTRODUCTION

Radiological classification of osteoarthritis (OA) remains the reference standard despite the emergence of new techniques such as magnetic resonance imaging (MRI). The explanation is feasibility and tradition, but also the fact that no clear cut-off or overall severity grade exists for OA in the MRI classification criteria.[1] The most widely used radiological classification criteria for knee OA are those developed by Kellgren and Lawrence (K&L) in 1957.[2] In epidemiological studies the cut-off point of 2 or more comprises the radiological definition of OA.[3] Clinical studies also use the K&L criteria to identify and select patients[4-7] with a certain grade of OA, or to assess OA progression.[8] A point of concern is the lack of consensus regarding the descriptions and interpretations of the K&L classification criteria.[9,10,11] In a concise report on 18 cohort studies we provided information on no less than five different versions/descriptions of the K&L criteria for knee OA in use in epidemiological studies.[9] Worse, even sequential studies on the same population used different versions. Although the differences between the versions seem small, the impact is of this variability remains unclear.[9] For instance, the number of cases classified as OA may differ between the descriptions.

Another criticism regarding radiological criteria is that they are not congruent with clinical criteria for OA, or with the presence of pain in the knee.[1,10] Although this criticism will remain for the different descriptions, the association between knee complaints (pain and/or stiffness) and these descriptions may differ.

This study explores the impact of different descriptions of the K&L criteria on the classification and distribution of severity of knee OA, and assesses the association between complaints of the knee and the different descriptions.

METHODS

Participants

The population used in the present study is an extension of the Rotterdam Study (RS-III-1) cohort.[12] The Rotterdam Study is a population-based cohort study in which the incidence and risk factors for chronic disabling diseases are investigated. All participants of the RS-III-1 cohort were 45 years and older and living in Rotterdam; the participants were included between 2006 and 2008.[12] The Medical Ethics committee of the Erasmus Medical Center approved the study and all participants gave written consent. A total of 3,071 participants out of the 3,932 people included in the RS-III-1 study had radiographs of both knees.

Radiographs and scoring method

All radiographs of the knees were weight-bearing antero-posterior radiographs taken at 70 kV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT, USA). Radiographs of the extended knees were obtained with the patella in central position. Radiographs were scored by two trained readers, who were blinded for clinical data. Both scored half of the radiographs. For the present study, the readers did the scoring using different descriptions of the classification criteria of K&L (Table 1). The different descriptions

were chosen based on our earlier report[9] but with one exception, i.e. the cut-off K&L≥2 for definite radiological OA in alternative 1 was based on definite osteophytes only (without joint space narrowing (JSN)). This is also an alternative of the K&L criteria used in large studies such as the Framingham[13] and the Chingford study.[14] In the present study, all radiographs were also scored using semi-quantitative separate lesion scoring, e.g. osteophytes (grading 0-3) and joint space narrowing (JSN) (grading 0-3).
Ninety percent of all X-rays (n=2,772) were scored using the original description. Additionally the radiographs were randomly scored with one of the four alternative

Table 1: Different descriptions of the classification criteria of Kellgren and Lawrence used in various epidemiological studies.

Original	Alternative 1	Alternative 2	Alternative 3	Alternative 4
Grade 0: No OA				
No osteoarthritis	No osteoarthritis	No osteoarthritis	No osteoarthritis	No osteoarthritis
Grade 1: Doubtful				
Doubtful narrowing of joint space and possible osteophytic lipping	Possible osteophytes	Minute osteophyte, doubtful significance	Possible osteophytes only	Possible osteophytic lipping
Grade 2: Mild				
Definite osteophytes and possible narrowing of joint space	Definite osteophytes	Definite osteophytes, unimpaired joint space	Definite osteophytes and possible joint space narrowing	Definite osteophytes and possible joint space narrowing
Grade 3: Moderate				
Multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends	Osteophytes and joint space narrowing	Moderate diminution of joint space (with osteophyte)	Moderate osteophytes and/or definite narrowing	Moderate multiple osteophytes, definite joint space narrowing, some sclerosis, and possible bone contour deformity (bony attrition)
Grade 4: Severe				
Large osteophyte, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends	Large osteophytes, marked narrowing of joint space and definite deformity	Joint space greatly impaired with sclerosis of subchondral bone	Large osteophytes, severe joint space narrowing and/or bony sclerosis	Large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony contour deformity (bony attrition)

descriptions (20% with each alternative description). The original description is the definition as described by Kellgren and Lawrence (1957)[2] and clarified in the World Health Organization (WHO) atlas (1963).[3]
Cut-offs points were placed at K&L≥1, K&L≥2 and at K&L≥3. Cut-off K&L≥2 is the most important of these as the one generally used for the presence of OA to determine eligibility for studies. A random selection of the radiographs (377 radiographs, 12%) was scored by both readers in order to determine the reproducibility of the scoring. Of this selection 659 knees were scored twice with the original description and twice with one of the other descriptions (74 with alternative 1; 114 with alternative 2; 152 with alternative 3, and 158 with alternative 4). Of 73 knees only a double score with alternative 1 was present and 22 knees were not scored twice due to debatable quality of the x-ray.
In the patient interview (held at baseline), all participants answered the question whether or not they had pain or other complaints in the knees. Participants who had experienced pain or complaints in the knee(s) for 1 month or longer were classified as having knee complaints.

Analysis

For reproducibility of the scoring a 4x4 weighted kappa was calculated for each alternative. To show differences between the two readers for each cut-off in the descriptions, a 2x2 kappa was calculated with the dichotomous data of each cut-off.
For each cut-off (K&L≥1, K&L≥2, K&L≥3) the percentage of people classified as having OA by each alternative was compared with that of the original description: both directly and by calculating sensitivity and specificity of each alternative description with the original description as reference standard. Weighted kappa's compared the agreement between the original description and the alternative descriptions of the K&L criteria: a 4x4 weighted kappa to compare all grades of the original and alternative descriptions, and a 2x2 kappa to compare these two per cut-off. A kappa value above 0.8 is considered very good, between 0.6 and 0.8 good, and between 0.4 and 0.6 moderate.[14,15] These analyses compared the total number of knees (and not the number per person).
Odds ratios (ORs) described the association between knee complaints and the different alternatives, adjusted for known risk factors such as age, body mass index (BMI) and gender. The results are on the person level, which means that the score K&L≥1 is a score of grade 1 or more in one or both knees, K&L≥2 is a score of grade 2 or more in one or both knees, and so on. The results also include percentages per cut-off and per alternative of the grading of osteophytes and JSN.

RESULTS

Participants

The study population had a mean age of 57 years old and a mean BMI of 27.7. Slightly more women than men were included (Table 2). The dataset comprised 3,071 radiographs of knees (i.e. a total of 6,142 knees scored), corresponding to 78% of the participants in the RS-III-1 study. Seventeen of these knees had been totally replaced, and no score could be given to 102 knees due to bad quality or a missing image. Approximately 90% of the

films were scored by the original K&L description (5378 knees, 87.6%) and about 20% of the radiographs with each alternative description. Most (3,048) participants supplied information on knee complaints. Although about one-third had such complaints, only about 5% had radiological OA (K&L≥2; Table 2).

Table 2: Characteristics of the study population (n=3,071)

Characteristics participants	
Age in years (mean, sd)	56.8 (6.7)
Body Mass Index (mean, sd)	27.7 (4.6)
Female gender (n, %)	1741 (56.7)
Complaints of the knee(s) lasting more than 1 month (n, %)	901 (29.6)*
Knees scored with original description	5378 knees
Grade 0 (n, %)	4374 (81.3)
Grade 1	701 (13.0)
Grade 2	241 (4.5)
Grade 3	53 (1.0)
Grade 4	9 (0.2)

* 3048 participants supplied information about knee complaints

Reproducibility

The radiographs randomly selected to determine the reproducibility of the two readers reflected the distribution of scores of the K&L criteria in the source population. The reproducibility of alternatives 1, 2, and 3 was good (weighted kappa 0.66, 0.69, and 0.63, respectively; Table 3). In contrast, reproducibility was poor-to-moderate for the original description and alternative 4 (weighted kappa 0.41 and 0.35). For the cut-off K&L≥2 the kappa was good. For cutoff K&L≥1 the kappa was low for both the original description and for alternative 4, moderate for alternative 3 and good for alternative 1 and 2 (Table 3).

Alternatives

The agreement between the original description and the alternatives was moderate (weighted kappa about 0.50; Table 4). For cut-off K&L≥1 all alternatives yield more cases than the original description: for alternatives 1, 2 and 3 this effect is small (24% versus 18%); however alternative 4 classifies almost 50% of all the knees as OA (Table 4). Because of these differences, kappa is low to moderate for all alternatives ($\kappa<0.45$). Sensitivity is moderate for alternatives 2 and 3 (±57%) with good specificity (84%); for alternative 1 sensitivity is 65% and specificity 83%, and for alternative 4 sensitivity is 100% and specificity 61%.

Alternative 3 and 4 yield about the same amount of cases as the original description in cut-off K&L≥2, with very good kappa and sensitivity. Alternative 2 yields slightly more

Table 3: Reproducibility of the two readers

Alternatives	Number of knees	Weighted Kappa	95% CI	K&L≥1		K&L≥2	
				% Agreement	Kappa	% Agreement	Kappa
Original description	659	0.41	0.32 – 0.49	76	0.32	95	0.62
Alternative 1	144	0.66	0.53 – 0.79	86	0.63	96	0.73
Alternative 2	114	0.69	0.58 – 0.80	86	0.66	94	0.72
Alternative 3	152	0.63	0.50 – 0.76	83	0.53	97	0.82
Alternative 4	158	0.35	0.24 – 0.46	61	0.31	97	0.70

K&L, Kellgren and Lawrence

Table 4: Comparison between the four alternative descriptions and the original description, at the three cut-off points.

			K&L≥1				K&L≥2				K&L≥3			
Descriptions	**Weighted kappa***	**95% CI**	**Cases alternative (%)**	**Cases original (%)**	**Kappa***	**Sens/ Spec* (%)**	**Cases alternative %)**	**Cases original (%)**	**Kappa***	**Sens/ Spec* (%)**	**Cases alternative (%)**	**Cases original (%)**	**Kappa***	**Sens/ Spec* (%)**
Alternative 1 (n=840**)	0.50	0.43-0.57	25.5	17.3	0.40	65/83	10.5	5.5	0.66	100/95	3.1	1.7	0.69	100/99
Alternative 2 (n=1102)	0.50	0.43-0.55	23.1	18.8	0.39	58/85	7.2	5.4	0.72	86/97	3.0	1.3	0.59	100/98
Alternative 3 (n=1180)	0.52	0.46-0.58	24.3	19.5	0.36	56/83	5.6	5.5	0.99	100/100	2.2	1.3	0.73	100/99
Alternative 4 (n=1189)	0.47	0.42-0.53	49.1	17.1	0.35	100/61	4.9	4.9	1	100/100	1.2	0.8	0.83	100/100

K&L, Kellgren and Lawrence; CI, Confidence interval; Sens, Sensitivity; Spec, Specificity; * reference original description; ** the same number of knees is used for the alternative and the original score per row

cases with a good kappa, good sensitivity and very good specificity. Alternative 1 yields twice as many cases as the original description, has a slightly lower kappa but 100% sensitivity and specificity.
For cut-off K&L≥3 all alternatives yield more cases than the original description: kappa is moderate to good, and sensitivity and specificity are 100% for all alternatives.
In conclusion, all four alternatives yield more cases than the original description at all cut-off points; for cut-off K&L≥2 the kappa, sensitivity and specificity are good.

Association between knee complaints and different descriptions

The presence of OA as defined by almost all cut-offs on almost all alternatives was significantly associated with the presence of knee complaints (ORs with p≤0.001; Table 5) for all cut-offs, with the exception of alternative 4: association between the presence of knee complaints and cut-off K&L≥1 not significant and for cut-offs K&L≥2 and ≥3 p≤0.01. Numerically the original description showed the strongest associations with knee complaints, although the differences were small and not significant compared with alternative 3.
Distributions of osteophytes and JSN grades are shown in Figure 1 and 2 (and appendix A). Where alternatives 1-3 show a similar distribution of osteophytes, the distribution is strikingly different in the original description and alternative 4 in cut-off K&L≥1 for grade 0 and grade 1 osteophytes. Also, in the original description in cut-off K&L=0 slightly more grade 1 and 2 osteophytes were scored than in the alternatives. Furthermore differences were seen in the distribution of JSN in cut-off K&L≥1 (a lot more grade 1 JSN than in the alternatives; Figure 2). Finally, in cut-off K&L≥2 in alternative 1 and 2 more grade 0 JSN and less grade 1 JSN was seen than in the other descriptions.
All other distributions were comparable.

Table 5: Association between the five different descriptions and knee complaints for the three cut-off points.

Cut-off	Original description (2678 persons)	Alternative 1 (654 persons)	Alternative 2 (523 persons)	Alternative 3 (584 persons)	Alternative 4 (577 persons)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
K&L≥1	2.2 (1.9 - 2.7)	2.0 (1.4 – 2.9)	2.1 (1.4 – 3.1)	2.8 (1.9 – 4.1)	1.5 (0.98–2.2) ns
K&L≥2	4.3 (3.2 – 5.7)	2.9 (1.8 – 4.8)	3.0 (1.6 – 5.5)	4.5 (2.4 – 8.5)	2.9 (1.5 – 5.6)
K&L≥3	18.3 (7.1 – 47.2)	10.0 (3.7 – 27.2)	9.3 (3.3 – 26.1)	14.2 (3.9 – 50.8)	6.5 (1.6–27.0)

Adjusted for the other risk factors: gender, age and Body Mass Index (ns, not significant); K&L, Kellgren and Lawrence; OR, Odds ratio; CI, Confidence interval

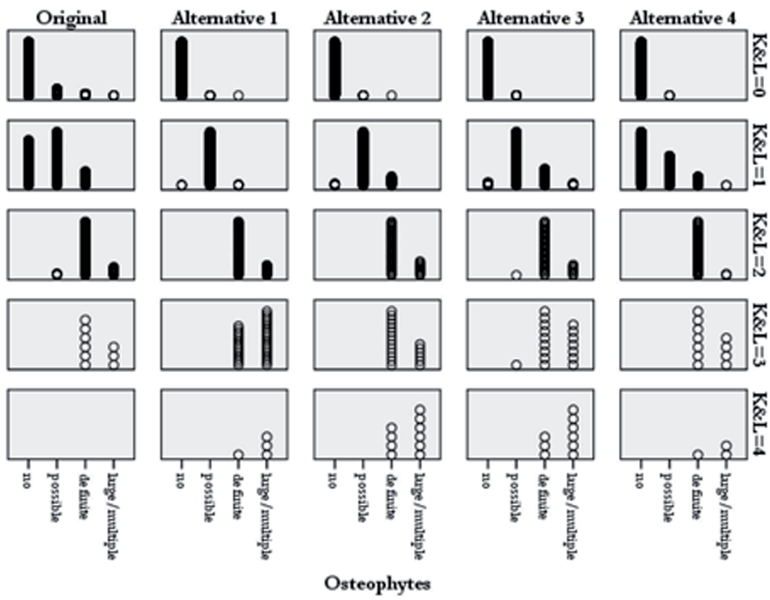

Figure 1: Distribution of grades of osteophytes in K&L score per alternative scoring method.

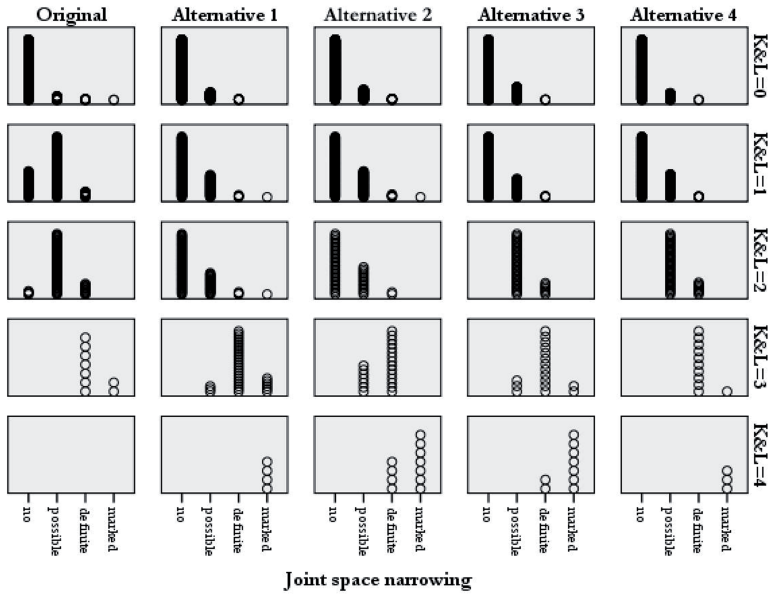

Figure 2: Distribution of grades of joint space narrowing in K&L score per alternative scoring method.

DISCUSSION

This study shows that the only real impact of variable descriptions of the K&L criteria on classification of OA occurs at the cut-off point K&L≥1, where all studied alternatives classified more knees as having OA. At higher cut-offs the impact was much smaller. At the cut-off of K&L≥1 the reproducibility of most alternatives was much better than the original description. The association of knee complaints with the descriptions was for the alternatives slightly less than for of the original description.

To our knowledge this is the first study to investigate the impact of the use of different descriptions of the K&L classification criteria for all the cut-off points. Felson et al. (1995) compared a modified grade 2 of the K&L classification criteria with the original grade 2 and found no support for their modified grade 2 based solely on JSN.[16]

Reproducibility problems of the original definition and alternative 4 are probably due to differences in the interpretation of K&L grade 1, especially for osteophyttic lipping. In addition the aberrant distribution of osteophytes in K&L≥1 in these two descriptions is due to the possible osteophyttic lipping described in this grade and the lack of description of possible osteophytes at all in these descriptions. For alternatives 1, 2 and 3 the weighted kappa was good, probably because these latter descriptions leave less room for personal interpretation. In the cut-off K&L≥3 of the original description the reproducibility was also low, which might be due to the small number of available cases. We left out the kappa for reproducibility of cut-off K&L≥3, because of the low number of cases.

All four alternatives result in a larger number of cases with K&L grade 1 compared to the original description. The original description of grade 1 is the only one where 'doubtful narrowing of joint space' is needed in grade 1. The distribution of osteophytes in the original description is therefore aberrant compared to the other alternatives in K&L grade 0 as well as the distribution of JSN in cut-off K&L≥1. This is because of the needed combination of osteophytes and JSN in cut-off K&L≥1 in the original description.

Whereas JSN is often considered more important for OA than osteophytes in joints other than the knee (e.g. the hip), even in grade 2 three of the five alternative descriptions require possible JSN with K&L grade 2. The original description includes JSN (as doubtful narrowing) in grade 1. Alternative 1 and 2 do not require JSN at all, which leads to a aberrant distribution of JSN seen in cut-off K&L≥2 in these descriptions compared to the other descriptions. For the association between definite knee OA and the presence of knee complaints, possible JSN in grade 2 of the descriptions seems important. These descriptions (i.e. the original description and alternative 3) yield the strongest association between definite knee OA and the presence of knee complaints. So 'possible JSN' needs to be in the description of definite knee OA. For cut-off K&L≥1 no additional value was found for doubtful JSN (included in the original description) in the association with knee complaints. For cut-off K&L≥3 the ORs are high, probably due to the small number of patients with K&L≥3.

The number of people with knee complaints is in all alternatives approximately 30%, but the actual number of people with knee complaints within the separate alternatives is small. This can lead to a different OR with the same grade-description, as seen in cut-off K&L≥2 for alternative 3 and 4. There are no significant differences between the ORs of

all descriptions within a cut-off.

This study has some limitations. First our study population was relatively young, explaining the large number of knees classified normal or possible OA, and low prevalence of severe OA. As the K&L criteria are frequently used in such populations, to discriminate between healthy/possible OA and mild but definite OA, it is particularly important in this context to avoid variability in the descriptions, especially when the cut-off K&L≥1 is applied. Second, we did not score all radiographs with all descriptions, which would make a comparison possible between all descriptions instead of only a comparison between the alternatives and the original description. A third limitation is the radiographs, extended knees and no skyline or lateral radiographs for patellofemoral OA. Semiflexed knees is preferred over extended knees to evaluate structural severity on radiographs, especially for joint space width.[17] Though, the K&L-criteria are developed in extended knees. The lack of information about patellofemoral OA is a limitation in the association between the different descriptions for tibiofemoral K&L-score and complaints of the knee, because patellofemoral OA also could be a cause of pain.[18] Moreover we only had information about the existence of knee complaints per person and not per knee. Therefore we could not do a knee specific analysis, which would provide more accurate information.

In conclusion, the different descriptions of the K&L classification criteria have a direct impact on the yield of cases especially with grade 1 and, to a lesser extent, with grade 2 as cut off. All descriptions have strengths and weaknesses. All alternatives yield more cases than the original description in grade 1. Reproducibility of grade 1 of the original description and alternative 4 is low, due to influence of personal interpretation of possible osteophyttic lipping. Alternative 1 and 2 have a aberrant distribution of JSN in grade 2. Alternative 3 is less extensive in grade 3 and 4 than the original description; both have a high association with knee complaints in all cut-offs. It depends on the purpose which is the best description. Based on these results we recommend use of the original description if you want to distinguish definite/mild OA (K&L≥2) from none/possible OA (K&L<2), and we recommend use of alternative 1, 2 or 3, or a modification of grade 1 of the original description ('doubtful narrowing of joint space and/or possible osteophytes') for distinguishing no osteoarthritis (K&L=0) versus possible osteoarthritis (K&L=1).

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Appendix A: Percentages of osteophyte and joint space narrowing grades per cut-off and per alternative.

	K&L=0					K&L≥1				
	Original	**Alt 1**	**Alt 2**	**Alt 3**	**Alt 4**	**Original**	**Alt 1**	**Alt 2**	**Alt 3**	**Alt 4**
Cases (knees)	4488	1034	847	908	605	1004	299	255	288	585
Osteophytes										
Grade 0	84.2	99.5	99.4	99.1	99.5	37.6	1.0	2.4	3.5	52.1
Grade 1	11.2	0.4	0.5	0.9	0.5	28.2	57.5	56.9	54.9	28.7
Grade 2	4.2	0.1	0.1	0	0	26.9	29.6	31.8	32.3	17.4
Grade 3	0.5	0	0	0	0	7.3	12.0	9.0	9.4	1.7
JSN										
Grade 0	92.8	87.9	84.2	82.0	89.4	8.8	61.5	58.0	57.6	64.4
Grade 1	6.3	10.8	14.2	17.5	10.1	74.6	23.7	28.2	30.6	30.8
Grade 2	0.8	1.2	1.7	0.4	0.5	13.5	10.7	10.6	8.7	4.1
Grade 3	0	0	0	0	0	3.1	4.0	3.1	3.1	0.7

	K&L≥2					K&L≥3				
	Original	**Alt 1**	**Alt 2**	**Alt 3**	**Alt 4**	**Original**	**Alt 1**	**Alt 2**	**Alt 3**	**Alt 4**
Cases (knees)	303	120	79	66	59	62	37	33	26	14
Osteophytes										
Grade 0	0	0	0	0	0	0	0	0	0	0
Grade 1	1.3	0	0	3.0	0	0	0	0	3.8	0
Grade 2	74.9	70.2	70.9	66.7	86.4	46.8	40.5	60.6	46.2	57.1
Grade 3	23.8	29.8	29.1	30.3	13.6	53.2	59.5	39.4	50.0	42.9
JSN										
Grade 0	2.0	48.3	38.0	0	0	0	0	0	0	0
Grade 1	55.8	20.0	26.6	54.5	62.7	0	8.1	21.2	11.5	0
Grade 2	32.7	22.5	26.6	31.8	30.5	59.7	64.9	57.6	53.8	71.4
Grade 3	9.6	9.2	8.9	13.6	6.8	40.3	27.0	21.2	34.6	28.6

Alt, Alternative; JSN, Joint space narrowing;K&L, Kellgren and Lawrence

Chapter 5

Determinants for pain in patients with different grades of knee osteoarthritis

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ABSTRACT

Objective: Discordance between having pain and radiological osteoarthritis (OA) is a well-established fact. It is suggested that this particularly applies to the less severe grades of OA. However, some people with a Kellgren and Lawrence (K&L) grade 3 or 4 for OA are without pain. This study aims to identify determinants and differences in the determinants associated with (no) pain in persons with different grades of knee OA.

Methods: In over 5,000 participants of a population based-cohort study, the Rotterdam Study (RS-I-1), we stratified the knees of participants based on the grade of knee OA. Multivariate General Estimating Equations logistic regression analysis was used to analyze the association with knee pain. We tested several determinants not directly related to structural damage of the knee, e.g. patient characteristics, co-morbidities, and other symptoms of OA. In case of observed differences, interactions with the grade of knee OA were tested.

Results: As expected, an increasing percentage of participants did not report pain with decreasing severity of knee OA: 25.8% for grade 3/4, and 84.5% for no knee OA. Being a female, general health complaints, familial OA, morning stiffness and widespread pain are determinants for knee pain, but not specific for a particular grade of radiographic knee OA. Depression and hip OA showed significant interactions with the grade of OA being a determinant for knee pain in knees with K&L grade 0, but not in the higher grades of OA. In addition, increasing age is protective for reporting pain in general.

Conclusion: Being a female, having widespread pain, reporting general health complaints, familial OA and morning stiffness are determinants for knee pain, but are not specific for a grade of radiographic knee OA. Depression and hip OA were associated with knee pain in the knee without signs of OA (K&L=0).

INTRODUCTION

Although pain is a symptom of osteoarthritis (OA) that is present in (almost) every classification criteria for OA, there is often discordance between reports of pain and radiological OA.[1-4] It is suggested that this discordance applies, in particular, to the less severe grades of knee OA and that pain is more common in more severe grades of OA.[1-2] However, there are people with a Kellgren and Lawrence (K&L) grade 3 or 4 of knee OA without any pain in the knee.[1-4] For example, in an open population study of persons with K&L grade 2 in the knee, 29.9% had at some time experienced pain, and with K&L grade 3 in the knee 64.1% had at some time experienced pain.[5]

Explanations for the discordance between radiological knee OA and pain in the knee include shortcomings in the measurement of pain, which can be influenced by recall or social/environmental factors,[1-3] as well as shortcomings in the definition of radiographic OA and in the definition of pain.[1] In addition, pain can be related to conditions other than OA, as well as to factors other than structural changes. For example, psychological factors (e.g. depression or anxiety) are suggested to be associated with pain.[6-7] Additional factors that may be related to the experience of pain include various co-morbidities and/or inferior general health status[1], as well as gender differences and education level.[8-9]

It is unclear why some people experience no pain at all when they have an established joint pathology. Little information is available on the determinants for pain and whether these determinants differ between the radiological grades. Therefore, the aim of this study was to identify determinants, and differences in determinants, that are associated with (absence of) pain in people with different grades of radiological knee OA in a population-based cohort.

METHODS

Study population

The data used in this study were baseline data obtained from the Rotterdam Study (RS-I-1). This is a population-based prospective cohort study of men and women (aged ≥55 years) in which the incidence and risk factors for chronic disabling diseases were investigated.[10-11] All 10,275 inhabitants in that age group in a district in Rotterdam were invited for a baseline examination between August 1990 and June 1993; of these, 7,983 participated. The Medical Ethics Committee of Erasmus University Medical Center approved the study. All participants gave written consent and were interviewed at home. Participants were also asked to visit the research center for radiographs and other medical examinations. Of the 7,983 participants, 6,450 visited the research center for the baseline measurements.

Radiographic assessment

Radiographs of the knees were taken at the research center at 70 KV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT, USA). Radiographs of the knees were weight-bearing anteroposterior radiographs.

A random set of 5,647 baseline radiographs of the knees was scored for OA using

the K&L scale.[12] Five trained readers evaluated the radiographs of the knee. Inter-rater reliability of the K&L score was good (κ=0.71). All readers were unaware of the participants' clinical status.
Possible knee OA was defined as K&L=1 in either knee (osteophyttic lipping or one osteophyte). Mild (or definite) OA was defined as K&L=2 in either knee (at least 2 definite osteophytes and possible joint space narrowing (JSN). Moderate to severe knee OA was defined as a K&L score ≤3 in either knee (at least 2 definite osteophytes and definite JSN). The 40 knees which had a total or partial knee replacement, or an osteotomy, were excluded from the analysis. Unilateral knee OA was defined as having K&L grade 2 or more in one of the knees, and bilaterality was defined as having K&L grade 2 or more in both knees.

Outcome

At baseline, trained interviewers conducted an extensive standardized home interview. Pain was determined to be present based on the answers to the following questions: "Have you had knee pain in the last month?" (yes/no). In addition, the same question was asked about knee pain during the last 5 years. If one of these questions was answered with "yes" for the knee, we classified the knee with pain, separately, for the left and the right knee.

Determinants

Determinants were selected based on evidence from data on determinants that might influence pain with radiological OA,[8, 12-13] and the determinants of interest should be available in the RS-I-1. Height and weight were measured and body mass index (BMI, kg/m^2) was calculated. Data on widespread pain was collected from the two pain questions mentioned above, following the definition of Wolfe et al., i.e. "pain is considered to be widespread when all of the following have been present for at least 3 months: 1) pain in the left side of the body, 2) pain in the right side of the body, 3) pain above the waist, 4) pain below the waist, and 5) in addition, axial skeletal pain (cervical or anterior chest or thoracic spine or lower back)".[13]
Education was categorized into low, middle, or college level. Lower level indicates primary education, lower general and lower vocational education; middle level indicates intermediate general, higher general and intermediate vocational; and college level indicates higher vocational and university education.
Answers to the questions in the interview were used to assess general health complaints and co-morbidities, such as feeling depressed and having had a heart attack. High blood pressure was defined as having a systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥100 mmHg, or the use of antihypertensive medication. Diabetes mellitus was diagnosed based on blood measures (glucose level >11.1 mmol/L) and/or use of antidiabetic drugs. Data on familial OA were obtained from the participants' answers to the question as to whether their parents or siblings have had OA in one or more of their joints. Presence of morning stiffness was defined as having morning stiffness in the legs for less than 30 min.

Hip OA is defined as having a K&L grade of 2 or higher in one or both hips. Hand OA is defined as having a K&L grade of 2 or higher in one the following joints: first carpometacarpal joint, proximal interphalangeal joints, distal interphalangeal joints, interphalangeal joint, metacarpophalangeal joints, trapezioscaphoid joint.[14]

Statistical analysis

For the association between the determinants and pain in the knee with a grade of OA we used multivariate logistic General Estimating Equations (GEE) analysis. Odds ratios (OR) with 95% confidence interval (CI) show the association between the determinants and pain. A GEE analysis adjusts for the correlations between the right and left knee of the same person. First we analysed the determinants for knee pain independent from the K&L grades. In addition we analysed the determinants in each K&L grade (K&L grade 0, 1, 2, 3/4) separately.

To evaluate if the significantly associated determinants are specific for a grade of OA (interaction), we used a standard normal approximation for z. Z was calculated as $z = (ß_1 - ß_2) / \sqrt{((se_1)^2+(se_2)^2)}$, where $ß_1$ is the log odds of the determinant (se_1 is the standard error of this determinant) for the specific grade of radiographic knee OA in which this determinant is significantly associated with knee pain. $ß_2$ is the log odds (and se_2 the standard error) of the same determinant for the other grades of radiographic knee OA. A two-sided test with a significance level of 0.05 was used. There is a significant difference in the determinant for the specific grade if $z<-1.96$ or if $z>1.96$.[15]

The determinants were on patient level and not on knee level. This means that, for the separate grade analyses, it is possible and highly likely that a person is included in the analysis, with one knee only. For example, in the analyses of K&L grade 1 only the knees with K&L grade 1 are in the analyses, but this group might include participants with K&L grade 2, 3 or 4 in the other knee (and grade 0 is also possible). This is indicated by the unilateral or bilateral knee OA determinant. The software package SPSS version 17 (SPSS Inc, Chicago, USA) was used for all analyses.

RESULTS

There were 5,527 participants with complete data on K&L score, pain, age, gender and BMI. A total of 11,022 knees were used for the analysis, which means that 32 participants were included with one knee; the other knee was excluded due to a total or partial knee replacement, or an osteotomy.

Table 1 shows the proportion of painful knees in the different grades of knee OA. Due to the small number of knees with K&L grade 3 or 4 these two grades were taken together in the analysis.

Regarding the knee with OA, a considerable proportion (25%) with moderate to severe OA was not painful during the last 5 years. The number of individuals without knee pain increased with decreasing grade of joint damage. More than half of the knees (60.4%) with K&L grade 2 were pain free, with an increasing number of pain free knees with K&L grade 0.

Table 1: Prevalence of pain per grade of knee OA (n=11,022 knees)

K&L grade of OA	Knees without pain (%)	Knees with pain (%)
Grade 0	5662 (84.5)	137 (15.5)
Grade 1	2128 (79.0)	564 (21.0)
Grade 2	824 (60.4)	540 (39.6)
Grade 3/4	69 (25.8)	198 (74.2)

Table 2 shows the associations between the determinants and pain in the knee, including the K&L grade. Irrespective of the K&L grade, the following are significantly associated with knee pain: being a female (OR=1.48; 95%CI 1.25-1.75), having widespread pain (OR=4.35; 95%CI 3.43-5.51), having general health complaints (OR=1.53; 95%CI 1.31-1.79), feeling depressed (OR=1.19; 95%CI 1.01-1.40), ever had a heart attack (OR=1.55; 95%CI 1.19-2.03), having hand OA (OR=1.22; 95%CI 1.03-1.45), familial OA (OR=1.36; 95%CI 1.13-1.62), and morning stiffness (OR=1.96; 95%CI 1.65-2.33). A higher age (OR=0.98; 95%CI 0.97-0.99) is a protective determinant for knee pain, irrespective of the grade of knee OA. Increasing ORs are shown with increasing grade of K&L, i.e. K&L=1: OR=1.42 (95%CI 1.21-1.67); K&L=2: OR=3.04 (95%CI 2.50-3.70); and K&L=3/4: OR=13.91 (95%CI 9.14-21.15).

Tables 3 to 6 present the associations between the determinants and knee pain with increasing grades of K&L. Being a female, having widespread pain, having health complaints and morning stiffness are determinants associated with knee pain in all K&L grades up to grade 2. Familial OA is a determinant which is significantly associated with knee pain in grade 0 and 1; in grade 2 familial OA is only borderline significant. In K&L grade 3/4 only widespread pain is still significant. In K&L grade 0 feeling depressed (OR=1.35; 95%CI 1.09-1.67), ever had a heart attack (OR=1.47; 95%CI 1.02-2.11) and hip OA (OR=1.44; 95%CI 1.01-2.06) are significantly associated with knee pain.

Depression and hip OA showed a significant interaction (z=10.41 and z=2.21, respectively) with grades of knee OA (K&L grade 0 vs. K&L grade 1 and higher). Ever had a heart attack and unilateral knee OA showed no interaction with the grades of knee OA (z=-0.386 for ever had a heart attack, and z=-0.21 and z=1.62 for unilateral knee OA).

Table 2: Associations between knee pain and the study determinants

Determinant		$N_{participants}$	**GEE analysis (N_{knees}=7900 (71.7%))**		
Participants characteristics			**OR**	**95% CI**	**p-value**
Age in years, mean (sd)	68.1 (8.0)	5527	**0.98**	**0.97 – 0.99**	**<0.001**
Body mass index, mean (sd)	26.3 (3.6)	5527	1.01	0.99 – 1.04	0.250
Female, n (%)	3191 (57.7)	5527	**1.48**	**1.25 – 1.75**	**<0.001**
Widespread pain, n (%)	525 (9.5)	5527	**4.35**	**3.43 – 5.51**	**<0.001**
Education, n (%)		5466			
Low	1995 (36.5)		1.14	0.86 – 1.52	0.357
Medium	2866 (52.4)		1.19	0.91 – 1.55	0.195
High	605 (11.1)		Ref.		
Health complaints, n (%)	2607 (47.2)	5522	**1.53**	**1.31 – 1.79**	**<0.001**
Co-morbidity					
Feeling depressed, n (%)	1809 (33.2)	5448	**1.19**	**1.01 – 1.40**	**0.035**
Diabetes, n (%)	539 (9.8)	5524	1.16	0.90 – 1.48	0.244
High blood pressure, n (%)	1536 (28.0)	5478	0.96	0.81 – 1.14	0.633
Ever had a heart attack, n (%)	478 (8.7)	5472	**1.55**	**1.19 – 2.03**	**0.001**
Hip OA (≥2), n (%)	518 (9.8)	5284	1.10	0.85 – 1.43	0.481
Hand OA (≥2), n (%)	3135 (62.9)	4985	**1.22**	**1.03 – 1.45**	**0.020**
Indicators of disease					
Familial OA, n (%)	1069 (20.6)	5195	**1.36**	**1.13 – 1.62**	**0.001**
Morning stiffness, n (%)	1023 (20.0)	5114	**1.96**	**1.65 – 2.33**	**<0.001**
Knees, n (%)		N_{knees}			
Kellgren & Lawrence grade 0	6699 (60.8)	11022	ref		
Grade 1	2692 (24.4)		**1.42**	**1.21 – 1.67**	**<0.001**
Grade 2	1364 (12.4)		**3.04**	**2.50 – 3.70**	**<0.001**
Grade 3/4	267 (2.4)		**13.91**	**9.14 – 21.15**	**<0.001**

OR, Odds ratio; CI, Confidence interval; sd, standard deviation; ref, reference category; OA, Osteoarthritis

Table 3: Association with knee pain in knees with K&L grade 0

Determinant		$N_{participants}$	**GEE analysis (N_{knees}=4855 (72.5%))**		
Participants characteristics			**OR**	**95% CI**	**p-value**
Age in years, mean (sd)	68.1 (8.0)	3797	**0.98**	**0.96 – 0.99**	**0.002**
Body mass index, mean (sd)	26.3 (3.6)	3797	1.00	0.97 – 1.03	0.932
Female, n (%)	2019 (53.2)	3797	**1.52**	**1.22 – 1.91**	**<0.001**
Widespread pain, n (%)	331 (8.7)	3797	**4.39**	**3.24 – 5.95**	**<0.001**
Education, n (%)		3749			
Low	1297 (34.6)		1.24	0.85 – 1.80	0.270
Medium	1995 (53.2)		1.24	0.88 – 1.76	0.224
High	457 (12.2)		Ref.		
Health complaints, n (%)	1749 (46.1)	3793	**1.53**	**1.24 – 1.90**	**<0.001**
Co-morbidity					
Feeling depressed, n (%)	1212 (32.4)	3741	**1.35**	**1.09 – 1.67**	**0.007**
Diabetes, n (%)	342 (9.0)	3794	1.30	0.92 – 1.83	0.141
High blood pressure, n (%)	996 (26.4)	3767	0.87	0.68 – 1.10	0.238
Ever had a heart attack, n (%)	334 (8.9)	3758	**1.47**	**1.02 – 2.11**	**0.037**
Hip OA (≥2), n (%)	292 (8.0)	3644	**1.44**	**1.01 – 2.06**	**0.046**
Hand OA (≥2), n (%)	2009 (58.1)	3460	1.20	0.97 – 1.50	0.099
Indicators of disease					
Bilaterality, no OA, n (%) unilateral OA, n (%)	3603 189 (5.0)	3792	ref 1.51	0.93 – 2.44	0.093
Familial OA, n (%)	728 (20.4)	3562	**1.33**	**1.04 – 1.69**	**0.023**
Morning stiffness, n (%)	640 (18.2)	3507	**1.88**	**1.48 – 2.39**	**<0.001**

OR, Odds ratio; CI, Confidence interval; sd, standard deviation; ref, reference category; OA, Osteoarthritis

Table 4: Associations with knee pain in knees with Kellgren & Lawrence grade 1

Determinant		$N_{participants}$	**GEE analysis (N_{knees}=1924 (71.5%))**		
Participants characteristics			**OR**	**95% CI**	**p-value**
Age in years, mean (sd)	68.6 (7.9)	1915	0.98	0.96 – 1.00	0.088
Body mass index, mean (sd)	26.7 (3.6)	1915	1.01	0.98 – 1.05	0.518
Female, n (%)	1162 (60.7)	1915	**1.45**	**1.07 – 1.96**	**0.017**
Widespread pain, n (%)	184 (9.6)	1915	**5.07**	**3.30 – 7.80**	**<0.001**
Education, n (%)		1898			
Low	723 (37.8)		0.93	0.56 – 1.53	0.771
Medium	994 (51.9)		1.09	0.68 – 1.74	0.725
High	181 (9.5)		Ref		
Health complaints, n (%)	908 (47.4)	1914	**1.68**	**1.27 – 2.22**	**<0.001**
Co-morbidity					
Feeling depressed, n (%)	631 (33.2)	1898	1.14	0.86 – 1.52	0.358
Diabetes, n (%)	196 (10.2)	1913	1.22	0.83 – 1.81	0.317
High blood pressure, n (%)	559 (29.4)	1899	1.11	0.82 – 1.48	0.506
Heart attack, n (%)	165 (8.7)	1898	1.50	0.93 – 2.42	0.100
Hip OA (≥2), n (%)	202 (10.9)	1847	0.84	0.54 – 1.31	0.440
Hand OA (≥2), n (%)	1191 (68.7)	1734	1.20	0.89 – 1.64	0.237
Indicators of disease					
Bilaterality, no OA, n (%) unilateral OA, n (%)	1478 (77.3) 433 (22.7)	1911	- **1.45**	- **1.05 – 1.99**	- **0.024**
Familial OA, n (%)	367 (20.4)	1797	**1.49**	**1.09 – 2.06**	**0.014**
Morning stiffness, n (%)	350 (19.8)	1771	**1.85**	**1.35 – 2.52**	**<0.001**

OR, Odds ratio; CI, Confidence interval; sd, standard deviation; ref, reference category; OA, Osteoarthritis

Table 5: Associations with knee pain in knees with Kellgren & Lawrence grade 2

Determinant		$N_{participants}$	**GEE analysis (N_{knees}=940 (68.9%))**		
Participants characteristics			**OR**	**95% CI**	**p-value**
Age in years, mean (sd)	71.5 (8.3)	1022	**0.98**	**0.96 – 1.00**	**0.048**
Body mass index, mean (sd)	27.8 (4.0)	1022	1.03	0.99 – 1.08	0.126
Female, n (%)	760 (74.4)	1022	**1.56**	**1.05 – 2.31**	**0.028**
Widespread pain, n (%)	134 (13.1)	1022	**3.32**	**2.01 – 5.49**	**<0.001**
Education, n (%)		1016			
Low	445 (43.8)		1.07	0.53 – 2.15	0.845
Medium	499 (49.1)		1.17	0.60 – 2.29	0.646
High	72 (7.1)		Ref		
Health complaints, n (%)	497 (48.6)	1022	1.35	0.97 – 1.88	0.075
Co-morbidity					
Feeling depressed, n (%)	348 (34.7)	1003	1.00	0.71 – 1.42	0.986
Diabetes, n (%)	122 (11.9)	1022	0.86	0.52 – 1.43	0.566
High blood pressure, n (%)	329 (32.5)	1012	0.95	0.67 – 1.35	0.772
Heart attack, n (%)	90 (8.9)	1013	**1.94**	**1.10 – 3.42**	**0.021**
Hip OA (≥2), n (%)	145 (15.2)	957	0.96	0.59 – 1.57	0.874
Hand OA (≥2), n (%)	719 (80.2)	896	1.33	0.89 – 1.98	0.164
Indicators of disease					
No OA, n (%)	-	1022	-	-	-
unilateral OA, n (%)	582 (56.9)		-	-	-
bilateral OA, n (%)	440 (43.1)		0.87	0.65 – 1.22	0.458
Familial OA, n (%)	214 (22.1)	967	1.45	0.99 – 2.14	0.059
Morning stiffness, n (%)	248 (26.0)	954	**2.20**	**1.51 – 3.20**	**<0.001**

OR, Odds ratio; CI, Confidence interval; sd, standard deviation; ref, reference category; OA, Osteoarthritis

Table 6: Association with knee pain in knees with Kellgren & Lawrence grade 3 or 4

Determinant		$N_{participants}$	**GEE analysis (N_{knees}=172 (64.4%))**		
Participants characteristics			**OR**	**95% CI**	**p-value**
Age in years, mean (sd)	74.0 (8.6)	213	0.97	0.92 – 1.02	0.213
Body mass index, mean (sd)	28.5 (4.1)	213	1.00	0.91 – 1.10	0.994
Female, n (%)	156 (73.2)	213	0.47	0.17 – 1.32	0.150
Widespread pain, n (%)	36 (16.9)	213	**10.16**	**1.65 – 62.76**	**0.013**
Education, n (%)		210			
Low	97 (46.2)		1.90	0.49 – 7.41	0.354
Medium	92 (43.8)		0.86	0.24 – 3.17	0.824
High	21 (10.0)		Ref		
Health complaints, n (%)	105 (49.3)	213	1.41	0.57 – 3.49	0.458
Co-morbidity					
Feeling depressed, n (%)	76 (36.0)	211	0.53	0.22 - 1.29	0.162
Diabetes, n (%)	32 (15.0)	213	1.48	0.34 – 6.39	0.602
High blood pressure, n (%)	72 (34.3)	210	2.11	0.83 – 5.37	0.117
Heart attack, n (%)	20 (9.5)	211	0.74	0.17 – 3.22	0.685
Hip OA (≥2), n (%)	43 (22.1)	195	0.65	0.22 – 1.90	0.430
Hand OA (≥2), n (%)	162 (87.1)	186	0.68	0.23 – 2.03	0.487
Indicators of disease					
No OA, n (%)	-	213	-	-	-
unilateral OA, n (%)	60 (28.2)		- (ref)	-	-
bilateral OA, n (%)	153 (71.8)		1.71	0.70 – 4.20	0.239
Familial OA, n (%)	49 (24.7)	198	0.73	0.28 – 1.93	0.523
Morning stiffness, n (%)	76 (37.8)	201	2.36	0.95 – 5.89	0.065

OR, Odds ratio; CI, Confidence interval; sd, standard deviation; ref, reference category; OA, Osteoarthritis

DISCUSSION

Widespread pain, health complaints, being a female, familial OA, and morning stiffness are determinants for knee pain, but not specific for a particular grade of radiographic knee OA. Age is a non-specific protective determinant for knee pain. Feeling depressed and having hip OA are determinants for knee pain in knees without signs of radiographic knee OA (K&L grade 0).

The protective effect of an older age has to be interpreted with some care. These participants are all above the age of 55 years, with a mean age of 68 years. Several possible explanations can be given. Recall bias can be an explanation, but other diseases that are more important for these participants might also be a possible explanantion. Furthermore, with increasing age there is a structural and functional decline of the somatosensory system, which can lead to reduction in pain detecting.[16]

Having hip OA can give referred pain in the knee, which is highly likely in participants with knee pain and no signs of knee OA.[17] Having family with OA may raise awareness about joint pain; in addition, genetic predisposition and/or social/environmental factors can influence the feeling and reporting of pain.

Morning stiffness is associated with knee pain in all grades of OA, including knees without radiographic OA. In the group with moderate to severe radiographic knee OA, the association was only borderline significant, probably due to a (statistical) power problem. One limitation regarding our definition of morning stiffness, is that it is unknown whether the stiffness occurred in the knee, the hip, or elsewhere in the legs. In addition, patients were not asked on which side the stiffness was present. Therefore, the association would probably have been higher had morning stiffness been measured in a knee-specific and side-specific way. Morning stiffness is one of the symptoms already included in the clinical diagnosis of OA.[18] Besides pain, it is seen as another symptomatic expression of OA. Apart from the above-mentioned limitations, morning stiffness is associated with knee pain in all grades of radiographic knee OA, even in K&L grade 0. This could indicate that, together with knee pain, morning stiffness is an important symptom of early knee OA.

Having OA in the knee other than the knee in the analysis is a significant determinant for knee pain in K&L grade 1, although it is not specific for the knees with this grade of radiographic OA. Bilateral knee OA or having knee OA might be a non-specific determinant for knee pain. Another study found that participants with bilateral knee OA had significantly more pain than participants with unilateral knee OA.[19]

Hand OA was significantly associated with knee pain irrespective of the grade of knee OA. However, this finding needs to be interpreted with caution because there is no consensus about the definition of hand OA.[14, 20] In the present study, the definition used is 'having OA in one or more joints of the hand', which results in a large number of participants diagnosed with hand OA. It is the definition most used in research,[14] but might well overestimate the number of participants with clinical hand OA.

Widespread pain is associated with knee pain in all grades of knee OA. In case of widespread pain, the central nervous system is involved and sensitization mechanisms are present.[21] That might explain why, in the present study, widespread pain was not specific for any stage of knee OA. Knee pain is a part of the widespread pain definition,

but if we defined widespread pain without knee pain the same results were found only with somewhat lower associations (data not shown).

We defined knee pain as 'having had pain in the knee in the last month and/or in the last 5 years'. This definition covers a considerable period of time for having knee pain. By separating these two time points, we may be able to observe differences in determinants for knee pain depending on different definitions of pain. For example, when pain was defined as having pain in the knee in the last month, no significant association was found for age, hand and hip OA and familial OA. K&L grade 1 was no longer significantly associated with knee pain, whereas K&L grade 2 and 3/4 were still significantly associated (data not shown). When the pain was defined as having knee pain in the last 5 years, the results were very similar to those of the combined pain definition (data not shown).

Feeling depressed is associated with knee pain in knees without signs of knee OA. Depression and pain can be in the same vicious circle. Having pain, when feeling depressed, is not always linked to structural damage. In our analysis is feeling depressed is also associated with widespread pain.

A limitation of the present study is the scarce amount of information available about the daily activities of the participants, and about other tissues of the joints, such as bone marrow lesions and effusion. Furthermore, definitions for the co-morbidities are somewhat limited; e.g. 'feeling depressed' is not based on a standardized questionnaire. Hawker et al. (2011) described that a painful knee OA determines disability and fatigue which, in turn, leads to a depressed mood and therefore a worsening of pain.[22] It would be interesting to see what determinants are associated with pain at follow-up; however, this is not possible because at follow-up the pain in the knee was not specified for left and right knee, separately.

In conclusion, being a female, having widespread pain, morning stiffness, familial OA and reporting general health complaints are determinants for knee pain, but are not specific for a particular grade of radiographic knee OA. Depression and hip OA were determinants for knee pain only in those knees without any sign of OA. Morning stiffness is a determinant for knee pain, even in knees without radiographic signs of knee OA. This could indicate that morning stiffness in combination with knee pain is a symptom of OA in early knee OA; this certainly warrants further investigation.

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Chapter 6

Risk factors and their association with MRI osteoarthritic features in female knees without radiographic signs of osteoarthritis

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ABSTRACT

Background: Few data are available on the association between different risk factors and early signs of osteoarthritis (OA) on MRI. It is unknown whether risk factors lead to different initial damage (different MRI features) or begin in different compartments of the joint, or which early MRI OA-features are related to pain.

Objectives: To assess how different risk factors are associated with early MRI OA-features in women without radiographic knee OA, and explore how these features are associated with pain in the knee.

Methods: Radiographs and MRIs of knees of women from a subcohort of the Rotterdam Study were scored with semi-quantitative scoring. Data based on interview and questionnaire were used for demographic information. Generalized Estimating Equations was used to analyse the associations.

Results: 771 women (mean age 53.5 years, mean BMI 26.8; total of 1404 knees) without radiographic OA were analyzed. Age and overweight were risk factors for osteophytes and cartilage lesions. Overweight was also associated with joint effusion. History of knee injury was associated with OA-related damage in the lateral tibiofemoral joint. Presence of Heberden's nodes was associated with OA-related damage in the medial tibiofemoral joint. Current knee pain was associated with joint effusion, and persistent knee pain with bone marrow lesions in the patellofemoral joint.

Conclusion: Two risk factors are associated with early MRI OA-features on a specific location in the knee. None of the risk factors is discriminative for a specific type of damage. Age and overweight are the most important risk factors for structural damage.

INTRODUCTION

Osteoarthritis (OA) of the knee is the most common joint disease among the middle-aged and elderly.[1,2] OA is characterized by joint degeneration which includes a progressive loss of cartilage. Osteoarthritic signs are uncommon in those aged ≤40 years, but most people aged ≥70 years have signs of OA.[2] The World Health Organization has estimated that 10% of the world's population aged 60 years and older has clinical problems caused by OA.[2,3]

Established risk factors for knee OA are ageing, female gender, overweight, malalignment, and history of injury of the knee.[4] The presence of Heberden's nodes, a marker of hand OA, is also suggested as a risk factor for knee OA.[4,5] An increase of body mass index (BMI) of 1 point when BMI is above 27 is associated with a 15% risk increase for OA.[6] The association between overweight and OA is stronger in women than in men, and is stronger in people who have malalignment of the knees.[6,7]

It remains unknown whether each of these risk factors leads to different initial damage in the joint and, therefore, to different early signs of OA. All these risk factors have a mechanism leading to degeneration of the cartilage, but the exact pathway is not yet fully understood. For malalignment and overweight the mechanism has a mechanical component,[8,9] although for overweight a systemic pathway is probably also involved.[1,10] Injury can damage the cartilage directly by the impact itself or indirectly by inflammatory responses after trauma, or through different loading of the joint after the injury.[5,11]

An early clinical symptom of OA is pain.[12] However, radiographic knee OA is not always accompanied by pain in the knee, just as clinical knee OA is not always accompanied by radiographic evidence of knee OA.[13] In the latter case people may have structural changes that are characteristic for OA, but are not yet seen on radiographs. Magnetic resonance imaging (MRI) has the advantage of direct assessment of the cartilage and other soft tissue of the joint. The semi-quantitative Knee Osteoarthritis Scoring System (KOSS)[14] scores different signs of structural change of OA in the knee. We hypothesize that early semi-quantitative measures on MRI may already show OA changes in persons at high risk of developing OA (older age, overweight, malalignment, history of injury, presence of Heberden nodes) and in people with pain, before structural changes are visible on X-ray.

Therefore, this study assesses how these risk factors in women are associated with early OA features measured semi-quantitatively on MRI in knees without radiographic sign of knee OA, and evaluates whether these risk factors differ in initial location and type of OA-related damage. We also investigated how pain in the knee is associated with semi-quantitative MRI measures of early OA.

METHODS

Population

The population used in the present study is a sample from the Rotterdam Study (RS-III-1) cohort,[15] a population-based cohort study in which the incidence and risk factors for chronic disabling diseases are investigated. All participants of the RS-III-1 cohort were 45 years and older and living in Rotterdam; the participants were included between 2006

and 2008.[15] The Medical Ethics committee of the Erasmus Medical Center approved the study and all participants gave written informed consent. The participants were interviewed at home for demographic data, and were invited to the research centre for a physical examination and radiography of the knees. Height and weight were measured at the research centre.
Of these participants of the RS-III-1 study, we invited all women aged 45-60 years to join a sub-study to investigate early signs of knee OA. Of 1116 women, we recruited 891 women who underwent MRI of both knees. All women were screened for contra-indications to undergo MRI. For the present study, only knees with a radiographic Kellgren & Lawrence (K&L) score of 0 were included.[16]

Clinical data

At date of MRI, age and BMI are determined. BMI was dichotomized at ≥27 kg/m^2, based on Reijman et al.[17]
During the interview, questions were asked about the participant's history of injury. An injury of the knee was defined as 'ever had a knee injury with a swollen knee' or 'ever visited a medical doctor for a knee injury'. Also registered was whether the injury occurred in the left or right knee. Presence of Heberden's nodes was established in a physical examination.
Pain was divided in current pain and persistent pain. Current pain in the knee was defined as pain at the moment of interview in the right and/or left knee. Persistent pain was defined as pain for more than 4 days a week in the last 12 months, or for most days of the last month, in the right and/or left knee.

Radiographs

Weight-bearing antero-posterior radiographs of both knees were taken at a 70 kV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT, USA). Two independent readers who were blind for any clinical or MRI data scored the radiographs using the K&L classification criteria [16] and additionally scored separate features such as joint space narrowing, osteophytes and the alignment of the knees. The interrater agreement for the K&L score was 95% with a Kappa of 0.62.[18] Alignment was measured as the medial angle formed by the femur and tibia as described by Moreland et al.[19] and also used by Brouwer et al.[7] Because we used an anatomical axis on knee radiographs instead of a radiograph of the full leg to measure alignment, we corrected the measurements with 4 degrees.[7] The following cut-off were used for varus, neutral and valgus: varus <177°, neutral=177°-179°, and valgus >179°.[7,18]

MRI protocol

We performed a multi-sequence MRI protocol on a 1.5-T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin, USA). All participants were scanned with an 8-channel cardiac coil, so that two knees could be scanned at once without repositioning the subject.

The protocol consisted of a sagittal fast spin echo (FSE) proton density and T2 weighted sequence (TR/TE 4900/11/90, flip angle of 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal FSE T2 weighted sequence with fat suppression (TR/TE 6800/80, flip angle 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal spoiled gradient echo sequence with fat suppression (TR/TE 20.9/2.3, flip angle 35, slice thickness 3.2 (1.6) mm, field of view 15 cm^2) and a fast-imaging employing steady-state acquisition (Fiesta) sequence (TR/TE 5.7/1.7, flip angle 35, slice thickness 1.6 mm, field of view 15 cm^2). This Fiesta sequence was acquired in the sagittal plan and could be reformatted into coronal and axial planes to enable 3D visualization of the knee. Total scanning time was 27 min for two knees.

Semi-quantitative scoring

A trained reader, who was blinded for any clinical or radiographic data, scored all MRIs of the knees with the semi-quantitative grading of the KOSS, described in detail elsewhere.[14] A trained radiologist, also blinded for any clinical and radiographic data, scored a random sample of 30 MRIs to determine the inter-observer reliability. The inter-observer reliability was moderate to good with an intraclass correlation coefficient (ICC) of 0.40-0.72 for cartilage defects, cysts, osteophytes, bone marrow lesions (BML), meniscal degeneration, Baker's cyst, and joint effusion in the tibiofemoral joint (TFJ) and patellofemoral joint (PFJ). However, for osteophytes and BMLs of the PFJ the inter-observer reliability was low (ICC 0.33 and 0.24, respectively).

Cartilage lesions (grade 0-3), osteophytes (grade 0-3), subchondral cysts (grade 0-3) and bone marrow lesions (grade 0-3) were scored at the following nine locations: crista patella, medial and lateral patella facet, medial and lateral trochlea facet, the medial and lateral femoral condyle and the medial and lateral tibia plateau. Other features such as meniscal lesions (degeneration (0-1), absence of a meniscal portion (0-1)), joint effusion (grade 0-3), and Baker's cysts (grade 0-3) were also scored. Cruciate ligament lesions (anterior (ACL), posterior (PCL)) were graded absent (0) or present (1). The scores for a specific compartment of the joint (medial, lateral TFJ or PFJ) were combined by adding the various scores. Each meniscal feature (degeneration, absence of a meniscal portion) was analyzed separately for the medial and for the lateral meniscus.

For analysis of the associations between pain and the MRI-OA features, current pain and persistent pain were the dependent variables. The MRI-OA features were dichotomized (absent=0, present (score of ≥1) =1), and are the independent variables in these analysis.

Statistical analysis

For the association between the various MRI-OA features and the risk factors (age, overweight, malalignment, history of injury, and presence of Heberden nodes) a linear Generalized Estimating Equations (GEE) regression model was used, which takes into account the correlations between the right and left knee within a person. We performed a univariate GEE analysis and reported the crude odds ratio (OR). For variables that had an OR with a p-value ≤0.10 we also performed a multivariable GEE analysis, and reported the adjusted OR with its 95% confidence interval (95% CI). If a feature was

present in ≤5% of the knees, it was left out of analysis.

RESULTS

Of the 1116 invited women, 891 women were recruited (1782 knees) and underwent MRI of the knee. Of 771 women at least one knee was included in the analysis, resulting in a total of 1404 knees. Of the excluded knees, 92% had a K&L score >0 (339 knees). Other reasons for exclusion were an unevaluable or incomplete MRI examination (27 knees), and 12 knees had missing values on the K&L score or MRI feature scores. Table 1 presents the characteristics of the included women. Only 623 women (71.9%) answered the questions about the injury of the knee in the interview; only 15 women (2.4%) could remember which knee was injured.

Table 1: Participants characteristics (K&L=0)

Participants	**N**	**%**
Age (mean, sd)	771	53.5 (3.8)
BMI (mean, sd)	771	26.8 (4.6)
BMI <27	442	57.3
BMI ≥27	329	42.7
Heberden's nodes	156	20.3
Knees	**N**	**%**
Total	1404	
Left / right	696/708	49.6/50.4
Alignment (mean, sd)	1396	177 (2.8)
Varus (<177)	575	41.2
Neutral (177-179)	532	38.1
Valgus (>179)	289	20.7
History of injury of the knee: yes/no	145/425	25.4/74.6
Current knee pain	163	11.6
Persistent knee pain	98	7.1

Table 2 shows the frequency of the lesions of the bone and cartilage for all three compartments. Cartilage lesions in lateral TFJ were present in ≤5% of the knees and were therefore left out of analysis. Table 3 presents data on soft tissue lesions. ACL and PCL lesions, meniscal tear, and absence of a meniscal portion were present in ≤5% of the knees and were therefore also left out of analysis.

Table 2: Frequency of lesions of the bone and cartilage of the knee in 1404 (K&L=0) knees

	MTFJ		LTFJ		PFJ	
	N	%	N	%	N	%
Cartilage lesions	142	10.1	61	4.3	286	20.4
Osteophytes	343	24.4	205	14.6	412	29.3
Cysts	81	5.8	73	5.2	206	14.7
Bone marrow lesions	176	12.5	99	7.1	298	21.2

MTFJ, Medial tibiofemoral joint; LTFJ, Lateral tibiofemoral joint; PFJ, Patellofemoral joint

Table 3: Frequency of lesions of the soft tissue in the knee scored in 1404 (K&L=0) knees

	N	%
Joint effusion	550	39.2
Baker's cysts	131	9.3
ACL lesion	22	1.6
PCL lesion	6	0.4
	Medial/Lateral	**%**
Meniscal degeneration	173/78	12.3/5.6
Meniscal absence portion	29/21	2.1/1.5

ACL, Anterior cruciate ligament lesion; PCL, Posterior cruciate ligament lesions

Table 4 presents the results of the crude and adjusted ORs of the association with MRI features. Adjusted ORs are adjusted for the other significant risk factors per MRI feature in a specific compartment.

Age

Age showed a significant association with cartilage lesions in the medial TFJ (OR=1.02, 95%CI=1.01-1.03) and in the PFJ (OR=1.06, 95%CI:1.04-1.09), and with osteophytes in all three compartments (OR_{MTFJ}=1.04, 95%CI=1.02-1.06; OR_{LTFJ}=1.04, 95%CI=1.02-1.05; OR_{PFJ}=1.05, 95%CI=1.02-1.07). In the PFJ ageing was a significant risk factor for cysts (OR=1.02, 95%CI=1.01-1.03), bone marrow lesions (OR=1.02, 95%CI=1.01-1.04), and lateral meniscal degeneration (OR=1.01, 95%CI=1.00-1.01).

Overweight

Overweight was a significant risk factor for cartilage lesions, and cysts in the PFJ (OR=1.51, 95%CI=1.23-1.87; OR=1.12, 95%CI=1.04-1.21, respectively), and for osteophytes in all compartments (OR_{MTFJ}=1.44, 95%CI=1.24-1.67; OR_{LTFJ}=1.28, 95%CI=1.34-1.45; OR_{PFJ}= 1.49, 95%CI=1.24-1.76). Overweight showed a significant association with joint effusion (OR=1.10, 95%CI=1.02-1.18).

Alignment

Not having malaligned knees was significantly associated with cysts (varus OR=0.96, 95%CI=0.92-1.00; valgus OR=0.94, 95%CI=0.90-0.98) and not having varus-aligned knees with lateral BMLs (varus: OR=0.93, 95%CI=0.86-1.00).

History of injury of the knee

History of injury of the knee was significantly associated with BMLs in the LTFJ (OR=1.18, 95%CI=1.04-1.33).

Heberden's nodes

The presence of Heberden's nodes was a risk factor for cartilage lesions, osteophytes, and cysts in the MTFJ (OR=1.25, 95%CI=1.10-1.41; OR=1.22, 95%CI=1.01-1.48; OR=1.06, 95%CI=1.01-1.11, respectively).

None of the risk factors were significantly associated with Baker's cyst.

Pain

Joint effusion, BMLs in the PFJ and lateral meniscal degeneration were significantly associated with current pain, adjusted for the other univariate significant variables and adjusted for age and BMI (Table 5). If pain persisted for 4 days a week or most days of the previous month it was significantly associated with BMLs in the PFJ.

Table 5: Association between MRI-OA features and current and persistent knee pain

	Current pain			**Persistent pain**		
	Crude OR	**Adjusted OR ***	**p-value**	**Crude OR**	**Adjusted OR ***	**p-value**
Cartilage lesions						
MTFJ	1.02			1.02		
PFJ	**1.11**	1.05 (0.98-1.12)	0.15	1.04		
Osteophytes						
MTFJ	**1.05**	1.00 (0.95-1.05)	0.95	**1.06**	1.04 (1.00-1.08)	0.08
LTFJ	**1.07**	1.02 (0.96-1.08)	0.56	**1.05**	1.01 (0.97-1.06)	0.65
PFJ	1.04			1.01		
Cysts						
MTFJ	1.04			1.01		
LTFJ	1.08			1.06		
PFJ	**1.09**	1.05 (0.98-1.11)	0.16	1.03		
BMLs						
MTFJ	1.01			1.03		
LTFJ	**1.10**	1.06 (0.98-1.16)	0.15	1.06		
PFJ	**1.11**	**1.06 (1.00-1.12)**	**0.04**	**1.06**	**1.05 (1.00-1.09)**	**0.04**
Meniscal degeneration						
medial	1.00			1.02		
lateral	**1.12**	**1.09 (1.01-1.19)**	**0.04**	**1.08**	1.07 (0.99-1.16)	0.08
Joint effusion	**1.07**	**1.05 (1.01-1.10)**	**0.01**	**1.04**	1.03 (1.00-1.06)	0.08
Baker's cysts	1.02			1.02		

OR, Odds ratio; MTFJ, Medial tibiofemoral joint; PFJ, Patellofemoral joint; LTFJ, Lateral tibiofemoral joint; Figures printed in bold indicate significant associations; * adjusted for all significant univariate variables and age and BMI

DISCUSSION

In evaluating whether the risk factors (age, overweight, malalignment, history of injury, and presence of Heberden nodes) differ in location and type of OA-related damage in early OA, we found that history of knee injury was associated with a specific location in the knee, namely with features in the lateral compartment of the TFJ. Also, the presence of Heberden nodes was associated with a specific location in the knee, namely the medial compartment of the TFJ. None of the risk factors was discriminative for a specific type of OA-related damage (a specific MRI-OA feature). Age and overweight were associated with the majority of the semi-quantitative MRI measures in most of the compartments of the joints in women without radiographic knee OA. Current knee pain was significantly associated with joint effusion, lateral meniscal degeneration and BMLs in the PFJ, after adjusting for the other univariate significantly associated features, and BMI and age. Persistent knee pain was only significantly associated with BMLs in the PFJ.

Considering that our population had a K&L score of 0 for knee OA, we found a substantial amount of lesions on MRI. In a similar (same age and BMI) but smaller cohort (n=43), the authors found many more cartilage lesions than found in our study (71% compared to 10% in the medial TFJ in women).[20] Even in comparison with women without radiographic knee OA or pain, our women showed less cartilage lesions (35% in our cohort compared with 57% of the cohort described by Sowers et al.).[21] The amount of BMLs and cysts were similar as found in other literature.[21-25] Asymptomatic middle-aged women at risk for OA from the Osteoarthritis Initiative (OAI) had similar percentages of osteophytes, subchondral cysts, BMLs, but had more cartilage lesions (77% vs 38%), and less joint effusion (24% vs 39%) than our population. However, the women of the OAI were slightly younger (50 vs 53 years) and did not have overweight or symptoms of OA.[25] The difference in cartilage lesions might be due to differences in the semi-quantitative scoring.

Age is a risk factor that is not discriminative for any compartment of the knee, or for MRI features. Overweight is also a non-discriminative risk factor. In all compartments overweight is a risk factor for osteophytes, which is consistent with other studies.[26,27] As suggested earlier,[28,29] overweight is a risk factor that may influence the knee joint not only via mechanical loading but also via biochemical pathways.[10] Although overweight may not be a discriminative risk factor, in contrast to ageing it is a modifiable risk factor. Losing weight is advised as treatment for symptomatic OA,[30] but might also prevent progression or onset of OA.[8] Our results show that being overweight is a risk factor for all compartments and many types of OA-related damage. Therefore, advice to lose weight is important in the prevention and treatment of OA.

The higher association of overweight with PFJ features might be explained by the biochemical pathway of overweight. Clockaerts et al. reviewed the role of the infrapatellar fat pad in the disease process of knee OA.[31] The patella is surrounded by the infrapatellar fat pad, which can produce cytokines that can contribute to the degenerative process.[10,11,31] Another possible explanation is that we could not exclude radiological patellofemoral OA due to a lack of lateral or skyline X-rays. Given that the prevalence of lesions seen in the PFJ is higher than in the TFJ, the percentage radiographic OA in the PFJ is probably higher than in TFJ in this selected population.

Malalignment is a risk factor for knee OA.[7,32,33] In two large cohort studies varus alignment was found to be a risk factor for incident knee OA.[7,32] In the present study (women without radiographic knee OA) we only found an association between not having varus-aligned knees and BMLs of the lateral TFJ, which can be explained by higher load in the lateral compartment when the knee has no varus alignment. The other finding of alignment was the association of a neutral aligned knee with the presence of cysts in the medial TFJ. This could be due to the small amount of subchondral cysts in the compartments, i.e. just above our cut-off of 5% needed to include this feature in the analysis. Other studies show a wide variation in alignment description;[34] e.g., the cut-off used for varus and valgus alignment is not the same in each study, nor is the method used to measure mechanical/anatomical alignment, or the amount of correction made due to short limb X-rays. This could a reason for the discrepancies in the association of alignment with incident knee OA.

The association of knee injury in history with lateral knee OA is consistent with earlier studies on differences in radiological characteristics between post-traumatic and non-traumatic knee OA.[35-37] Swärd et al. showed that in the post-traumatic cohort (with ACL injury) osteophytes and joint space narrowing were evenly distributed between medial and lateral compartment whereas in the non-traumatic cohort the structural changes were found predominantly in the medial compartment.[35] Therefore, after an injury of the knee, structural changes occur more often in the lateral knee compartment than in those without a history of injury. The finding that joint effusion and BMLs are associated with pain is in line with a recent review.[38] Moreover, Javaid et al. found that subjects with BMLs in the patella were more likely to develop frequent symptoms than those without BMLs in knees at risk for OA.[22]

The present study has some limitations. First, we could not exclude PFJ OA, because of the lack of skyline or lateral radiographs. Second, inter-rater reliability was limited, especially for osteophytes and BMLs. In our analysis we used the scores of the reader who, on assessment of the inter-rater agreement, was found to score osteophytes and BMLs with less frequency than the other reader. This could have led to an underestimation of the associations. Furthermore, the selection of MRI sequences was not only based on semi-quantitative scoring of the images, but also used for assessing quantitative measures of cartilage and bone. In combination with limited scan time and the use of a cardiac coil that enabled bilateral knee imaging (but less optimal than a dedicated knee coil), this could have influenced the quality of the images. Finally, because this is a cross-sectional study no conclusions can be drawn about causality.

In conclusion, two risk factors were associated with a specific location in the knee. Knee injury in history was associated with the lateral TFJ and presence of Heberden nodes was associated with the medial TFJ. None of the risk factors is discriminative for a specific type of OA-related damage. Age and overweight were associated with almost all types of OA-related damage on almost all locations. Joint effusion and BMLs are associated with knee pain. These results might help in the development and testing of preventive strategies for early treatment of knee OA.

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Chapter 7

Crepitus is a first indication of patellofemoral osteoarthritis

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ABSTRACT

Background: The patellofemoral joint (PFJ) is important in early detection of knee osteoarthritis (OA). Little is known about the relationship between specific clinical findings and MRI-OA-features of PFJ.

Aim: to examine the relationship between clinical findings and MRI-OA-features of the PFJ in females (45-60 years) with and without knee OA.

Methods: Radiographs and MRI of knees of women of a sub-study of the Rotterdam Study were scored with semi-quantitative scoring. Specific patellar tests were performed in a physical examination. Current knee pain and history of patellar knee pain were reported. Binomial logistic generalized estimated equations were used to determine the association (odds ratio (OR)) between clinical findings of OA and MRI-OA-features of the PFJ. All associations were adjusted for age, BMI and MRI-OA-features of the tibiofemoral joint.

Results: In 888 women (1776 knees, mean age: 55.1ys and mean BMI: 27.0 kg/m^2) we found significant associations between crepitus and all MRI-OA-features of PFJ (ORs ranged from 2.77 to 4.58). A history of patellar pain was significantly associated with all MRI-OA-features of the PFJ were significant (OR ranged from 1.62 to 2.07). In women without knee OA, the ORs are almost similar.

Conclusion: Crepitus and history of patellar pain are clinical findings that indicate OA-lesions seen on MRI at the PFJ. These tests could help to indicate signs of patellofemoral OA. Follow-up data needs to confirm whether these tests have an additional diagnostic value on early knee OA.

INTRODUCTION

Knee osteoarthritis (OA) is very common among older individuals and is a leading cause of disability.[1-2] Traditionally, research on knee OA has been primarily focused on the tibiofemoral joint (TFJ), however the awareness of the importance of the patellofemoral joint (PFJ) has increased in recent years.[3-5] Research has revealed that PFJ OA is very common; in a study in patients with knee pain by Duncan et al. a prevalence of 40% was found for combined TFJ and PFJ OA, and 28% for isolated PFJ OA.[6]

In a population with symptoms of knee OA without radiographic abnormalities, Cibere et al. found that several clinical findings, for example crepitus and pain, are associated with cartilage defects on magnetic resonance imaging (MRI) of the knee joint.[7] In a cross-sectional study among OA patients, an association between knee pain and osteophytes scored on MRI was found only when an osteophyte was located in the patellofemoral compartment or when more than four osteophytes were present anywhere in the knee.[8]

The importance of the patellofemoral joint to explain clinical symptoms was suggested by Duncan et al.[5] who found an association between an increased severity of radiographic isolated PFJ OA and higher levels of pain, stiffness and functional limitations.

To identify early knee OA in clinical practice, the identification of PFJ OA seems to play an important role. Previous studies have assessed radiographic PFJ OA features to study the association with pain and function [5], but little is known about the relationship between specific physical examination findings of the PFJ and MRI-OA-features of the PFJ. MRI allows another perspective of structural PFJ abnormalities associated with PFJ OA. Bone marrow edema, osteophytes, and cartilage lesions are MRI features that may be associated with specific clinical findings from clinical history and physical examination. These associations may occur even at an early stage and help us to identify PFJ OA.

Therefore, the present study aims to examine the relationship between clinical findings of the PFJ and prevalent MRI-OA-features of the PFJ in females aged 45-60 years.

METHODS

Population

The population used in the present study is a subpopulation (RS-III-1) of the Rotterdam Study, a population-based cohort study in which the incidence and risk factors for chronic disabling diseases are investigated. All participants of the RS-III-1 cohort were 45 years and older and live in Rotterdam; the participants were included between 2006 and 2008.[9] The Medical Ethics committee of the Erasmus Medical Center approved the study and all participants provided written consent. All participants were interviewed at home for demographic data, and were invited to visit the research centre for a physical examination and radiographs of the knees. Height and weight were measured at the research centre. Of these participants of the Rotterdam Study (RS-III-1) we invited all women between the age of 45 and 60 years to join a sub-study for investigation of early signs of knee OA. They underwent MRI and physical examination of both knees and filled in a questionnaire. All women were screened for contra-indications for MRI.

Clinical data

Height, weight, body mass index (BMI (kg/m^2)) and age were determined at date of MRI. During anamnesis we asked whether participants experienced pain in the knee in general (current knee pain) and if participants had a history of pain of the patella (i.e. sometimes in combination with locking and grinding, especially during walking stairs, headwind cycling, squatting and sitting). In the physical exam we tested pain at the medial and lateral patellar edges on palpation, pain at the quadriceps tendon and patellar ligament, and pain at the tibial tuberosity. In addition, we tested whether the participants reported pain with the patellar compression test,[10] and we tested if there was crepitus in the knee during active flexion or extension of the knee. Crepitus was defined as hearing of a grinding noise and/or palpable vibrations in the knee, detected by the hand of the investigator rested on the patella of the participant.

MRI – protocol

We performed a multi-sequence MRI protocol on a 1.5T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin). All participants were scanned with an 8-channel cardiac coil, so that two knees could be scanned at once without repositioning the subject. The protocol consisted of a sagittal fast spin echo (FSE) proton density and T2 weighted sequence (TR/TE 4900/11/90, flip angle of 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal FSE T2 weighted sequence with fat suppression (TR/TE 6800/80, flip angle 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal spoiled gradient echo sequence with fat suppression (TR/TE 20.9/2.3, flip angle 35, slice thickness 3.2 (1.6)mm, field of view 15 cm^2) and a fast imaging employing steady state acquisition (Fiesta) sequence (TR/TE 5.7/1.7, flip angle 35, slice thickness 1.6 mm, field of view 15cm^2). This FIESTA sequence was acquired in the sagittal plan and could be reformatted into coronal and axial planes to enable three dimensional visualization of the knee. Total scanning time was 27 minutes for two knees.

Semi-quantitative scoring

A trained reader, who was blind for any clinical or radiographic data, scored all MRI's of the knees with the semi-quantitative grading of the KOSS.[11] A trained musculoskeletal radiologist, also blind for any clinical and radiographic data, scored a random sample of thirty MRIs of the knees to determine inter-observer reliability. The inter-observer reliability for the PFJ features was good for diffuse cartilage lesions and cysts (ICC=0.64; ICC=0.72 respectively), and low for osteophytes and bone marrow lesions (ICC=0.33; ICC=0.24 respectively). For focal lesions an ICC calculation was not possible, because of empty cells, but the agreement was 90%. Cartilaginous lesions, osteophytes (grade 0-3), subchondral cysts (grade 0-3) and bone marrow lesions (grade 0-3) were scored at the following five locations for the PFJ: crista patellae, medial and lateral patellar facet, medial and lateral trochlear facet. The cartilage lesions were graded as diffuse or focal lesions, with a depth score and a surface score both graded on a 0 to 3 scale. For the present analysis, we dichotomised all scores (absent =0, present =1 (score of ≥1).

MRI-OA-definition

To identify the participants with present OA in the PFJ or TFJ we used the MRI-definition recently described by Hunter et al.[12]. For PFJ OA a definite osteophyte and partial or full thickness cartilage loss was required in the patella and/or the trochlea (anterior femur). For TFJ OA the presence of a definite osteophyte and full thickness cartilage loss was required or one of these features and two of the following features: 1) subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments, 2) meniscal subluxation, maceration or degeneration (including a horizontal tear), 3) partial thickness cartilage loss, or 4) bone attrition. We modified the definition slightly. Bone attrition was left out of the definition, because we did not score bone attrition on the MRI. A knee still needed two of the three remaining features to be defined as having TFJ OA.

Statistical analysis

We performed the analyses in all participants and separately in all participants without OA (based on the MRI-OA-definition of Hunter et al.[12]) to identify possible differences in the association between the clinical findings and the MRI-OA-features when participants with knee OA were in or out the association. Participants without OA still could have MRI-OA-features, although not enough to get the diagnosis of knee OA.
Descriptive statistics (means, standard deviations (SD)) were applied to describe the participant characteristics. If a physical exam outcome or feature was found in 1% or less we left it out of the analyses. For the association between the various MRI-OA-features of the PFJ and clinical findings we used a binomial logistic Generalized Estimating Equations (GEE) regression model, which takes into account the correlations between the right and left knee within a person. We performed a GEE analysis for all physical examination tests and current knee pain and patellar knee pain. We adjusted all analysis of associations for age, BMI, and the presence of MRI-OA-features (cartilage lesions, osteophytes, cysts and bone marrow lesions) of the TFJ (0-4). For comparison we also performed the same analysis for associations between MRI-OA-features of the TFJ and the clinical findings to show the difference between PFJ and TFJ, with those clinical findings. We reported the odds ratios (OR) with corresponding 95% confidence intervals (CI). Furthermore we calculated the pre- and post-test probabilities of the clinical findings that showed a good association with an MRI-feature to show the probability of having an MRI-lesion when testing positive on a clinical test. Since we performed multiple testing (seven clinical tests for four features), we describe only the results with a p-value less than .001. All analyses are performed with PASW Statistics 17 (SPSS Inc, Chicago, USA).

RESULTS

Of 1116 invited women, 891 women were recruited (1782 knees) and underwent MRI of the knees. We excluded three women of whom we did not have data on age and/or BMI. Characteristics of the remaining 888 women are shown in Table 1, as well as the physical exam outcomes and prevalence of MRI-OA-features of their knees. Mean age

was 55.1 year (SD: 3.7), mean BMI was 27.0 kg/m^2 (SD: 4.8). Hundred-eighty women had PFJ OA and/or TFJ OA in one or both knees (based on the MRI-definition) [12]; 56 knees were defined as having both PFJ-and TFJ-OA, 81 knees were defined as having only PFJ-OA, and 105 knees were defined as having isolated TFJ-OA. Of those who did not have PFJ-OA or TFJ-OA still 15% had cartilage defects and 25% had osteophytes in the PFJ and 10% had cartilage defects and 24% had osteophytes in the TFJ. Pain at tibial tuberosity was found in 1% of the knees and therefore left out of analyses. Table 2a shows the ORs (95%CI) of the association between the physical exam outcomes and the MRI-OA-features of the PFJ in all 888 women; Table 2b shows the same associations for the TFJ. Table 3a and 3b show the ORs (95%CI) of the associations between the physical exam outcomes and the MRI-OA-features of the PFJ and TFJ, respectively, in the knees without OA (based on the MRI-definition).

Associations in all participants

Clinical findings and MRI-OA-features of the PFJ (Table 2a)

Pain at the patellar edge (medial and/or lateral), pain at the patellar ligament and a positive patellar compression test were not significantly associated with any MRI-OA-feature. The presence of crepitus was significantly associated with all MRI-OA-features (ORcartilage lesions=4.58 (3.42-6.15); ORosteophytes=2.80 (2.20-3.57); ORcysts=2.77 (2.05-3.76); ORbone marrow lesions=3.44 (2.62-4.52).

History of patellar pain was significantly associated with all MRI-OA-features of the PFJ (ORcartilage lesions=2.07 (1.56-2.75); ORosteophytes=1.62 (1.27-2.08); ORcysts=1.80 (1.34-2.41); ORbone marrow lesions=1.69 (1.28-2.24)). Current knee pain was associated with bone marrow lesions (OR=1.77 (1.25-2.51; p=0.001)).

Clinical findings and MRI-OA-features of the TFJ (Table 2b)

None of the clinical findings was significantly associated with MRI-OA-features of the TFJ. History of patellar pain was only significantly associated with osteophytes of the TFJ (OR=1.59 (1.23-2.06)).

Table 1: Demographics of study population

	All			Without any OA in one or both knees (based on the MRI definition)*		
Participants	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Age (mean, sd)	888	55.1	3.7	824	54.9	3.7
BMI (mean, sd)	888	27.0	4.8	824	26.8	4.5
Knees	**1776**	**N**	**%**	**1518**	**N**	**%**
Left/right	1776	888/888	50/50	1518	772/746	50.9/49.1
History of patellar pain	1772	505	28.5	1515	371	24.5
Current knee pain	1774	248	14.0	1516	173	11.4
Physical exam						
Pain at the patellar edges	1769	48	2.7	1513	29	1.9
Pain at the quadriceps tendon	1771	24	1.4	1517	19	1.3
Pain at the patellar ligament	1772	60	3.4	1518	46	3.0
Pain at the tibial tuberosity	1768	17	1.0	1514	12	0.8
Compression test pain	1762	350	19.9	1510	274	18.1
Crepitus	1744	771	44.2	1493	608	40.7
MRI-features PFJ						
Cartilage defect	1759	403	22.9	1516	235	15.5
Osteophytes	1764	596	33.8	1517	384	25.3
Cysts	1765	269	15.2	1513	194	12.8
Bone marrow lesions	1765	397	22.5	1513	285	18.8
PFJ OA	1760	137	7.8	1518	-	-
MRI-features TFJ						
Cartilage defect	1763	301	17.1	1517	162	10.7
Osteophytes	1766	593	33.6	1517	374	24.7
Cysts	1765	216	12.2	1513	142	9.4
Bone marrow lesions	1765	364	20.6	1513	236	15.6
TFJ OA	1768	161	9.1	1518	-	-

OA, Osteoarthritis ; PFJ, Patellofemoral joint; TFJ, Tibiofemoral joint

* The MRI-definition for knee OA (PFJ and/or TFJ) is described earlier in the method section and by Hunter et al. (2011).[12]

Table 2a: Association between clinical findings and PFJ-MRI-OA-Features in all participants

OR (95%CI)	Cartilage lesions in PFJ	Osteophytes in PFJ	Cysts in PFJ	Bone marrow lesions in PFJ
Pain at the patellar edges	1.30 (0.56-3.02)	2.11 (1.12-3.96)	0.71 (0.29-1.72)	1.27 (0.59-2.72)
Pain at the quadriceps tendon	2.32 (0.84-6.39)	0.91 (0.40-2.03)	0.43 (0.10-1.82)	1.89 (0.45-3.13)
Pain at the patellar ligament	2.23 (1.14-4.38)	1.44 (0.83-2.52)	0.88 (0.42-1.86)	1.21 (0.61-2.39)
Positive Compression test	1.53 (1.11-2.11)	1.24 (0.93-1.65)	1.04 (0.73-1.48)	0.98 (0.71-1.35)
Presence of Crepitus	**4.58 (3.42-6.15)**	**2.80 (2.20-3.57)**	**2.77 (2.05-3.76)**	**3.44 (2.62-4.52)**
History of patellar pain	**2.07 (1.56-2.75)**	**1.62 (1.27-2.08)**	**1.80 (1.34-2.41)**	**1.69 (1.28-2.24)**
Current knee pain	1.65 (1.13-2.43)	1.22 (0.88-1.69)	1.31 (0.88-1.95)	**1.77 (1.25-2.51)***

Adjusted for age, BMI and TFJ-MRI-OA-features; bold OR(95%CI) has a p<0.001; *p=0.001

Table 2b: Associations between clinical findings and TFJ-MRI-OA-Features in all participants

OR (95%CI)	Cartilage lesions in TFJ	Osteophytes in TFJ	Cysts in TFJ	Bone marrow lesions in TFJ
Pain at the patellar edges	1.56 (0.77-3.14)	1.97 (1.03-3.76)	0.23 (0.05-0.98)	0.63 (0.24-1.63)
Pain at the quadriceps tendon	0.99 (0.35-2.78)	3.00 (1.25-7.23)	1.28 (0.38-4.32)	0.49 (0.14-1.76)
Pain at the patellar ligament	1.69 (0.92-3.10)	1.55 (0.88-2.73)	0.92 (0.39-2.13)	0.84 (0.41-1.73)
Positive Compression test	1.10 (0.80-1.54)	1.31 (1.00-1.72)	1.46 (1.04-2.06)	1.31 (0.96-1.78)
Presence of crepitus	0.96 (0.70-1.31)	1.18 (0.91-1.53)	1.24 (0.87-1.75)	0.99 (0.74-1.32)
History of patellar pain	1.57 (1.17-2.10)	**1.59 (1.23-2.06)**	1.08 (0.77-1.51)	1.38 (1.05-1.81)
Current knee pain	1.57 (1.11-2.23)	1.43 (1.03-1.97)	1.10 (0.73-1.65)	1.35 (0.96-1.90)

Adjusted for age, BMI and PFJ-MRI-OA-features; bold OR(95%CI) has a p<0.001;

Associations in participants without OA in the PFJ and the TFJ

Clinical findings and MRI-OA-features in the PFJ (Table 3a)

No significant associations were found with pain at the patellar edge, pain at the quadriceps tendon, pain at the patellar ligament, and with a positive patellar compression test. The presence of crepitus was significantly associated with all MRI-OA-features of the PFJ (ORcartilage lesions=5.49 (3.79-7.94); ORosteophytes=2.61 (2.00-3.40); ORcysts=2.82 (2.00-3.98); ORbone marrow lesions=3.70 (2.71-5.04).

History of patellar pain was significantly associated with almost all MRI-OA-features of the PFJ (ORcartilage lesions=1.95 (1.39-2.72); ORcysts=1.86 (1.32-2.61); ORbone marrow lesions=1.83 (1.33-2.50)). Current knee pain was only associated with bone marrow lesions (OR=2.09 (1.38-3.15)).

Clinical findings and MRI-OA-features in the TFJ (Table3b)
No significant associations were found between any clinical finding and MRI-OA-features of the TFJ.

Pre- and post-probabilities of crepitus on MRI-OA-features

The pre-test probability of having a cartilage lesion in the PFJ seen on MRI in all participants was 23% and in participants without any OA in the knee the pre-test probability was 15%. After testing positive on crepitus, the probability of having cartilage lesions in the PFJ increased to 39% in all participants and 29% in participants without any knee OA. The probability of having cartilage lesions in the TFJ increased hardly after testing positive on crepitus (4% (from 17% to 21%) in all participants and 1.5% (from 11% to12.5%) in participants without any knee OA). The same applies for having bone marrow lesions and cysts in the PFJ the probability increased in a range of 7% to 15% after testing positive for the presence of crepitus.

Table 3a: Associations between clinical findings and PFJ-MRI-OA-Features in participants without any knee OA based on MRI*

OR (95%CI)	Cartilage lesions in PFJ	Osteophytes in PFJ	Cysts in PFJ	Bone marrow lesions in PFJ
Pain at the patellar edges	0.88 (0.31-2.50)	1.31 (0.58-2.98)	0.50 (0.11-2.20)	1.38 (0.58-3.31)
Pain at the quadriceps tendon	2.41 (0.89-6.49)	0.66 (0.25-1.77)	-	0.91 (0.26-3.18)
Pain at the patellar ligament	2.02 (0.98-4.17)	1.14 (0.62-2.12)	0.79 (0.32-1.97)	0.98 (0.42-2.28)
Positive Compression test	1.60 (1.10-2.31)	1.18 (0.86-1.61)	1.18 (0.80-1.75)	0.97 (0.67-1.40)
Present of crepitus	**5.49 (3.79-7.94)**	**2.61 (2.00-3.40)**	**2.82 (2.00-3.98)**	**3.70 (2.71-5.04)**
History of patellar pain	**1.95 (1.39-2.72)**	1.40 (1.07-1.85)	**1.86 (1.32-2.61)**	**1.83 (1.33-2.50)**
Current knee pain	1.54 (0.93-2.55)	0.90 (0.60-1.35)	1.58 (0.98-2.56)	**2.09 (1.38-3.15)**

Adjusted for age, BMI and TFJ-MRI-OA-features; bold OR(95%CI) has a p<0.001; *The MRI-definition for knee OA (PFJ and/or TFJ) is described earlier in the method section and by Hunter et al. (2011).[12]

Table 3b: Associations between clinical findings and TFJ-MRI-OA-Features in participants without any knee OA based on MRI*

OR (95%CI)	Cartilage lesions in TFJ	Osteophytes in TFJ	Cysts in TFJ	Bone marrow lesions in TFJ
Pain at the patellar edges	1.18 (0.37-3.81)	1.25 (0.57-2.75)	-	0.43 (0.10-1.85)
Pain at the quadriceps tendon	0.86 (0.19-3.87)	3.19 (1.23-8.27)	2.64 (0.84-8.33)	0.67 (0.15-2.97)
Pain at the patellar ligament	1.67 (0.74-3.76)	1.29 (0.68-2.45)	0.83 (0.28-2.46)	0.79 (0.32-1.95)
Positive Compression test	0.68 (0.42-1.09)	1.08 (0.80-1.46)	1.59 (1.07-2.36)	1.19 (0.82-1.73)
Present of crepitus	0.98 (0.67-1.44)	1.22 (0.91-1.61)	1.46 (0.99-2.17)	1.05 (0.75-1.46)
History of patellar pain	1.13 (0.77-1.66)	1.21 (0.91-1.62)	1.04 (0.70-1.55)	1.00 (0.71-1.41)
Current knee pain	0.95 (0.55-1.66)	1.02 (0.69-1.51)	0.88 (0.50-1.53)	0.78 (0.48-1.28)

Adjusted for age, BMI and PFJ-MRI-OA-features; bold OR(95%CI) has a p<0.001; * The MRI-definition for knee OA (PFJ and/or TFJ) is described earlier in the method section and by Hunter et al. (2011).[12]

DISCUSSION

Our study showed that the presence of crepitus in the knee and history of patellar pain are significantly associated with all prevalent MRI-OA-features of the PFJ in women aged 45 to 60 years with and without knee OA. Crepitus did not show these associations with prevalent MRI-OA-features of the TFJ in the same women. We demonstrated that the increased probability of having cartilage lesions in the presence of crepitus on physical exam is more than 5 times higher for the PFJ than for the TFJ. History of patellar pain did not show any associations with prevalent MRI-OA-features in TFJ in participants without any knee OA. It only showed a significant association with osteophytes in the TFJ when using all participants in the analysis.

To our knowledge this is the first study that investigates the association between clinical findings of the PFJ alone and PFJ MRI-OA features. Several previous studies investigated the relationship between clinical features (such as crepitus) and radiological OA in all compartments of the knee.[7, 13] Duncan et al. investigated how radiographic severity and compartmental involvement influenced symptoms in the knee, showing that radiographic PFJ OA is associated with symptoms.[14]

Crepitus of the knee is often described as a grinding noise with a clearly palpable vibration, which could indicate cartilage damage in the PFJ. It is one of the signs for diagnosis of both TFJ and PFJ OA especially usefull in primary care, as described in the european league against rheumatism (EULAR) recommendation for diagnosis of knee OA.[15] In the present study we showed that crepitus is a sign of lesions in the PFJ rather than in the TFJ. This should be kept in mind when diagnosing knee OA with these recommendations.

Several population-based studies [7, 13] found a similar frequency of crepitus. In these symptomatic cohorts a significant association between crepitus and radiological OA (K&L≥2) was found. Cibere and colleagues [7] showed, however, that crepitus did not associate with pre-radiological OA, which was based on contour defect of cartilage

thickness seen on MRI in combination with K&L≤2 for all knee compartments combined. In our study we analyzed the PFJ and TFJ separately. This enables us to demonstrate the association between crepitus and cartilage lesions for the PFJ, and not for the TFJ. No other studies have investigated MRI findings of PFJ OA in relation to clinical features. In knees with OA (n=242 knees) we found that crepitus still was associated with MRI-OA-features of the PFJ and not with MRI-OA-features of the TFJ (data not shown). In the presence of a positive test for crepitus on the physical exam, the increase in probability of having cartilage lesions in the PFJ was approximately 5 times higher than the increase in probability on having cartilage lesions in the TFJ. This strengthens the conclusion that the presence of crepitus is a sign of lesions in the PFJ rather than in the TFJ.

As far as we know history of patellar pain has never been investigated before in relation to MRI features of OA. The association between history of patellar pain and all MRI-OA-features could indicate that the changes in the knee seen on MRI (damage of the cartilage, osteophyte, cysts, bone marrow lesions, or joint effusion) started at an earlier time-point. We did not have information about the cause and circumstances of the patellar pain. There could have been a trauma. Adjusting for knee injury in history ("did you ever had a knee injury with a swollen knee or contacted a medical doctor for a knee injury?" yes/no) did not change the results in significance of MRI-OA-features (data not shown). History of patellar pain could therefore also be an indicator of early knee OA in the PFJ. In the knees without OA no knees had both cysts and pain at the patellar edge. Therefore no odds ratio could be calculated.

A limitation of the present study is that we did not measure the reproducibility of the physical exam, due to the high strain of the research on these people already. It has been reported in the literature that reproducibility of physical examination of the knee is in general low or undetermined.[16] For crepitus Cibere et al.[7] reported an interobserver agreement of 54%. Another limitation is the low inter-rater reliability of osteophytes and bone marrow lesions of the PFJ. The score of the reader we used in analysis did not score as many osteophytes and bone marrow lesions as the second reader. This fact may have led to an underestimation of the associations. Furthermore, we modified the MRI definition of OA. We did not use bone attrition as one of the features to define knee OA as described by Hunter et al.[12] Still two of the other features (bone marrow lesions or cyst, meniscal degeneration or partial thickness cartilage lesions) in combination with a definite osteophyte or full thickness cartilage loss were required to diagnose OA. We think this is justified because bone attrition is a feature of a more advanced knee OA, while our population is a young and relatively healthy cohort.

In summary, the presence of crepitus is an important clinical feature which is an indicator for osteoarthritic lesions in the PFJ seen on MRI in women with and without knee OA, but not for the TFJ. History of patellar pain is also an indicator of early osteoarthritic lesions of PFJ seen on MRI in these women. Follow-up data needs to confirm whether these tests have an additional diagnostic value on early stage knee OA.

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Chapter 8

Cartilage volume associated with semi-quantitative radiographic and MRI measures in an open female population

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ABSTRACT

Background and Objective: Osteoarthritis (OA) research generally uses semi-quantitative measures based on radiographs and magnetic resonance imaging (MRI), but quantitative measures are now playing an increasingly important role. This study compares cartilage volume with radiographic and MRI OA features of knees of women aged 45-60 years.

Methods: Radiographs and MRI of both knees were made. Radiographs were scored for OA with Kellgren and Lawrence (K&L) grades, and for the presence of osteophytes and joint space narrowing. MRIs were scored with the Knee Osteoarthritis Scoring System (KOSS). Cartilage volume of the medial femur, medial tibia and the patella of all knees was quantified with a fully automatic quantification method.

Results: A total of 859 women (1,709 knees) were included in the analysis; mean age was 55.0 years and mean body mass index (BMI) was 27.0 kg/m^2. A negative trend in cartilage volume was found for increased age in all three compartments, as well as for joint space narrowing in the medial femur, and for cartilage degeneration in the medial tibia and patella. A positive trend in cartilage volume was found for BMI in the medial tibia and the patella, and for osteophytes in the medial femur and medial tibia. No significant trends were seen for pain, K&L grades, bone marrow lesions, or subchondral cysts.

Conclusion: As expected, cartilage volume was lower in women at higher age, and with more severe grades of cartilage degeneration and joint space narrowing. The higher cartilage volumes associated with BMI and osteophytes was unexpected.

INTRODUCTION

Osteoarthritis (OA) of the knee is the most common joint disease among the middle-aged and elderly.[1] Knees and hips are more often affected than other joints. In persons aged ≥70 years, 40% suffer from OA of the knee. With older age the prevalence of OA in women increases dramatically compared to men; i.e. the prevalence of radiographic knee OA is 14.1% for men and 22.8% for women aged ≥45 years.[2]

Radiography is still the main diagnostic tool in clinical and epidemiological research and the accepted technique to evaluate progression. However, radiographs cannot directly depict cartilage, an important tissue for OA, and scores derived from radiographs correlate poorly with clinical symptoms.[3-4] Nowadays, in both clinical and epidemiological studies, magnetic resonance imaging (MRI) is increasingly used to assess OA-related features and changes in these features. Unlike radiography, MRI is as 3D technology and can visualize cartilage and other soft tissues of the joints and is increasingly used as a diagnostic tool for OA. MRI protocols for OA imaging are currently being developed and evaluated. Similar to radiography, MRI is mostly used for semi-quantitative OA scoring but, until recently, no semi-quantitative MRI definition was available with a cut-off for knee OA.[5] Objective quantitative measures are needed to monitor treatment effects with MRI.[6] Therefore cartilage quantification protocols were introduced,[7-9] which generally use laborious manual or semi-automatic cartilage segmenting methods.[9] Dam et al. developed a fully-automatic method for segmentation and quantification of the cartilage.[8] This method has been validated in a population with healthy individuals and in patients with varying degrees of OA symptoms on low field (0.18T) MRI scanner. It shows promising results in distinguishing healthy subjects from OA patients, even in borderline OA cases. The framework has not yet been validated in an open population using high-field MRI scans.

Comparisons have been made between quantitative measures of cartilage and semi-quantitative scores assessed on MRI and radiographs in different study populations,[7-8,10-17] but with conflicting results. Some studies found a good correlation between quantified cartilage volume with semi-quantitative cartilage scores based on MRI (WORMS, KOSS) or radiography (Kellgren & Lawrence; K&L), whereas others did not.

Therefore, the question arose whether the fully-automatic method for quantification of cartilage applied in high-field MRI would provide improved quantitative cartilage scores that might better correlate with semi-quantitative MRI scores. More specifically, this study evaluates the correlation of the cartilage volume of the medial femur, medial tibia and patella of the knees with semi-quantitative KOSS MRI score and the K&L radiographic classification score. Our hypothesis is that cartilage volume is lower with increasing severity of radiographic and MRI features as tested in both knees in an open population of women.

METHODS

Population

The study population was a sample of the Rotterdam Study, a population-based study in the Netherlands that investigates prevalence, incidence and risk factors of various

chronic disabling diseases among elderly persons aged 55 years and over.[18] The Medical Ethics committee of Erasmus University Medical Center approved the study and all participants gave written consent.
In 2006 the cohort was extended with subjects aged ≥45 years, who were not yet included in the original study. Of this latest population, we invited women aged 45-60 years to join a sub-study investigating early signs of knee OA. Of the 1,116 invited women, 891 women who underwent radiography, MRI, physical examination of both knees and completed a questionnaire were included. All women were screened for contra-indications for MRI.

Radiography

Weight-bearing antero-posterior radiographs of both knees were taken at 70 kV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT, USA). No lateral or skyline views were taken. Two independent readers who were blinded for any clinical or MRI data scored the radiographs using the K&L[19] and also scored the separate features: joint space narrowing (JSN), and osteophytes for the tibiofemoral compartment. Both features were graded using a scale from 0-3; 0=no osteophyte/JSN; 1=possible osteophyte(s)/JSN; 2=definite osteophyte(s)/JSN; 3=severe osteophyte(s)/JSN. The inter-rater agreement for the K&L score was 95% with a kappa of 0.62.[20]

MRI

We performed a multi-sequence MRI protocol on a 1.5-T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin, USA). All participants were scanned with an 8-channel cardiac coil, so that two knees could be scanned at once without repositioning the subject.
The protocol consisted of a sagittal fast spin echo (FSE) proton density and T2 weighted sequence (TR/TE 4900/11/90, flip angle of 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal FSE T2 weighted sequence with fat suppression (TR/TE 6800/80, flip angle 90-180, slice thickness 3.2 mm, field of view 15 cm^2), a sagittal spoiled gradient echo sequence with fat suppression (TR/TE 20.9/2.3, flip angle 35, slice thickness 3.2 (1.6) mm, field of view 15 cm^2) and a fast-imaging employing steady-state acquisition (FIESTA) sequence (TR/TE 5.7/1.7, flip angle 35, slice thickness 1.6 mm, field of view 15 cm^2). This FIESTA sequence was acquired in the sagittal plane. Total scanning time was 27 min for two knees.

Semi-quantitative scoring

A trained reader, who was blinded for any clinical or radiographic data, scored all MRIs of the knees with the semi-quantitative Knee Osteoarthritis Scoring System (KOSS), described in detail elsewhere.[21] A trained radiologist, also blinded for any clinical and radiographic data, scored a random sample of 30 MRIs to determine the inter-observer reliability. The inter-observer reliability was moderate to good with an intraclass correlation coefficient (ICC) of 0.40-0.72 for cartilage defects, cysts, osteophytes, bone

marrow lesions (BML), meniscal degeneration, Baker's cyst, and joint effusion in the tibiofemoral joint (TFJ) and patellofemoral joint (PFJ). However, for osteophytes and BMLs of the PFJ the inter-observer reliability was low (ICC 0.33 and 0.24, respectively). Cartilage lesions (grade 0-3), osteophytes (grade 0-3), subchondral cysts (grade 0-3) and BMLs (grade 0-3) were scored at the following nine locations: crista patellae, medial and lateral patellar facet, medial and lateral trochlear facet, the medial and lateral femoral condyle, and the medial and lateral tibia plateau. Other features such as meniscal lesions [degeneration (0-1), absence of a meniscal portion (0-1)], joint effusion (grade 0-3), and Baker's cysts (grade 0-3) were also scored. Cruciate ligament lesions (anterior (ACL), posterior (PCL)) were graded absent (0) or present (1). The scores for a specific compartment of the joint (medial, lateral TFJ or PFJ) were combined by adding the various scores. Each meniscal feature (degeneration, absence of a meniscal portion) was analyzed separately for the medial and the lateral meniscus.

Automatic cartilage quantification

The automatic cartilage quantification method is described in detail by Dam et al..[8] The FIESTA sequence was used for the automatic cartilage quantification method. The articular cartilage of the medial femur, medial tibia and patella of 25 knees was manually segmented by slice-wise outlining by two researchers. Intra-observer correlation for volume quantification from manual segmentations was excellent for all three compartments (r=0.89 for the medial tibia, r=0.97 for the medial femur and r=0.98 for the patella). The manual segmentations were used to train a voxel classification scheme based on a multi-scale k-nearest neighbor framework.[22] This method provides automatic segmentation of the medial femoral, medial tibial and patellar cartilage compartments. The cartilage volume was computed directly from the segmentation by counting the number of voxels for cartilage volume of the medial femur, the medial tibia and patella separately. The correlation between the cartilage volumes derived from manual segmentation and automatic segmentation were excellent for the medial femur (r=0.90) and patella (r=0.87), and moderate for the medial tibia (r=0.55). Cartilage volume assessments were normalized by the width of the tibial plateau in order to adjust the results for knee size. Osteophytes were disregarded when measuring the tibial width.

Pain

Pain was defined as having pain at the moment of interview or having pain in the last year in the right and/or left knee.

Statistics

Descriptive statistics were used to yield mean and standard deviation (sd) values. Frequencies of determinants (pain, K&L grade, JSN, osteophytes and the KOSS MRI features) were calculated for the whole population, and cartilage volumes were calculated for each determinant and grade of the determinant in each compartment (medial femur, medial tibia and patella).

To determine the associations between the volumes of the medial femur, medial tibia

and patella and the various determinants (semi-quantitative scored MRI features, K&L scores) a linear Generalized Estimating Equations (GEE) regression analysis was performed. A GEE analysis adjusts for the correlations between the right and left knee of the same person. Determinants were analyzed as covariates, so that the associations represent trends. First we performed univariate GEE analysis; (age and BMI as continuous variables). Then we performed a multivariate analysis including all determinants with a univariate p-value of ≤0.1. Results are presented as regression coefficients (ß) with a standard error (se) that represent the linear trend between cartilage volume and severity of the determinant.

RESULTS

Population

Of the 1,782 included knees 1,741 knees (882 women) were used in the analysis with complete data on age, BMI, K&L score and quantified cartilage volume from MRI. Of 23 women only one knee was included (7 with only the left knee and 16 with only the right knee), owing to missing cartilage volume data or K&L score due to bad quality of the MRI or radiograph.

Tables 1 and 2 present data on demographics, pain scores, and the semi-quantitative scores from radiography and MRI of the participants/knees included in the analysis. Mean age was 55.0 (sd=3.7)years, mean BMI was 27.1 (sd=4.8) kg/m^2. Of the 1,741 knees, 83.0% (1,445 knees) were scored with a K&L grade of 0. Only 4.6% of the knees were scored with a K&L ≥2. Most knees (70.8%, 1,226 knees) had no degree of cartilage degeneration. A total of 701 knees (40.5%) had no sign of semi-quantitative lesion on MRI. In 544 knees (31.4%) no lesions were seen on radiography or MRI.

Table 3 shows the mean volumes (raw and normalized by tibial width) per anatomic region derived from the automatic cartilage quantification method.

Figure 1 shows scatter plots of normalized cartilage volumes as function of age and BMI with trendlines. Figures 2 and 3 show the normalized cartilage volumes per radiographic and MRI feature.

Table 1: Characteristics of the study population

Participants (n=882)	
Age in years (mean, sd)	55.0 (3.7)
BMI (mean, sd)	27.1 (4.8)
Knees (n=1741)	**n (%)**
Right / left	875/866 (50.3/49.7)
Pain in the knee (yes) *	486 (28.1)
Radiograph features	
K&L score	
Grade 0	1445 (83.0)
Grade 1	215 (12.3)
Grade 2	68 (3.9)
Grade 3/4	13 (0.7)
Joint space narrowing	
Grade 0	1377 (79.1)
Grade 1	322 (18.5)
Grade 2/3	42 (2.4)
Osteophytes	
Grade 0	1411 (81.0)
Grade 1	195 (11.2)
Grade 2	103 (5.9)
Grade 3	32 (1.8)

* Missing data of 12 knees

Table 2: Prevalence of MRI features (per grade) of the knees (n=1741)

	Medial femur	**Medial Tibia**	**Patella**
	n (%)	**n (%)**	**n (%)**
Cartilage degeneration	5*	6*	8*
Grade 0	1562 (90.0)	1614 (93.0)	1387 (80.0)
Grade 1	142 (8.2)	88 (5.1)	277 (16.0)
Grade 2	31 (1.8)	33 (1.9)	60 (3.5)
Grade 3	-	-	9 (0.5)
Osteophytes	4*	5*	5*
Grade 0	1279 (73.8)	1417 (81.6)	1392 (80.2)
Grade 1	406 (23.4)	317 (18.3)	315 (18.1)
Grade 2	51 (3.0)	2 (0.1)	28 (1.6)
Grade 3	1 (0.1)	-	1 (0.1)
Bone marrow lesions	11*	12*	11*
Grade 0	1529 (88.4)	1662 (96.1)	1391 (80.4)
Grade 1	145 (8.4)	32 (1.9)	329 (19.0)
Grade 2	45 (2.6)	20 (1.2)	9 (0.5)
Grade 3	11 (0.6)	15 (0.9)	1 (0.1)
Subchondral cysts	11*	12*	11*
Grade 0	1679 (97.1)	1658 (95.9)	1496 (86.5)
Grade 1	45 (2.6)	56 (3.2)	231 (13.4)
Grade 2	5 (0.3)	11 (0.6)	3 (0.2)
Grade 3	1 (0.1)	4 (0.2)	-

* Number of knees with missing data

Table 3 : Data on volumes per anatomic region (n=1741 knees)

	Volume (mean ± sd) mm^3	
	Raw	**Normalized***
Tibial width (mm)	68.7 ± 3.1	
Cartilage volume		
Medial femur	3882 ± 878	3895 ± 883
Medial tibia	1352 ± 274	1353 ± 266
Patella	1928 ± 760	1935 ± 764

*Normalized by tibial width (mm^3)

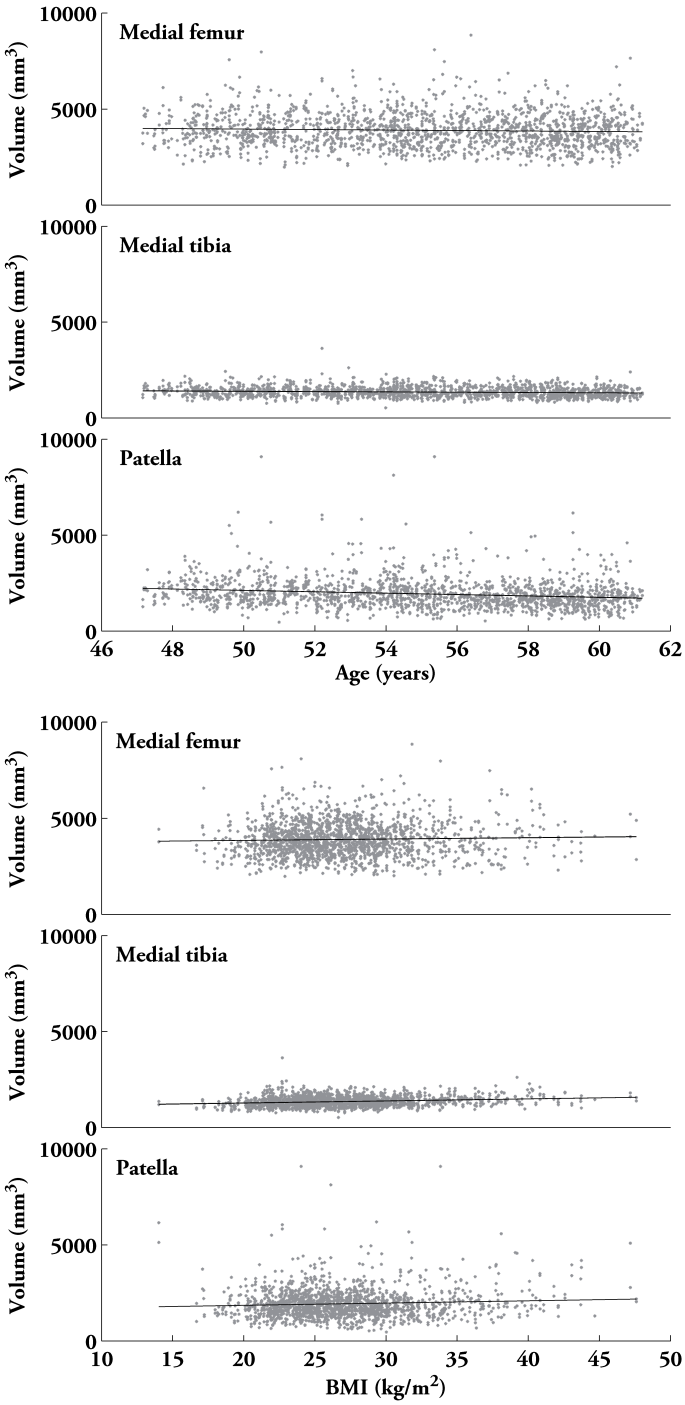

Figure 1: Scatter plots with trendline of the cartilage volume as function of age and BMI.

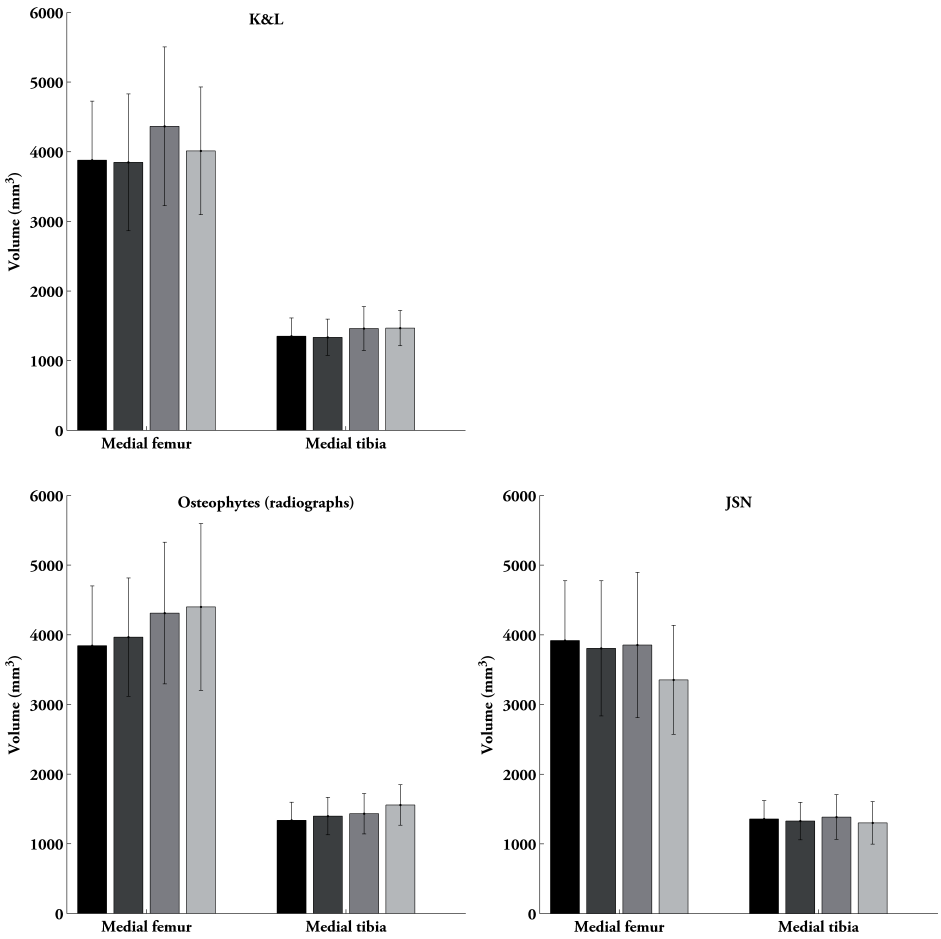

Figure 2: The mean (and sd) of the cartilage volumes per radiographic feature. For the K&L scores (columns 1-4 from left to right): first column=grade 0/ no OA; second column=grade 1/ possible OA; third column= mild/definite OA; fourth column=grades 3 and 4 together (moderate to severe OA). For osteophytes (from left to right): first column=no osteophytes; second column=possible osteophytes; third column=definite osteophyte(s); fourth column=large/multiple osteophytes. For joint space narrowing (JSN) the grading is: first column=no JSN; second column=possible JSN; third column=definite JSN; fourth column=severe JSN.

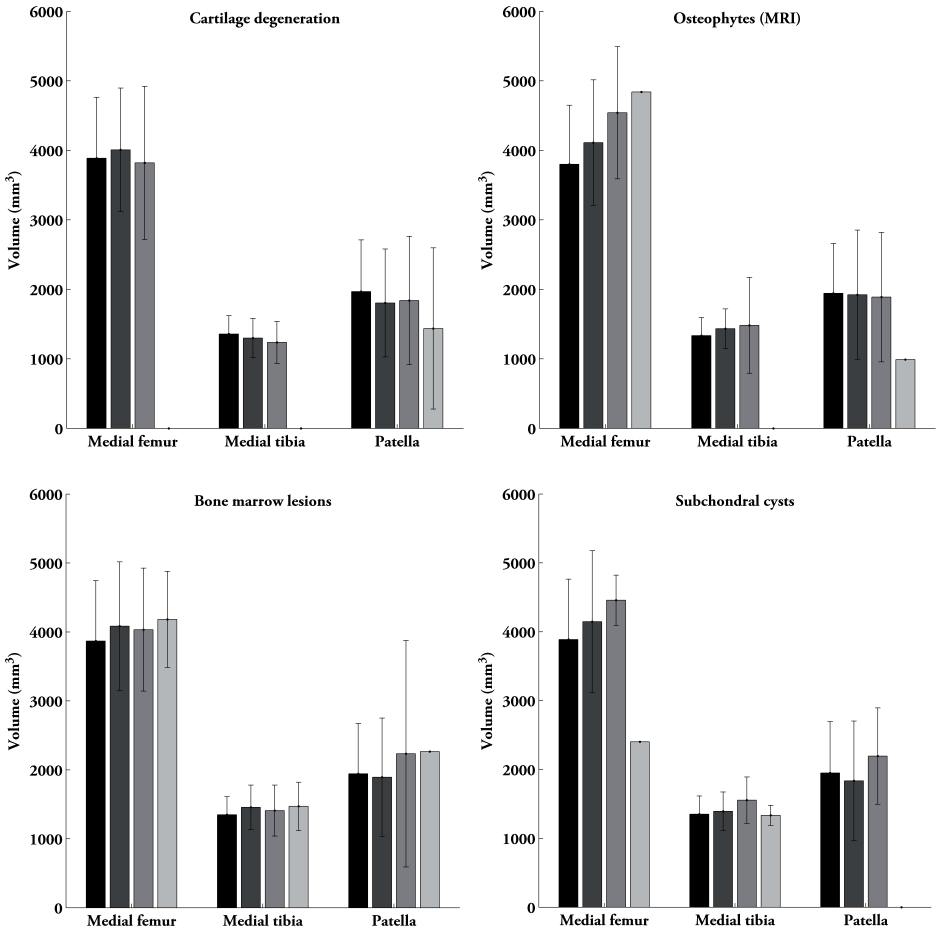

Figure 3: The mean (and sd) of the cartilage volumes per MRI feature. For all four figures the following grading is used (columns from left to right): first column=grade 0/ no lesion(s); second column=grade 1/ possible lesion(s); third column=grade 2/ definite lesion(s); fourth column=grade 3/ severe lesion(s). In the figure for cartilage degeneration the fourth columns are not shown for the medial femur and medial tibia, because no knee had severe cartilage degeneration in these compartments; in the other figures the same applies to osteophytes in the medial tibia, and to subchondral cysts in the patella.

Tables 4a-c show the trends of the GEE regression analysis. In multivariate analysis we found that increasing age is associated with a lower cartilage volume in the medial femur (ß=-22.67, p=0.001), the medial tibia (ß=-9.41, p<0.001) and the patella (ß=-34.91, p<0.001). A higher BMI is associated with a higher cartilage volume in the medial tibia (ß=9.11, p<0.001) and in the patella (ß=13.53, p=0.019). No trend was seen for pain and K&L grades in either the medial femur or medial tibia. A positive trend was seen for osteophytes scored on the radiographs with cartilage volume of the medial femur (ß=100.80, p=0.044) and the medial tibia (ß=60.10, p<0.001) and a negative trend was seen for JSN scored on radiographs with cartilage volume of the medial femur

(ß=-309.66, p<0.001). For the MRI features, a negative trend was seen for cartilage degeneration with cartilage volume of the medial tibia (ß=-116.46, p<0.001) and the patella (ß=-95.71, p=0.032). No significant trend was seen for cartilage degeneration with cartilage volume of the medial femur. Furthermore, a positive trend was seen for osteophytes (scored on MRI) with cartilage volume of the medial femur (ß=299.55, p<0.001) and the medial tibia (ß=77.16, p<0.001).

Table 4a: Trend analysis of the normalized cartilage volume (mm3) of the medial femur

	Univariate analysis			**Multivariate analysis (<0.1 included) n=1716 (98.6%)**		
	ß	**se**	**P**	ß	**Se**	**P**
Age	-13.50	7.06	0.056	**-22.67**	**6.84**	**0.001**
BMI	7.07	5.99	0.238			
Pain	**144.80**	**53.73**	**0.007**	73.68	50.71	0.146
Radiographs						
K&L grade	**112.74**	**50.91**	**0.027**	141.35	73.46	0.054
Osteophytes	**196.60**	**42.48**	**<0.001**	**100.80**	**49.98**	**0.044**
Joint space narrowing	-95.74	52.55	0.068	**-309.66**	**67.86**	**<0.001**
MRI-features						
Cartilage grade	47.43	71.00	0.504			
Osteophytes	**334.04**	**46.79**	**<0.001**	**299.55**	**47.72**	**<0.001**
Bone marrow lesions	**127.82**	**47.79**	**0.007**	68.31	46.72	0.144
Subchondral cysts	174.55	125.23	0.163			

Table 4b: Trend analysis of the normalized cartilage volume (mm^3) of the medial tibia

	Univariate analysis			**Multivariate analysis (<0.1 included) n=1714 (98.4%)**		
	ß	**se**	**P**	**ß**	**Se**	**P**
Age	**-7.95**	**2.12**	**<0.001**	**-9.14**	**2.08**	**<0.001**
BMI	**10.80**	**1.71**	**<0.001**	**9.11**	**1.66**	**<0.001**
Pain	**39.74**	**16.07**	**0.013**	20.81	15.52	0.180
Radiographs						
K&L grade	**29.51**	**14.52**	**0.042**	-21.89	15.56	0.159
Osteophytes	**58.41**	**12.16**	**<0.001**	**60.10**	**13.76**	**<0.001**
Joint space narrowing	-15.32	16.21	0.345			
MRI-features						
Cartilage grade	**-60.42**	**22.08**	**0.006**	**-116.46**	**17.02**	**<0.001**
Osteophytes	**100.10**	**19.64**	**<0.001**	**77.16**	**19.50**	**<0.001**
Bone marrow lesions	**45.49**	**22.13**	**0.040**	30.04	22.53	0.182
Subchondral cysts	49.02	25.44	0.054	34.25	24.07	0.155

Table 4c: Trend analysis of the normalized cartilage volume (mm^3) of the patella

	Univariate analysis			**Multivariate analysis (<0.1 included) n=1724 (99.0%)**		
	ß	**se**	**P**	**ß**	**se**	**p**
Age	**-36.58**	**5.66**	**<0.001**	**-34.91**	**5.68**	**<0.001**
BMI	**12.00**	**5.89**	**0.041**	**13.53**	**5.76**	**0.019**
Pain	13.91	47.08	0.768			
MRI features						
Cartilage grade	**-122.53**	**43.28**	**0.005**	**-95.71**	**44.56**	**0.032**
Osteophytes	-28.23	52.64	0.592			
Bone marrow lesions	-24.04	60.57	0.691			
Subchondral cysts	-101.61	59.63	0.088	-37.11	61.97	0.549

DISCUSSION

In this cross-sectional study of 882 women, our hypothesis of a lower cartilage volume with increased severity of radiographic and MRI features could only partly be rejected; a positive trend was found for cartilage volume with osteophytes in the medial femur. The cartilage volume of all compartments was lower with increasing age. There was a negative relationship between cartilage volume and JSN for the medial femur. For the medial tibia, a negative trend was found for cartilage degeneration and a positive trend for BMI and osteophytes (scored on radiographs and MRI). For the patella, a negative trend was found for cartilage degeneration and a positive trend for BMI. The cartilage volume showed no significant change with severity of K&L grade and pain.

Several studies support our finding of lower cartilage volume with increasing age.[13,23] Ding et al. found a decrease in cartilage volume of the patella with aging, but not in the medial tibia.[24]

Most studies found a decrease in cartilage volume with increasing BMI.[13,25] Over a 2.3 year period, Antony et al., showed that this relation was only present in subjects with greater baseline cartilage volume.[26] Because the present study is cross-sectional no statement can be made about changes in volume. The study population is relatively healthy with a relatively high number of individuals with a K&L score of grade 0 and 1 compared to grades 2-4. It is possible that the positive trend we found represents the trend 'from healthy to borderline or possible OA', whereas the trend 'from healthy to severe OA' is outweighed. Because we analysed the separate K&L grades, the positive trend is seen in the K&L grade 0 and 1 for the cartilage volume in the medial tibia, but not for K&L grade 2 or higher (data not shown). It was not possible to perform the same analysis for the patella, because we had no radiographs of the patella and thus no K&L scores for the PFJ.

In accordance with similar reports, a lower cartilage volume was seen with increasing severity of JSN on radiographs.[10-11,27-28] Similarly, as in other studies, a lower cartilage volume is seen with increasing severity of cartilage degeneration in the medial tibia and the patella.[7,27] In a 2.7 year follow-up study, Dore et al. reported significantly more

cartilage volume loss in the presence of cartilage defects at baseline in the medial tibia, but not in the medial femur.[14]

The positive trend of osteophyte severity and cartilage volume in the medial femur and medial tibia has not been reported previously, i.e. there are no reports on a positive association between osteophyte severity and cartilage volume.[10] Nevertheless, it is not entirely surprising that we found such a relationship in our relatively healthy population. It is known that an osteophyte is covered with cartilage.[29-30] In our relatively healthy/young population, only 2% had (definite) cartilage defects seen on MRI. Therefore, the cartilage may not yet have deteriorated in this population or, possibly, there was even more cartilage due to the osteophytes.

In our analysis we used the osteophytes- and JSN-scores of the whole tibiofemoral compartment (medial and lateral together). In a part of the knees we scored these features apart for medial and lateral compartment. Analysis in this selection of knees (n=557) with only the medial osteophytes and medial JSN did not change the results (data not shown).

The fact that we found no significant difference in volume with increased severity of K&L grade is in line with others. Reichenbach et al.[12] found no difference in cartilage volume on MRI between mild radiographic OA (K&L=2) and non OA individuals (K&L=0), whereas Harada et al. found a decrease in cartilage volume of medial femur and medial tibia with increased K&L grade.[17] This difference might be due to differences in the study populations. Harada et al. included men and women with more severe OA in the knee; 70% of the population had a K&L≥2, compared to 18% of the female population that participated in the study of Reichenbach et al. and 4.4% in the female population in the present study.[12,17] The K&L scale is described as having both osteophytes and JSN, which have an opposite relationship with cartilage volume. This might also explain why we found no relation with severity of K&L grades. In addition, in an earlier study of the shape of the knee we found that knees with OA have wider tibial and femoral bones. The wider tibial and femoral bones were significantly related to higher K&L grades, a narrower joint space, to osteophytes and also to cartilage defects.[31] In the present study we did not find a relation with K&L severity, after we normalized the cartilage volume by the tibial width, but we did so without normalization. With the present more extended study population and another measurement for tibial width we still found the relation between the tibial width and the K&L grades (data not shown). In follow-up data we have to investigate if bones get wider and concurrent decrease in cartilage volume with progression of the disease.

In the multivariate analysis we found no significant trend for BML, which is consistent with Guymer et al. and Baranyay et al., who also reported no significant association between BMLs and cartilage volume of the medial tibia in their cross-sectional studies.[15-16]

To the best of our knowledge, this is the first study to use this fully-automatic method to quantify the cartilage volume in ≥1,700 knees in the medial femur, medial tibia and patella. Our cartilage volume measures were in line with the literature.[7,11-14,23,25,28,32] The automatic MRI framework was previously validated for the medial compartment on low-field MRI. In the present study, we extended the method to cover the patella and also validated its use on high-field MRI (1.5T). Automatic quantification of cartilage

volumes is feasible for high-field MRI, also for the patella.

The present study has several limitations. The first is the moderate correlation of the cartilage volumes between the manual segmentations and the automatic segmentations of the medial tibia. This might have led to an over- or underestimation of the relations between the cartilage volume of the medial tibia and the determinants investigated. Thus, these results have to be interpreted with caution. Another limitation is the low inter-rater reliability of the semi-quantitative scoring for osteophytes and BML in the patella. In our analysis we used the scores of the reader who, on assessment of the inter-rater agreement, was more conservative in scoring osteophytes and BMLs than the other reader. This could have led to an underestimation of the associations. Furthermore, the MRI protocol was not optimized for robust automatic quantifications of the cartilage alone, since we also wanted to use the images for semi-quantitative scoring and for assessing quantitative measures of the bone. In combination with a limited scan time and the use of a cardiac coil that enabled bilateral knee imaging (but less optimal than a dedicated knee coil), this could have influenced the quality of the images and, therefore, assessment of cartilage volume. Finally, the present study is unable to draw conclusions about causality due to its cross-sectional design.

In conclusion, the automatic cartilage quantification method applied to a FIESTA sequence on high-field MRI (1.5T) can provide automatic segmentation and cartilage quantification of the medial femur, the medial tibia and the patella. The hypothesis of a lower cartilage volume in the medial femur, medial tibia and patella with increased age and severity of radiographic and MRI features appeared to be accurate for cartilage degeneration and JSN, but was not confirmed for osteophyte severity and increasing BMI. No significant differences were found in the association with K&L severity, BML and cysts.

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Chapter 9

Variation in joint shape of osteoarthritic knees

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ABSTRACT

Objective: Currently, no osteoarthritis biomarker exists that is sufficiently robust for use in clinical trials. Considering that bone is involved in osteoarthritis, the shape of the knee on radiographs might be a potential source for novel biomarkers. To investigate this potential, we determined which aspects of bone shape are different in osteoarthritic knees compared to controls.

Methods: Using a Statistical Shape Model we compared knee shape on radiographs of osteoarthritic knees to the shape of control knees in a population of 609 females. Furthermore, we compared shape in knees with cartilage defects to knees without these defects as examined on MRI.

Results: Three Statistical Shape Modes, referring to three distinct aspects of the shape of the knee were significantly associated with the presence of radiologic osteoarthritis (mode 2, 4 and 15). Mode 2 reflected the width of the femoral and tibial bone, which was larger in osteoarthritic subjects. Furthermore, knees with cartilage defects had a wide femoral and tibial bone compared to knees without defects. Mode 4 reflected the variation in flexion of the knee during radiography. Osteoarthritic knees were more extended compared to controls. Mode 15 showed that osteoarthritic subjects had an elevated lateral tibial plateau, which was associated with pain.

Conclusion: In women, knees with osteoarthritis were wider, more extended during radiography and had an elevated lateral tibial plateau. These results show that the shape of the knee plays a definite role in osteoarthritis, which might lead to novel imaging biomarkers to monitor or predict knee OA.

INTRODUCTION

Osteoarthritis (OA) is an inherently complex disease which arises due to an interaction between various systemic and local (biomechanical) factors. One of these local factors is the shape of a joint, which dictates its biomechanical behaviour. Typical examples of malformations in a joint that biomechanically compromise cartilage loading and lead to OA are dysplasia of the hip[1] and malalignment of the knee.[2] Another example is impingement of the hip joint due to a cam-type deformity in the femoral head-neck junction or a pincer-type deformity of the acetabular roof.[3]

In the hip, the effect of joint geometry on the development of OA has been investigated in more detail. Some studies used direct measures on radiographs to show that shape features like the asphericity of the femoral head and the neck-shaft angle associate to the presence of OA.[4] Alternatively, other studies used Statistical Shape Modeling to investigate the complete shape of the proximal femur or the entire hip joint on radiographs and showed that several distinct varieties in hip joint geometry associate to OA.[5,6] A difficulty in analyzing the involvement of shape of the joints in OA is that shape can both play a role in the initiation of OA and be changed by the OA process itself.

Changes in bone also occur in the knee joint.[7] The results of animal studies suggested that these changes in bone occur in the early phases of the disease.[8,9] Studies that investigate the role of shape of the knee joint are limited so far. Most attention has been paid to the flattening and widening of the tibial plateau in OA.[10] The objective of this study was to determine aspects of bone shape in the knee that relate to OA in a population based cohort of women. We assessed which aspects of the shape of radiographic defined OA knees were different from control knees and whether the presence of these shape aspects depend on severity of OA as determined from radiographs and MRI.

METHODS

Study population

All subjects were participants in the population based Rotterdam study, from the third cohort RS-III-1.[11] The Rotterdam Study is a prospective cohort study, in which the incidence and risk factors for chronic disabling diseases were investigated. Inclusion criteria for the RS-III-1 cohort were age 45 years and over, and living in the Ommoord district of Rotterdam, the Netherlands. For this particular cross-sectional study all women (aged 45-65 years) with MR scan of the knees, available on March 1st 2009, were selected.

Data assessment

In the RS-III-1 cohort, data on various domains is collected. Besides demographic data, we asked for the presence of pain in the knee in the last 12 months and the severity of pain (in left and right knee separately) using the Visual Analog Scale (VAS).

Radiographs

For this study, we used conventional radiographs obtained at baseline to assess shape and radiographic OA status. All radiographs of the knees were weight-bearing antero-posterior (AP) radiographs taken at 70 KV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT). Radiographs of the extended knees were obtained with the patella in central position. Two trained readers who were blinded for clinical data scored all radiographs. The Kellgren & Lawrence scoring (K&L 0-4) was used as combined score for severity of OA features. In addition all radiographs were scored with semi-quantitative scoring for all OA features separately (joint space narrowing, osteophytes, sclerosis, cysts and joint deformity). Interobserver ICC values were: K&L=0.76, JSN, Osteopytes=0.72.

MR imaging

We performed a multi-sequence MRI protocol in a sagittal plane on a 1.5T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin). The knees of all participants were scanned using an 8-channel cardiac coil, so two knees could be scanned in one session by re-localizing. The multi-sequence protocol contained: a fast spin echo (FSE) proton density/T2 weighted sequence, a FSE T2 weighted fatsat sequence, a spoiled gradient echo sequence and a Fiesta C-T1/T2 weighted sequence. Total scanning time was 27 minutes for two knees.

One experienced reader examined the MR scans. Diffuse cartilage defects were scored in each compartment (medial femur, lateral femur, medial tibia and lateral tibia) separately. Possible scores were 0 (no defect), 1 (minimal defect), 2 (moderate defect) and 3 (severe defect). We added the scores for all compartments resulting in a total cartilage score with range 0-12 and defined absence of cartilage defects when this score was zero. A score of one or higher was defined as presence of cartilage defects. Interobserver ICC values for cartilage defect scores were 0.64.[12]

Statistical shape model

To analyze the shape of the knee on AP radiographs, we used Statistical Shape Models (SSM). A SSM separates all variation in shape of, in this case, the knee into distinct aspects of shape that are present in a population. The model consists of quantitative modes that each relate to a different shape aspect and which values describe the extent to which each aspect is present in an individual knee. To construct a SSM of the knee we used the freely available Active Shape Models (ASM) toolkit (Manchester University, Manchester, UK).

In our extensive 105 points model that described the total knee, we outlined the contours of the femoral and tibial bone, the patella and the back of the medial femoral condyl (Figure 1).

Radiographs of insufficient quality were left out of the model.

After all radiographs were processed, the software overlays the contours of all radiographs at the mathematical center. The contours are corrected for size and rotation to obtain

an optimal fit. Through Principal Component Analysis (PCA), the software produces independent modes of shape variation. In short, a covariance matrix of the matrix containing the coordinates of each landmark point for each image is computed. This covariance matrix is decomposed into its eigenvectors. These eigenvectors represent the different modes, while the mode values are obtained by multiplying the eigenvectors with the original data matrix. Each mode is thus expressed numerically, where 0 denotes the mean shape and negative and positive values represent the deviance from this mean, in either direction. These mode values can then be analysed with statistical software.
We retained enough modes to describe 95% of the shape variation in the study population.

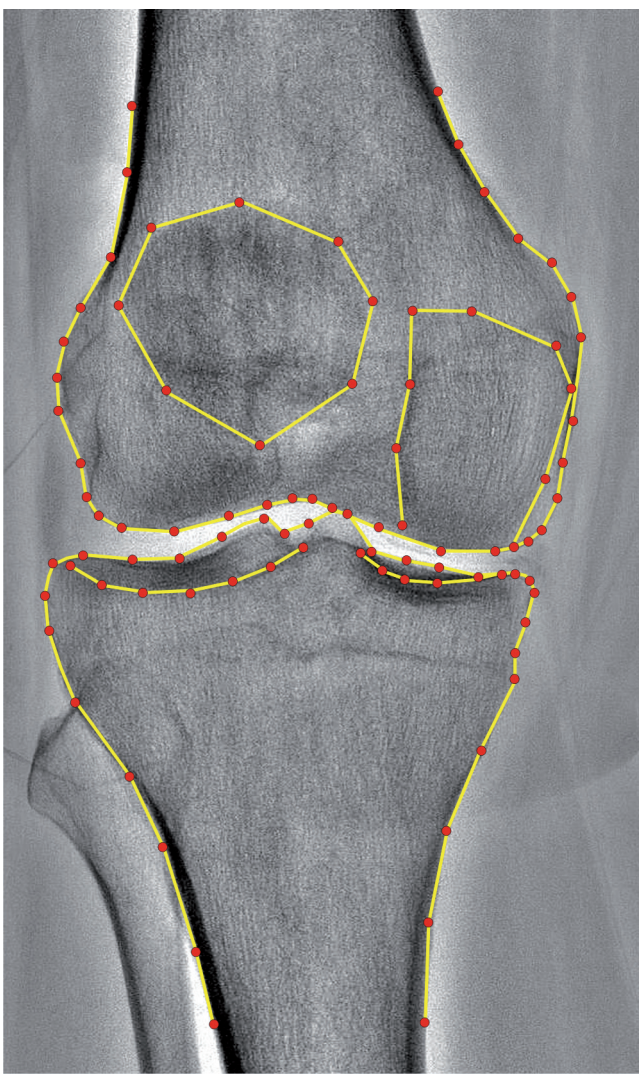

Figure 1: Statistical Shape Model knee. Definition of the Statistical Shape Model, consisting of 105 points along the contours of the femur, tibia, patella and the backside of the medial condyle.

Statistical analysis

We tested the association between the various shape modes and the presence of OA (K&L≥2) using a logistic Generalized Estimating Equations (GEE) regression model, which takes into account the correlation between left and right knees within one person. We reported crude and adjusted odds ratios (OR) (adjusted for age and BMI) with 95% CI for one standard deviation change in mode value. We reported all modes with a p-value below 0.05. However, taking into account multiple testing, we used the Bonferroni correction by dividing the p-value (0.05) by the number of modes needed to describe 95% of the shape variation to obtain the threshold below which p-values were considered significant. For modes that gave a significant association with OA, we assessed the presence of a linear trend between mode values and increasing K&L grades, using linear GEE. Here, we combined cases with K&L grade 3 and 4 into one group because of the limited number of cases for the separate grades. The significance level for a linear trend was set at p=0.05.

Further, using linear GEE we tested if the modes with a significant association with radiographic OA (K&L≥2), were also different for knees with cartilage defects compared to knees without cartilage defects as apparent on MR images. In this model, mode value was the dependent variable (continuous); cartilage score (fixed factor) and K&L grades (covariate) were the independent variables. Cartilage score was significant in the model when $p<0.05$. All statistical analyses were performed in SPSS version 15.0.

RESULTS

Description of the study population

On March 1st 2009, MR scans of the knees were available of a total of 609 female participants of the RS-III-1 cohort (number of knees =1218). Due to exclusion criteria or missing data, we could use MR data of 1209 knees. Of the 1218 knee radiographs available, we could apply the SSM to 1206 knees. Reasons for missing data were incorrect radiographs (n=8) and previous surgical treatment (n=4). Combined, we had both MR data and shape models for 1201 knees. The average time between taking the radiographs and MR imaging was 13.3 months, ranging from 3.3 till 31.3 months. Table 1 shows demographic and cartilage data for each K&L grade separately.

In total, 70 knees had radiographic OA defined as K&L≥2. Although not significant, left knees were more often affected by OA compared to right knees (40 vs. 30, p=0.34). The range for total score of diffuse cartilage defects as seen in MRI scans was 0-12. The majority (n=1031 knees, 85.3% of total) had no diffuse cartilage defects in any compartment. In 128 non OA knees (87 knees with K&L grade 0; 41 knees with K&L grade 1) we observed some diffuse cartilage defects. In this group mean cartilage defect score was 2.4. In 24 OA knees (20 knees with K&L grade 2; 4 knees with K&L grade 3 or 4) we observed no diffuse cartilage defects. In the OA knees with cartilage defects, the mean cartilage defect score was 3.9. (32 knees with K&L grade 2; 15 knees with K&L grade 3 or 4).

Table 1: Characteristics for 1,206 knees (cartilage data for 1,201 knees)

	K&L=0	K&L=1	K&L=2	K&L=3/4	Total
No. of knees (%)	911 (75.5)	223 (18.5)	52 (4.3)	20 (1.7)	1,206 (100)
Age*	53.9 ± 3.9	54.9 ± 3.4	56.3 ± 3.0	55.7 ± 3.0	54.2 ± 3.8
BMI*	26.4 ± 4.6	27.3 ± 4.7	29.0 ± 5.3	35.7 ± 6.9	26.9 ± 4.99
No cartilage defects (%)	90.4	81.6	38.5	21.1	85.4
Total diffuse cartilage score**	0-8	0-6	0-10	0-12	0-12
No. of painful knees (%)	204 (22%)	59 (26%)	30 (58%)	9 (45%)	302 (25%)
VAS if pain present (#)	4.8 (1-8)	5.0 (1-8)	5.3 (1-10)	7.4 (6-9)	5.0 (1-10)

Characteristics of 1206 knees included in the analysis. * Mean ± SD; ** Range

Shape modes

To describe 95% of the shape variation, 24 modes (0-23) were retained. To correct for multiple testing, this led to a p-value of 0.05/24 = 0.002 as the threshold for statistical significance.

The amount of variation in knee shape described by the SSM ranged from 46.4% (mode 0) to 0.02% (mode 23).

Relation of shape with radiographic OA

Mode 2, 4 and 15 were significantly associated with the presence of knee OA (Table 2). After adjustment for age and BMI, these associations remained statistically significant (all p<0.001). Associations with age, BMI and separate K&L features are shown in table 3.

Table 2: Association between the presence of OA (K&L≥2) and mode values in 1,206 knees

	Unadjusted			Adjusted*		
	OR	95% CI	p-value	OR	95% CI	p-value
Mode 1	1.14	(0.95-1.38)	0.165	1.25	(1.00-1.54)	0.047
Mode 2	**2.03**	**(1.55-2.66)**	**<0.001**	**1.94**	**(1.44-2.62)**	**<0.001**
Mode 3	1.43	(1.08-1.89)	0.013	1.51	(1.12-2.05)	0.008
Mode 4	**1.81**	**(1.38-2.38)**	**<0.001**	**1.62**	**(1.25-2.10)**	**<0.001**
Mode 6	1.67	(1.18-2.37)	0.004	1.43	(1.01-2.02)	0.047
Mode 9	1.35	(1.04-1.74)	0.023	1.37	(1.04-1.80)	0.025
Mode 13	1.37	(1.05-1.77)	0.019	1.38	(1.05-1.80)	0.020
Mode 15	**1.67**	**(1.31-2.11)**	**<0.001**	**1.67**	**(1.27-2.20)**	**<0.001**
Mode 21	1.47	(1.11-1.94)	0.007	1.35	(1.01-1.81)	0.046

Only those modes are listed for which the association resulted in adjusted p-values <0.05.
Values are the odds ratios (OR), 95% confidence intervals (95% CIs) and p-values from the Generalized Estimating Equations (GEE) models for OA with standardized modes value as independent variable.
* Adjusted for age and body mass index (BMI, kg/m^2). Bold denotes statistically significant result (p<0.002).

Table 3: Assocation between the significant modes and demographics and K&L features

	Age	BMI	JSN	Osteophytes	Sclerosis	Joint deformity	Pain presence	VAS score
Mode 2	**0.003**	0.220	**<0.001**	**<0.001**	0.083	**0.037**	0.155	0.167
Mode 4	0.456	**<0.001**	0.278	**<0.001**	**0.016**	**<0.001**	0.915	0.641
Mode 15	0.240	0.760	**0.003**	**<0.001**	0.070	**<0.001**	**0.001**	**0.002**

Values are p-values for univariable linear GEE models with mode value as dependent variable and age, body mass index (BMI, kg/m^2) or K&L features as dependent variables. Bold denotes a statistically significant result.

Mode 2

Mode 2 (3.7% of shape variation) reflects the width of the femoral and tibial bone (figure 2A). OA knees have a significantly lower value for mode 2 compared to control knees, which corresponds to a wider femoral and tibial bone. Mode values decrease with increasing K&L grade (linear GEE, p<0.001; Figure 3A).

Both a narrow joint space width and the presence of osteophytes were significantly related to low mode 2 values (p<0.001) whereas sclerosis was not associated (p=0.083). For joint deformity, this association was slightly stronger (p=0.037).

Knees with cartilage defects exhibited lower mode 2 values, corresponding to a wider femoral and tibial bone, compared to knees without these defects (p<0.001, Figure 3A). We observed this difference for all K&L grades.

Mode 2 values were not associated with the presence (p=0.155) or the severity of pain (p=0.167).

Mode 4

Mode 4 (2.1% of shape variation) appears to represent the variation in amount of flexion in the knee when the radiograph was taken (Figure 2B). Mode 4 values are significantly higher in OA knees compared to control knees (Table 2), which corresponds to more extended knees at the moment the radiograph was taken. This mode value also increases with increase of K&L grade (linear GEE, p<0.001, Figure 3B).

Although the presence of osteophytes was associated (p<0.001), joint space narrowing was not associated with mode 4 (p=0.278). For joint deformity we observed a strong relationship (p<0.001). Sclerosis was mildly associated (p=0.016) with the amount of extension.

Mode 4 values were not different between the two cartilage groups (p=0.273). The presence and severity of pain were also not associated with this shape feature (p=0.915 and p=0.641 respectively).

Mode 15

Mode 15 (0.1% of shape variation) reflects a combination of subtle variations in shape. The most obvious variation is the shape of the lateral tibial plateau which is elevated at high mode values (figure 2C). This shape feature of the lateral tibial plateau is particularly present in OA knees. Mode values increase with K&L grade in a linear model (linear

GEE, p<0.001, Figure 3C).
Both joint space narrowing and osteophytes (p=0.003 and p<0.001 respectively), as well as joint deformity (p<0.001) were significantly related to mode 15. An elevated lateral tibial plateau was, however, not associated with sclerosis (p=0.070).
Mode 15 values were not different for knees with cartilage defects compared to knees without these defects.
An elevated lateral tibial plateau was significantly associated with the presence of pain (p=0.001). Furthermore, the shape of the lateral tibial plateau (a higher mode 15 value) was associated with the severity of pain, as measured by VAS (p=0.002).

DISCUSSION

In this cross-sectional study of 882 women, our hypothesis of a lower cartilage volume with increased severity of radiographic and MRI features could only partly be rejected; a positive trend was found for cartilage volume with osteophytes in the medial femur. The cartilage volume of all compartments was lower with increasing age. There was a negative relationship between cartilage volume and JSN for the medial femur. For the medial tibia, a negative trend was found for cartilage degeneration and a positive trend for BMI and osteophytes (scored on radiographs and MRI). For the patella, a negative trend was found for cartilage degeneration and a positive trend for BMI. The cartilage volume showed no significant change with severity of K&L grade and pain.
Several studies support our finding of lower cartilage volume with increasing age [13,23] Ding et al. found a decrease in cartilage volume of the patella with aging, but not in the medial tibia.[24]
Most studies found a decrease in cartilage volume with increasing BMI.[13,25] Over a 2.3 year period, Antony et al., showed that this relation was only present in subjects with greater baseline cartilage volume.[26] Because the present study is cross-sectional no statement can be made about changes in volume. The study population is relatively healthy with a relatively high number of individuals with a K&L score of grade 0 and 1 compared to grades 2-4. It is possible that the positive trend we found represents the trend 'from healthy to borderline or possible OA', whereas the trend 'from healthy to severe OA' is outweighed. Because we analysed the separate K&L grades, the positive trend is seen in the K&L grade 0 and 1 for the cartilage volume in the medial tibia, but not for K&L grade 2 or higher (data not shown). It was not possible to perform the same analysis for the patella, because we had no radiographs of the patella and thus no K&L scores for the PFJ.
In accordance with similar reports, a lower cartilage volume was seen with increasing severity of JSN on radiographs.[10-11,27-28] Similarly, as in other studies, a lower cartilage volume is seen with increasing severity of cartilage degeneration in the medial tibia and the patella.[7,27] In a 2.7 year follow-up study, Dore et al. reported significantly more cartilage volume loss in the presence of cartilage defects at baseline in the medial tibia, but not in the medial femur.[14]

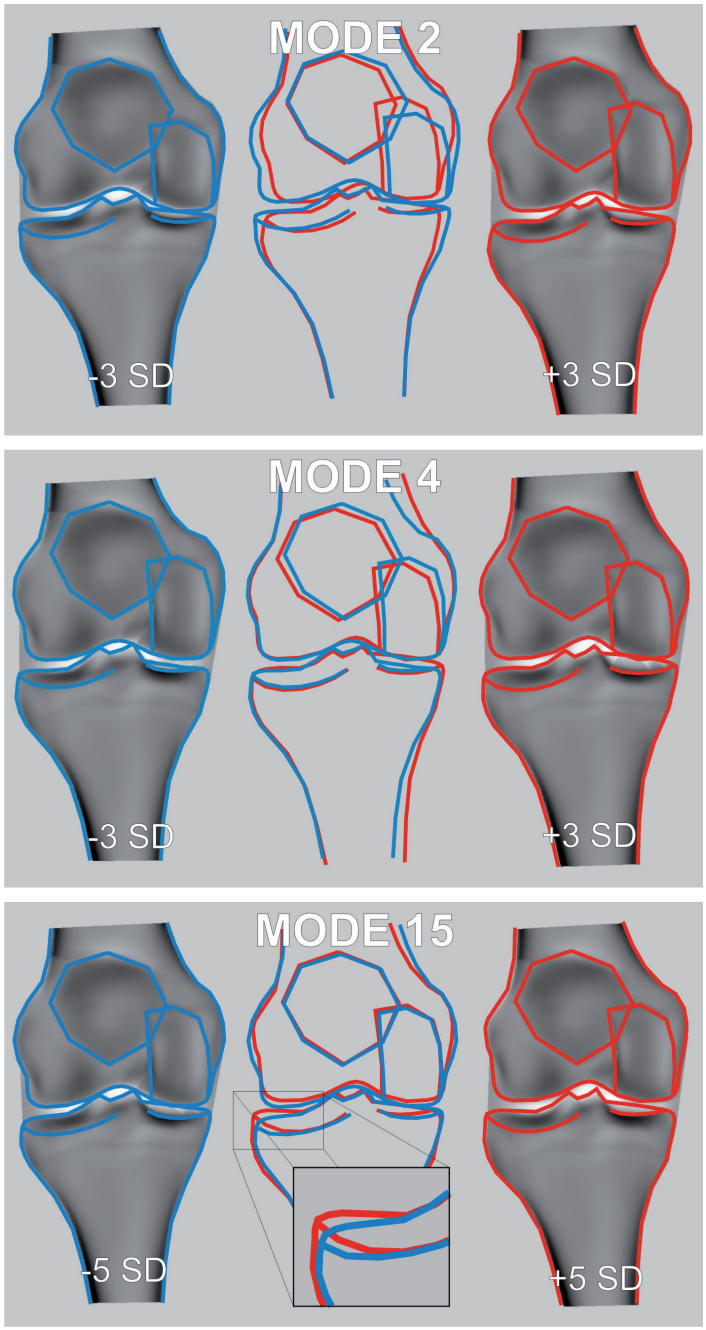

Figure 2: Mode descriptions. Visual representation of the modes that associated with OA. Left and right images show the two opposite extremes in the specific variation described by the mode, while the center shows the extremes overlaid as contours. A) Mode 2 at ±3 standard deviation. B) Mode 4 at ±3 standard deviation. C) Mode 15 at ±5 standard deviation.

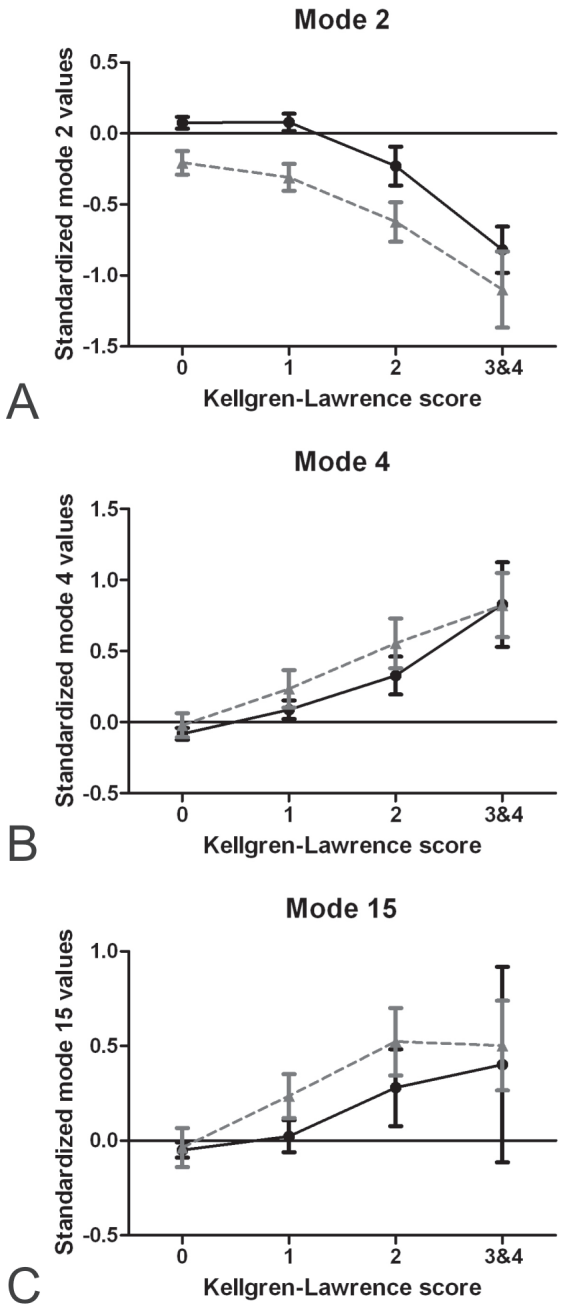

Figure 3: Mode values and K&L grades. Mode values as a function of K&L-score, separated into knees with and without cartilage damage for A) mode 2, B) mode 4 and C) mode 15. Error bars represent standard errors of the mean.

The positive trend of osteophyte severity and cartilage volume in the medial femur and medial tibia has not been reported previously, i.e. there are no reports on a positive association between osteophyte severity and cartilage volume.[10] Nevertheless, it is not entirely surprising that we found such a relationship in our relatively healthy population. It is known that an osteophyte is covered with cartilage.[29-30] In our relatively healthy/young population, only 2% had (definite) cartilage defects seen on MRI. Therefore, the cartilage may not yet have deteriorated in this population or, possibly, there was even more cartilage due to the osteophytes.

In our analysis we used the osteophytes- and JSN-scores of the whole tibiofemoral compartment (medial and lateral together). In a part of the knees we scored these features apart for medial and lateral compartment. Analysis in this selection of knees (n=557) with only the medial osteophytes and medial JSN did not change the results (data not shown).

The fact that we found no significant difference in volume with increased severity of K&L grade is in line with others. Reichenbach et al.[12] found no difference in cartilage volume on MRI between mild radiographic OA (K&L=2) and non OA individuals (K&L=0), whereas Harada et al. found a decrease in cartilage volume of medial femur and medial tibia with increased K&L grade.[17] This difference might be due to differences in the study populations. Harada et al. included men and women with more severe OA in the knee; 70% of the population had a K&L≥2, compared to 18% of the female population that participated in the study of Reichenbach et al. and 4.4% in the female population in the present study.[12,17] The K&L scale is described as having both osteophytes and JSN, which have an opposite relationship with cartilage volume. This might also explain why we found no relation with severity of K&L grades. In addition, in an earlier study of the shape of the knee we found that knees with OA have wider tibial and femoral bones. The wider tibial and femoral bones were significantly related to higher K&L grades, a narrower joint space, to osteophytes and also to cartilage defects.[31] In the present study we did not find a relation with K&L severity, after we normalized the cartilage volume by the tibial width, but we did so without normalization. With the present more extended study population and another measurement for tibial width we still found the relation between the tibial width and the K&L grades (data not shown). In follow-up data we have to investigate if bones get wider and concurrent decrease in cartilage volume with progression of the disease.

In the multivariate analysis we found no significant trend for BML, which is consistent with Guymer et al. and Baranyay et al., who also reported no significant association between BMLs and cartilage volume of the medial tibia in their cross-sectional studies.[15-16]

To the best of our knowledge, this is the first study to use this fully-automatic method to quantify the cartilage volume in ≥1,700 knees in the medial femur, medial tibia and patella. Our cartilage volume measures were in line with the literature.[7,11-14,23,25,28,32] The automatic MRI framework was previously validated for the medial compartment on low-field MRI. In the present study, we extended the method to cover the patella and also validated its use on high-field MRI (1.5T). Automatic quantification of cartilage volumes is feasible for high-field MRI, also for the patella.

The present study has several limitations. The first is the moderate correlation of the

cartilage volumes between the manual segmentations and the automatic segmentations of the medial tibia. This might have led to an over- or underestimation of the relations between the cartilage volume of the medial tibia and the determinants investigated. Thus, these results have to be interpreted with caution. Another limitation is the low inter-rater reliability of the semi-quantitative scoring for osteophytes and BML in the patella. In our analysis we used the scores of the reader who, on assessment of the inter-rater agreement, was more conservative in scoring osteophytes and BMLs than the other reader. This could have led to an underestimation of the associations. Furthermore, the MRI protocol was not optimized for robust automatic quantifications of the cartilage alone, since we also wanted to use the images for semi-quantitative scoring and for assessing quantitative measures of the bone. In combination with a limited scan time and the use of a cardiac coil that enabled bilateral knee imaging (but less optimal than a dedicated knee coil), this could have influenced the quality of the images and, therefore, assessment of cartilage volume. Finally, the present study is unable to draw conclusions about causality due to its cross-sectional design.

In conclusion, the automatic cartilage quantification method applied to a FIESTA sequence on high-field MRI (1.5T) can provide automatic segmentation and cartilage quantification of the medial femur, the medial tibia and the patella. The hypothesis of a lower cartilage volume in the medial femur, medial tibia and patella with increased age and severity of radiographic and MRI features appeared to be accurate for cartilage degeneration and JSN, but was not confirmed for osteophyte severity and increasing BMI. No significant differences were found in the association with K&L severity, BML and cysts.

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Chapter 10

General discussion

GENERAL DISCUSSION

The overall aim of this thesis was to evaluate the different classification criteria of knee osteoarthritis (OA) and to identify radiographic and magnetic resonance imaging (MRI) features that are related to the different aspects of clinical symptoms and risk factors of (early) knee osteoarthritis. A part of this evaluation (**Chapter 5**) was done using the baseline data of the first cohort of the Rotterdam study (RS-I-1) and using the baseline data of the third cohort of the Rotterdam Study (RS-III-1) (**Chapter 4**); however, most of this evaluation was done using the data of all females of RS-III-1, that we referred to as the nested cohort study (**Chapters 6-9**). The relatively young and healthy female population of the nested cohort study provides the opportunity to see how OA is defined by the different classification criteria, and how OA-related radiographic and MRI features appear in the early stages of knee OA. In addition, differences in these features might emerge in the presence of different risk factors. This final chapter summarizes the findings from this thesis and discusses the results in a broader context. Also addressed are the implications of the findings for clinical practice and future research.

The main findings of this thesis are that the intra- and interrater reliability of the 25 different classification criteria is good, but the validity (discrimination between healthy and diseased, relationship with known risk factors, representation of all facets of knee OA) of the criteria is questionable. As expected, the construct validity (discrimination between healthy subjects and subjects with knee OA) of the radiological classification criteria is low when compared with the clinical classification criteria, and vice versa (**Chapter 2**).

The various descriptions of the most frequently used radiological classification criteria, i.e. the Kellgren and Lawrence (K&L) classification criteria, have particular impact on the distribution of knees with different grades of OA in the lowest grade (K&L=1). The association with knee complaints shows no significant difference between the different descriptions, but is strongest for the original description and one alternative. The decision as to which description can best be used for a study, depends on the purpose for which it is required (**Chapters 3 and 4**).

Being a female, having widespread pain and reporting general health complaints are determinants for knee pain, but are not specific for a particular grade of radiographic knee OA. Depression and hip OA were determinants for knee pain only in those knees without any sign of OA. Morning stiffness is a determinant for knee pain, even in knees without radiographic signs of knee OA. This could indicate that morning stiffness in combination with knee pain is a symptom of knee OA in early phase (**Chapter 5**).

Two risk factors (history of knee injury and Heberden's nodes) were associated with a specific location [i.e. the lateral tibiofemoral joint (TFJ) and medial TFJ, respectively] of OA features in the knee, and none of the risk factors was discriminative for a specific type of damage. In this relatively young study population, overweight and age are the most important risk factors for structural damage that can be identified on MRI (**Chapter 6**).

Additional evidence for the importance of the patellofemoral joint (PFJ) for OA is found in the clinical symptoms crepitus and history of patellar pain. These symptoms indicate OA lesions seen on MRI at the PFJ, but not at the TFJ (**Chapter 7**).

Cartilage volume was lower in women with a higher age, with more severe grades of cartilage degeneration, and severity of JSN, whereas higher cartilage volumes were seen with higher BMI and severity of osteophytes in this relatively healthy female population (Chapter 8). In addition, wider bones, extended knees and an elevated lateral tibial plateau were associated with radiographic osteoarthritic knees (K&L≥2). These altered shape aspects were also associated with pain. Apparently, subtle shape alterations of the knee play an important role in OA (**Chapter 9**).

Classification criteria

In our review (**Chapter 2**) we showed that 25 different definitions for OA were used in 18 epidemiological studies. These differences in classification criteria lead to differences in the prevalence and incidence in knee OA, and also hamper performing a large meta-analysis and making comparisons between study populations in the literature. Researchers on OA worldwide need to reach consensus as to which definition should be used for clinical OA and which for radiographic OA. Our review did not include studies with MRI definitions, because no cut-off for MRI-defined OA has yet been established. Recently, Hunter and colleagues developed and presented a consensus for a cut-off for knee OA based on MRI features.[1] However, the definition of OA on MRI needs to be further tested and validated, especially with respect to early-stage disease.

Radiographic classification criteria

K&L classification criteria

The most widely used radiographic classification criteria are the Kellgren and Lawrence (K&L) classification criteria; moreover, they are probably the most criticized criteria. Nevertheless, the World Health Organization (WHO) adopted them as standard criteria for the radiological classification of OA. The criticism arises due to the lack of agreement with clinical criteria of OA; however, we observed that all radiographic criteria are of questionable validity when compared with clinical definitions of OA. The K&L criteria are also widely criticized due to the differences in the descriptions of the grades. We summarized the different descriptions used in epidemiological studies (**Chapter 3**) and investigated the impact of these different descriptions in an open population of 3,071 people (**Chapter 4**). Our conclusion was that the decision as to which description can best be used, depends on the purpose for which it is required. For example, for clinical or epidemiological research, if the purpose is to distinguish between knees without (or with doubtful) OA and knees with OA (mild or moderate/severe), the cut-off is K&L grade 2. The different descriptions do not have a significant impact on the distribution of knees based on these cut-offs and are, therefore, of less importance. In comparing the radiographically defined OA knees with clinical symptoms of knee OA, the best definitions to use are the original description and alternative 3 (in both descriptions grade 2 is described as definite osteophytes and possible JSN). When aiming to distinguish knees with early or doubtful signs of knee OA (K&L grade 1) from healthy knees and knees with definite knee OA (K&L grade 2), it is more difficult to select the best description; this needs further investigation. Our conclusion was that the differences

in description mainly have an impact in the early stage of OA (grade 1) and that (in particular) in this first grade of OA the reproducibility of the original definition is low, due to the subjective interpretation of "possible osteophytic lipping".
It is questionable whether precise measurement of osteophytes will resolve this problem. Knee Images Digital Analysis (KIDA) is a method that quantifies individual radiographic features of knee OA in a raher standardized manner using a computer model.[2] and might therefore be more objective. However, for osteophytes the smallest detectable difference was relatively large compared to the other features, and the measurement will be influenced by the degree of mineralization of the osteophyte.[2]
Apart from difficulties in the reliability of scoring possible osteophytes, several researchers in the field of OA want to 'tone down' the importance of the osteophyte for the presence of knee OA. Felson et al. recently proposed a new definition for incidence of knee OA, [3] i.e., that the incidence of knee OA should be defined as a new-onset of K&L grade 2 in which the knee has to have both JSN and an osteophyte, with at least one of these being new.[3] The drawback of this proposed definition of incident knee OA, is that Felson et al. want to put knees with osteophytes only (and no JSN) into a separate category. In order to define prevalent knee OA, we recommend (**Chapter 4**) to use the original description (definite osteophytes and possible narrowing of joint space). However, using this recommendation, Felson et al. rightly point out that knees with large osteophytes and no JSN are thereby left unclassified. They suggest that to define prevalent knee OA "definite osteophytes (without narrowing)" needs to be a new grade.[3] In our population (**Chapter 4**) of more than 6,000 knees, only 4% had definite osteophytes and no JSN. This 4% was divided over different grades of K&L, most of them (55.8%) were defined as grade 1, some of them (31.7%) as grade 2, and a minority was classified as grade 0 (12.5%). We do not know how these knees will progress. This needs to be further investigated before we separate these knees from other categories. Furthermore, we have to keep in mind that the importance of joint space width (JSW) on radiographs might not be as great as it seems; on MRI it was shown that JSW can partly be explained by the position and degeneration of the meniscus.[4-5]

Type of X-ray
JSW can also be influenced by the position (extension versus flexion) of the knees during the radiographic acquisition. For the TFJ, the standard weight-bearing radiographic view in a clinical setting is: standing with fully extended knees, toes pointing straight ahead and weight evenly distributed over both feet.[6] A problem arises when considering the definition of 'full extension of the knees'. Full extension can vary between patients; even with repeated visits from one patient, this full extension can vary.[6] There is variation in the extension of the knees due to variation in the amount of soft tissue (between patients), and also due to variation in the level of pain (even within the same patient).[7] The variation in extension of the knees will lead to less reliable joint space width and narrowing. Therefore, for longitudinal assessment of OA of the TFJ, we recommend semi-flexed radiographs with the first metatarsophalangeal joint of each foot positioned immediately below and in line with the front edge of the film cassette, with the X-ray beam in line with the joint space at the back of the knee.[6] In our study population,

the radiographs of the knees are short-limb anteroposterior (AP) radiographs of extended knees. To some extent this limits the reliability of the JSW (or JSN) scores. In addition, much debate has focused on which planes and which combination of planes the radiographs should be made for scoring the features of OA. The knee consists of three compartments: the TFJ with a medial and lateral compartment, and the PFJ compartment. To define OA for the whole knee all compartments have to be assessed and more than one radiograph has to be taken. For the PFJ there are two options to view this joint, with a lateral view and with a so-called skyline view. With only the AP view, slightly more than 50% of the radiographic knee OA cases of a symptomatic population is detected. If one of the two views for the PFJ is added to the AP radiograph, the sensitivity for the radiographic knee OA is increased to about 90% and over.[8-9] Research in the UK showed that if both PFJ views were added to the AP view, especially the number of subjects with isolated PFJ OA increased considerably.[9] The definition of pain, the grading of radiographic severity, and the variation in study population (e.g. age, gender, ethnicity) all influence the estimates of an association between pain and radiographic OA.[10] A part of the lack of agreement between the radiographic and clinical definitions of OA also lies in the amount of different radiographic views used in the studies. A wide range in the increase in the prevalence of radiographic knee OA is seen when including lateral and/or skyline views to the AP radiograph of the symptomatic knees.[10] For example, in an open population the sensitivity of defining a symptomatic knee with radiographic knee OA increased from 38.1% to 62.3% due to inclusion of the patellofemoral radiograph.[11] This indicates that our radiographic data have some limitations due the limited number of knee radiographs. In **Chapter 4**, more participants with knee complaints would have been defined as having radiographic knee OA (especially isolated PFJ OA) had we added additional radiographic views. In a population with knee pain the proportion with isolated PFJ OA is approximately 24%.[9,12] In a population without knee pain the proportion is approximately 4%.[12] Therefore, in the study population described in Chapter 4, which had a very similar age and gender distribution as the studies mentioned above, 10% may have isolated PFJ OA: (24% of the participants with knee pain and 4% of the remaining population (901*24% + 2170*4%≈350 (≈10%)). In **Chapter 5**, neglecting isolated PFJ OA might have influenced the difference in the determinants of knee pain. There is a proportion of the population that has isolated PFJ OA, which is now classified as having no knee OA, or possible knee OA. Being able to define PFJ OA would have increased our power in (especially) the knees with definite and moderate to severe knee OA. In **Chapter 6**, the limitation of having only one view (the AP view), and missing the PFJ view (and therefore the undefined isolated PFJ OA), probably had an impact on the tested associations. In the selected population there will be a small number of isolated PFJ OA knees (K&L=0 based on the TFJ compartment). This resulted in a slightly higher prevalence of lesions on MRI in the PFJ, and probably in the association between pain and bone marrow lesions in the PFJ compartment.

Other aspects, such as bone shape

An aspect of radiographs which is underexposed in the knee, is the shape of the bone. There are differences in shape at an early stage that are associated with K&L grades,

osteophytes and JSN, i.e. wider femoral and tibial bones, and an elevated lateral tibial plateau are associated with all three features (**Chapter 9**). Furthermore, on the radiograph, osteoarthritic knees (K&L≥2) were more extended than non-osteoarthritic knees. This is in contrast to what is typically seen in OA, although the knees with OA that cannot fully extend are mostly painful knees[7] or knees with contractures in end-stage OA.[13] As our study population described in **Chapter 9** is relatively young and healthy, evident radiographic OA is not frequent (<5%) and most OA will probably be in an early stage.

Classification criteria based on MRI

Cartilage

A shortcoming of using radiographs in OA is the limited sensitivity to see or measure change in a feature of OA over time, and its inability to visualize tissues other than bone. In addition, the pathology seen in the joint structure only appears on radiographs in an advanced stage of the disease.[14] With MRI we can visualize the cartilage tissue itself, instead of joint space width or narrowing between the bony ends on radiographs. As described above, we now know that JSN, which is always assumed to be a surrogate measure for cartilage degeneration, could be partly explained by the position and degeneration of the meniscus.[4-5] Another advantage of the increasing use of MRI in epidemiological studies investigating OA, is that the gap between the structural changes and symptoms of OA becomes smaller. Other features, such as bone marrow lesions, effusion, and synovitis, which are not visible on a radiograph, do show associations with pain (**Chapters 6 and 7**).[15-16] Even in the knees without any radiographic sign of OA (K&L=0 for TFJ) this association was found for joint effusion in the whole knee and bone marrow lesions in the PFJ (**Chapters 6 and 7**).

Scoring systems

Scoring of the separate features on MRI is more extended than on radiographs, because more features are visible. Semi-quantitative whole-organ assessment has the ability to score the severity or grades of the degeneration of specific OA features visible on MRI, and lesion progression is more sensitive than on radiographs.[14] There are three semi-quantitative whole-organ scoring systems for knee OA, i.e. the KOSS (Knee Osteoarthritis Scoring System)[17], the BLOKS (Boston Leeds Osteoarthritis Knee Score)[18], and the WORMS (Whole-Organ Magnetic Resonance Imaging Score).[19] All scoring systems score more-or-less the same MRI features, but with small differences in the scoring methodology. At the time we started scoring the MRIs, the BLOKS method was not yet available. We decided to use the KOSS (**Chapters 6-9**) rather than the WORMS. Although the KOSS later became less widely used than the WORMS, [20-21] both showed good reproducibility and there was no consensus about which scoring system was the best.[17] Neither one of the scoring systems gave a cut-off for knee OA, and the KOSS gives no sum-score possibilities. Therefore, for the analyses in **Chapters 6-9** we used the separate lesion scores of each feature. More than 100 features were scored with the KOSS at nine locations: crista patella, medial and lateral patella facet, medial and lateral trochlea facet, medial and lateral femoral condyle, and the medial and lateral tibia plateau. We combined various scores in order to arrive at a set of features and,

possibly, made some arbitrary decisions. In hindsight, it would have been easier had we used the WORMS, as this is now more widely used and would simplify comparisons with other studies. A new semi-quantitative scoring system has been developed (the MRI Osteoarthritis Knee Score; MOAKS), based on the limitations identified in the existing tools.[22] This scoring system is likely to be used worldwide in future studies, instead of the KOSS or the WORMS.

Separate lesions
The separate lesion score provides insight into which feature is best associated with pain, and also which feature can be visualized first in case of OA. In our cross-sectional study (**Chapter 6**), we found no risk factor that was discriminative for a particular type of feature. This might be better visualized in the follow-up, planned for 5 years post-baseline (August, 2012), where we will see the changes in features within the same knee. Nevertheless, we found that a history of injury was associated with damage in the lateral TFJ, and that the presence of Heberden's nodes was associated with more damage in the medial TFJ.

Quantification
MRI has another advantage compared to radiography; it allows to observe the knee three- dimensionally instead of the two dimensions with radiography. This enables to quantify the volume of the structures in the knee. Although this quantification is time consuming, it may reveal possible changes that are small and not easily seen with the human eye. We looked at the volume of the cartilage using a fully-automatic method (**Chapter 8**), which was developed on low-field MRI but feasible for use on high-field MRI. Our hypothesis was only partly confirmed: with increasing age and more severe JSN the cartilage volume was lower. Counter-intuitively, however, with increasing severity of osteophytes and increasing BMI, the cartilage volume was higher. This result might be due to our relatively young and healthy population. In this population, with such a small number of women with definite knee OA and a much larger number of knees with possible OA (K&L=1), the effects we observed might be the effects between healthy, and possible or borderline OA. Other quantitative variables might provide more insight into this result. Recently, some quantitative measures have shown a good ability to distinguish between healthy and OA cartilage. Homogeneity of the cartilage (based on the signal intensity inside the cartilage compartment), and the curvature of the cartilage (the overall surface shape of the cartilage) are variables that can be quantified and may be promising biomarkers for identification of early knee OA.[23-24]

MRI Sequences
The selection of MRI sequences (used in **Chapters 6-9**) was based on a multiplicity of ideas. We wanted to assess the knees with semi-quantitative scoring for OA (KOSS parameters), in addition to quantitative assessment (e.g. automatic volume measure) of the cartilage and the trabecular bone. In combination with limited scan time and the use of a cardiac coil that enabled bilateral knee imaging (but less optimal than a dedicated knee coil), the selection of MRI sequences could have influenced the quality of the

images. A so-called FIESTA (fast-imaging employing steady-state acquisition) sequence was used for the automatic quantitative assessment, and for the scoring with the semi-quantitative criteria (in combination with the other sequences). It was recently concluded that the FIESTA sequence can not only be used for quantification of the cartilage, but also for the trabecular bone, and has good diagnostic performance in evaluating semi-quantitative lesions.[25-26] Therefore, we think that this FIESTA sequence in combination with the FSE (fast-spin echo) proton density and the FSE T2-weighted sequence with fat suppression gives a complete view for semi-quantitative and quantitative assessment of OA features in the knee. The choice for the cardiac coil, instead of the knee coil, was because many women were overweight (46% of the nested study population) and could not comfortably fit into a 'normal' knee coil.

Clinical classification criteria

Pain

Of the 25 different classification criteria, seven were clinical criteria (**Chapter 2**). Furthermore, four classification criteria were a combination of clinical criteria and radiological criteria. Knee pain is the symptom that is part of all clinical classification criteria, although it is defined in several ways. Apart from the explanation for the discordance between radiological and clinical criteria described above, this wide variation in pain definitions used is postulated as another explanation.[10,27] However, it is unrealistic to think that all discordance between the radiological and clinical criteria will disappear if we all use the same definition for pain. Pain in the knee can have causes other than the structural changes seen on radiographs. For example, in our study, pain associates independently (**Chapter 6**), as well as in other studies[16], with bone marrow lesions and intra-articular effusions. However, pain in the knee might also be due to other reasons, such as effusion and bone marrow lesions after injury, referred pain, soft tissue pathology of bursa or tendon, or simply overuse.[10,28] Furthermore, different pain phenotypes in OA have been described. Hawker et al. identified two different types of pain, a persistent 'background' pain and an intermittent, intense pain.[29] In addition, some patients with knee OA report burning pains and numbness, which are typically associated with peripheral nerve disease (neuropathic pain).[30] Even more central pain mechanisms might be present in OA, such as diffuse noxious inhibitory control and temporal summation.[31] All these different pain phenotypes have not yet been considered in the different associations between radiographic severity or MRI features of knee OA and pain, and might further fill the gap between the structural pathology of the OA and the clinical symptoms. In the study populations included in this thesis we do not have specific measures for pain, and could not distinguish between these separate phenotypes. However, non-weightbearing pain and weightbearing pain seem to differ from one another[32] and will be further elucidated in future studies.

We attempted to find differences in more general (non-knee structure related) determinants for pain for different grades of knee OA (**Chapter 5**). In knees with moderate to severe OA, bilateral knee OA is a determinant for knee pain. Being female or having widespread pain and health complaints are specific determinants for knee pain, but not specific for those with or without radiographic knee OA. Having hip OA or

feeling depressed seem to be determinants for knee pain, more specifically for those without any grade of radiographic knee OA. Participants with hip OA probably have referred pain in the knee. Morning stiffness was associated with knee pain in all K&L grades. Apart from all limitations in the measurement of morning stiffness in our study population (not hip or knee specific), morning stiffness is already related to knee pain in the non-OA cases. Morning stiffness together with pain might be a symptom of early OA and should be studied more thoroughly.

Other clinical symptoms

Although the PFJ has received less attention than the TFJ, there is evidence that the PFJ is important in terms of pain and disability occurring with OA. About 25% of a symptomatic population has isolated PFJ OA, compared with about 5% isolated TFJ OA, and about 40% combined PFJ and TFJ OA.[9,12,33] This underlines the importance of the PFJ, especially in clinical research. In **Chapter 7** we examined the relationship between clinical findings and OA-related MRI features, and found that crepitus is highly associated with all OA-related MRI features of the PFJ but not with MRI features of the TFJ. This is important to keep in mind when testing crepitus, which may only tell us something about the PFJ. The recommendations for the diagnosis of knee OA of the EULAR (the EUropean League Against Rheumatism) include crepitus as one of the three signs for the diagnosis of knee OA.[34] Therefore, the PFJ is already included in the clinical diagnosis of knee OA. A history of patellar pain was also associated with almost all OA-related MRI features of the PFJ, as described in **Chapter 7**. We have not yet tested the combination of the clinical findings (e.g. crepitus with a history of patellar pain). This combination might increase the predictive value of OA-related damage in the PFJ.

SUBTYPES OF OA

Osteoarthritis is a heterogeneous disease, which can be defined with pathological or clinical symptoms or, better, a combination of these two. But is OA a single disease? Or do we have to separate it into several subtypes of phenotypes? Suggestions for the idea of multiple separate subtypes of OA are common and have increased in number in the last decade.[35-37] The suggestions for different subtypes are divergent; ranging from distinctions between joint-specific OA to clinical phenotypes, and subtypes based on hormones.[36,38-39]

Proposed subtypes

As shown in **Chapter 6**, within the knee the OA-related features in the different compartments might be associated with different risk factors. This difference in compartmental OA could be due to a different etiology. The association of lateral TFJ OA with the history of injury has a specific reason for the development of OA. This is often referred to as secondary OA (the cause is known) in contrast to primary OA where the cause is unknown. The division into primary and secondary OA has been debated since MR images often showed meniscal and ligament lesions in knees without a (known

or remembered) history of trauma. Earlier, these knees would be classified as having primary knee OA, but when these lesions are visualized on MRI they might be classified as secondary knee OA. Furthermore, OA is seen as a disease with multifactorial etiology, and the various factors might interact with each other. For example, knee OA becomes increasingly severe over time with knee injury[40] and the combination of varus alignment and overweight leads to the development and progression of knee OA.[41]

The association of medial TFJ OA with Heberden's nodes of the hands indicates a systemic or genetic subtype of knee OA. There is evidence for a polyarticular OA with Heberden's nodes and medial TFJ OA, which has been confirmed as a type 1 polyarticular OA: nodal generalized OA is primarily found in females.[42] PFJ OA also seems to be a distinctive subgroup in knee OA, not only because PFJ OA is frequently observed in isolation, but also because PFJ OA seems to be a major source of symptoms.[9,12,33,43] We have shown an association between OA-related MRI features and crepitus (**Chapter 7**). Therefore, it is possible that PFJ OA is the cause of clinical symptoms other than the clinical symptoms caused by TFJ OA.

Subtypes based on clinical symptoms

Attempts to create subtypes based on clinical symptoms have not yet been well investigated. Many epidemiological studies make a distinction between radiological and clinical classification criteria of OA (**Chapter 2**). In a recent article, identification based on clinically relevant patient characteristics such as radiographic severity of OA, BMI, muscle strength and depression, has identified 5 different subtypes of knee OA (a minimal joint disease subtype, a strong muscle subtype, a non-obese and weak muscle subtype, an obese and weak muscle subtype, and a depressive subtype).[31] Females were more often classified in the 'non-obese and weak muscle subtype', the 'obese and weak muscle subtype' and the 'depressive subtype', of which the latter two had significantly worse outcomes on both pain and activity limitations than the other three subtypes.[38] These five different subtypes might represent different pathophysiologic etiological subtypes of OA, such as e.g. inactive persons in which inactivity resulted in muscle weakness. The 'non-obese' subtype is older than the other subtypes, which may represent an age-induced knee OA subtype, and the 'obese' subtype could represent the biomechanic-induced and metabolic-induced knee OA subtype. In another study, an age-related subtype is also considered, besides a hormone-dependent subtype and a genetic subtype.[39] These subtypes are based on a literature search and were not tested in a population. Outside the scope of this thesis, we also studied associations between female hormonal aspects and early degenerative signs of knee OA on MRI. We found that hormonal aspects were associated with osteophytes and bone marrow lesions in overweight females. There might be a subtype of women with overweight who are more susceptible to knee OA in the transitional menopausal period.

Subtypes based on different tissues

McGonagle and colleagues proposed a sub-classification based on the different tissues of the joint, to overcome the problem with former division into primary and secondary

OA. They distinguished six subtypes of OA with recognized causes (chondrogenic OA, ligamentogenic OA, Meniscogenic OA, synoviogenic OA, osteogenic OA, mixed pattern disease).[44] Such an anatomic division might be useful for early OA, although with the present available imaging techniques it does not seem feasible to make such a differentiation in early cases. In our relatively young and healthy study population we showed that most knees with lesions had lesions in more than one tissue, even though these were minor lesions.

Overall view on subtypes

Most subtypes described above are for established OA, and in these subtypes specific treatment might be more effective for a specific subtype. However, for early OA, before clinical onset, no subtypes have yet been determined. Additional knowledge on these possible differences in etiology might lead to differences in prevention of OA or early treatment.

IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

The results of the studies described in this thesis have more implications for future research than for present clinical practice, because all the studies are based on cross-sectional data of an open population. However, after the follow-up analysis of our nested study population in the coming years, the data may well have more implications for clinical practice. The follow-up data might reveal changes in OA-related features that may allow to identify possible causal or predictive relationships. The results presented in **Chapter 6** may have some clinical impact. For example, for someone presenting in primary care with pain in the knee and with Heberden's nodes, the awareness for possible knee OA should increase, even if there are no evident signs of OA. In addition, in the recommendations for diagnosis of knee OA for primary care, crepitus is one of the three tests to perform in a physical examination.[34] We have shown that crepitus is a feature that is associated with OA-related MRI features in the PFJ. This needs to be kept in mind when using the recommendations to diagnose knee OA. The knee may have isolated PFJ OA, which might be missed if a clinical standard AP radiograph is made to confirm knee OA. Furthermore, the treatment for isolated PFJ OA may need to differ from that for isolated TFJ OA, or a combination of these two; this also needs further investigation. Trials for the different treatments for the different compartments are ongoing in Australia.[45] Within the scope of the proposed subtype of PFJ OA, the patellofemoral pain syndrome warrants further investigation. We found no significant association between the patellofemoral pain syndrome at early age and OA-related damage at age 45-60 years, although there was a trend towards this association. Lack of power, but also recall bias, might be responsible for this result. There are suggestions that the patellofemoral pain syndrome at early age might lead to OA at older age.[46] Future research, especially studies on early OA, should consider taking the patellofemoral pain syndrome into account. The patellofemoral pain syndrome could be another risk factor for OA, or it could be a subtype of OA.

Based on the conclusion regarding the impact of the different descriptions of the K&L

classification criteria, researchers need to be aware of the impact of which particular description they choose to use. This effect on the classification of the knee in grade 0 or grade 1 was higher than on the classification of the knee in grade 2 or higher. Therefore, especially in early knee OA and classification of the non-OA knee and possible OA knee, the choice of the definition used is important. If large epidemiological studies do not use the same definition of OA, the results cannot be easily compared in systematic reviews and meta-analysis.

Considering the number of OA-related lesions seen on MRI in a population without radiographic signs of OA (K&L=0; **Chapter 6**) we suggest that MRI is essential for research of early knee OA. The follow-up of our nested cohort will reveal predictive features for evident knee OA that will enable us to identify high-risk groups for knee OA. It might be possible to find a risk factor, or a combination of risk factors, that contribute to a specific type of OA-related damage in the knee joint. Furthermore, the follow-up results may allow to confirm that crepitus and a history of patellar pain (**Chapter 7**) might help to indicate PFJ OA at an early stage.

MRI allows us to see early and potentially reversible pathological processes. These processes may help in the aim to develop preventive interventions for OA.[14] Although the potential reversible pathologic processes are still unclear, a study on joint distraction as treatment for even late stage knee OA (patients with an indication for knee replacement) shows that distraction in the joint for two months can result in an increase in cartilage thickness, and a decrease of the denuded bone area, as evaluated on MRI.[47] Bone marrow lesions and effusion are reported to fluctuate in severity, whereas osteophytes are thought not to disappear once established. However, in early phases of OA it seems feasible that small (or possible) osteophytes can disappear in case of a change in the internal joint environment, or in case of changed load; these aspects need to be further elucidated.

Besides the semi-quantitative changes that will provide more insight into the associations with risk factors and clinical symptoms, quantitative measures can also provide more information on the process of OA. Especially for possible early or even preventive interventions (e.g. insoles, exercise therapy, weight loss, and treatment with safe disease-modifying drugs), there is no sensitive quantitative measure. The volume measures we assessed in a probably very early stage of OA indicated more volume with more severe osteophytes and higher BMI. Could this be a sign of early knee OA, or is this something else? It will be interesting to see whether these women with more volume developed OA at follow-up, or developed more OA-related lesions. Furthermore, volume is not the only quantitative measure that is of interest for OA. As research has shown, there are more measures, and there might be even better measures, such as homogeneity and curvature of the cartilage, to indicate the difference between healthy people and those with early OA signs,[23-24] although this has to be investigated in an open population using high-field MRI.

Investigating the shape of the bone of the knee is still in an explorative phase. Observing the differences revealed in this relatively young and healthy population, the shape of the bone certainly deserves more attention in OA research.

Overall, symptomatic treatment and disease-modifying treatment might be more effective at an earlier clinical stage (or for disease-modifying treatment even at a pre-

clinical stage) than at the clinical stage where clinical OA is evident. Besides identifying predictive features for evident OA, identifying specific high-risk groups, and finding measures for changes in early OA, future research should also focus on whether there are early subtypes that might need subtype-specific treatment.

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Summary

Osteoarthritis (OA) is a progressive and disabling joint disease. It is one of the most frequently occurring health problems for middle-aged and older people. When a patient presents in healthcare with symptoms of OA, it is likely that there is already pathological damage in the knee, perhaps for a long period. Symptomatic treatment (e.g. exercise and mechanical interventions, like insoles) might be more effective at an earlier clinical stage; the same probably applies to disease-modifying treatment. In a pre-clinical stage with early pathological damage of the knee joint, such disease-modifying treatment might be even more promising. However, it is not yet possible to define a study population at this pre-clinical or early clinical stage - for example, a population with an extremely high risk for developing OA or a population with early OA signs or symptoms. Therefore, to study the effect of treatment in an early or pre-clinical stage, first the early predictive signs for evident (clinical) knee OA need to be identified. It is probably easiest to study these early predictive signs in a population with known risk factors for knee OA. In a cross-sectional study, possible early features and signs of OA should be identified before we can explore their predictive ability. The overall aim of this thesis was to evaluate the different classification criteria of knee osteoarthritis and to identify radiographic and magnetic resonance imaging (MRI) features that are related to the different aspects of clinical symptoms and risk factors of (early) knee osteoarthritis. Data of different cohorts of the Rotterdam study was used in this thesis. The Rotterdam Study is a prospective cohort study among persons living in the Ommoord district in the city of Rotterdam (the Netherlands) and investigates the incidence of, and the risk factors for, a variety of invalidating diseases. Of the last included cohort of the Rotterdam Study we invited women for a nested cohort study to identify early predictive signs of pre-clinical knee OA. Data of the women included in this nested cohort study was extended with a knee specific physical examination, a knee-specific questionnaire and MRI of both knees. **Chapter 4** is based on baseline data of the RS-III-1, **Chapter 5** on baseline data of the RS-I-1 and **Chapters 6-9** are based on data of the nested cohort study.

Despite extensive epidemiological and clinical research, there is no consensus on classification criteria to define knee osteoarthritis. No gold standard is available and many different definitions are used. For future research and interpretation of epide¬miological studies we evaluated in **Chapter 2** the reliability and validity of commonly used classification criteria. Systematic searches were performed in Medline/Pubmed and Embase for articles evaluating reliability, con¬struct validity, and content validity of knee OA classification criteria. We found in 18 articles, 25 classification criteria that could be summarized in three categories (radiological clinical and radiological combined classification criteria, and clinical classification criteria). No classification criteria based on magnetic resonance im¬aging could be included. In general, intra-and interrater reliabilities were good. Construct validity was low when radiological criteria were compared with clinical classification criteria. Associations between classification criteria and symptoms and risk factors like pain and obesity were moderate. To create uniformity in epidemiological research we recommended separate lesion scoring, overall scoring, and pain registration to define knee OA.

Of the most used classification criteria, the Kellgren and Lawrence (K&L) classification system we summarised in **Chapter 3** the different descriptions used in epidemiological

studies and searched for evidence on the impact of such variations on classification of knee OA in epidemiological studies. We identified five different descriptions. The different descriptions were compared with the original description. We concluded that major OA cohort studies disagree between each other and even among themselves on the definition and grading of disease according to the original K&L system, and that none of the included articles studied the impact of the use of different descriptions. Therefore we identified the impact of the use of alternative versions of the K&L-criteria in **Chapter 4** and evaluated which description has the highest association with knee complaints. Two readers scored 3,071 radiographs of the knees of participants of the RS-III-1 with the original K&L-description (90%). In addition, each alternative description was used in a random part (20%) of the radiographs. We calculated reproducibility of all descriptions, and compared sensitivity and specificity of the alternative descriptions for three cut-off points with the original description as reference standard (K&L≥1, K&L≥2, and K&L≥3). We calculated kappa statistics to compare agreement between the original and alternative descriptions, and evaluated the association with knee complaints. For cut-off K&L≥1 all four alternatives classified more people as OA than the original description; the kappa was low, and sensitivity and specificity were moderate to good. For cut-offs K&L≥2 and K&L≥3 there was little difference in number of cases and the kappa, sensitivity and specificity were good to perfect. The original description and alternative 3 showed the strongest association with knee complaints. The overall conclusion was that the different descriptions of the K&L-criteria have impact on the classification of OA in the lowest grade (K&L≥1). It depends on the purpose which is the best description.

In **Chapter 2** we confirmed the discordance between clinical and radiological defined OA. It has been suggested that this is particularly true for the less severe grades of OA. However there are people with K&L grade 3 or 4 of OA without pain. In **Chapter 5** we, therefore, aimed to identify determinants and differences in determinants associated with pain in people with different grades of knee OA. In over 5,000 participants of the RS-I-1 cohort, we stratified the knees of participants based on the grade of knee OA. Multivariate General Estimating Equations logistic regression analysis was used to analyze the association with knee pain. As expected, an increasing percentage of participants did not report pain with decreasing severity of knee OA: 25.8% for grade 3/4, and 84.5% for no knee OA. We concluded that being a female, having widespread pain, reporting general health complaints, familial OA and morning stiffness are determinants for knee pain, but are not specific for a grade of radiographic knee OA. Depression and hip OA were associated with knee pain in the knee without signs of OA (K&L=0).

MRI is upcoming in OA research, but there is few data available on the association between different risk factors and early signs of OA on MRI. It is unknown whether risk factors lead to different initial damage (different MRI features) or begin in different compartments of the joint, or which early MRI OA-features are related to pain. To assess how different risk factors are associated with early MRI OA-features in women without radiographic knee OA, and to explore how these features are associated with pain in the knee we describe in **Chapter 6** how these risk factors associate with early OA-related MRI features. Age and overweight were risk factors for osteophytes and cartilage lesions. Overweight was also associated with joint effusion. History of knee injury was associated

with OA-related damage in the lateral tibiofemoral joint. Presence of Heberden's nodes was associated with OA-related damage in the medial tibiofemoral joint. Current knee pain was associated with joint effusion, and persistent knee pain with bone marrow lesions in the patellofemoral joint. The conclusion of **Chapter 6** was that two risk were associated with early MRI OA-features on a specific location in the knee and none of the risk factors was discriminative for a specific type of damage. Age and overweight are the most important risk factors for structural damage.

In **Chapter 7** we examined the relationship between clinical findings and MRI-OA-features of the PFJ in females (45-60 years) with and without knee OA, because little is known about this relationship and the PFJ is an important compartment in early detection of knee OA. We did this with radiographs and MRI of knees of the women of the sub-study of the Rotterdam Study, which were scored with semi-quantitative scoring. In a physical examination specific patellar tests were tested and current knee pain and history of patellar knee pain were reported. We found significant associations between crepitus and all MRI-OA-features of PFJ (ORs ranged from 2.77 to 4.58). A history of patellar pain was significantly associated with all MRI-OA-features of the PFJ were significant (OR ranged from 1.62 to 2.07). In women without knee OA, the ORs are almost similar. Therefore our conclusion was that crepitus and history of patellar pain are clinical findings that indicate OA-lesions seen on MRI at the PFJ. These tests could help to indicate signs of patellofemoral OA. Follow-up data needs to confirm whether these tests have an additional diagnostic value on early knee OA.

Another measure than the semi-quantitative measure which can be used on MR images are quantitative measure. A fully automatic method for quantification of the cartilage volume of the knees was developed and validated on low field MRI. In **Chapter 8** we assessed with this fully automatic method the cartilage volume of all the knees of the women of the substudy of the Rotterdam Study on high field MRI and compared these volumes with radiographic scores and semi-quantitative measures of the MRI. A total of 859 women (1,709 knees) were included in the analysis. As expected, cartilage volume was lower in women at higher age, and with more severe grades of cartilage degeneration and joint space narrowing. The higher cartilage volumes associated with BMI and osteophytes was unexpected. No significant trends were seen for pain, K&L grades, bone marrow lesions, or subchondral cysts.

All tissues of the joint are involved in OA, bone is as important as cartilage. Therefore we describe in **Chapter 9** a novel potential biomarker, the bone shape. We determined which aspects of bone shape are different in osteoarthritic knees compared to controls. We found that there were three shape modes referring to three aspects of the shape of the knee were significantly associated with the presence of radiological OA. The width of the femoral and tibial bone, which was larger in osteoarthritic subjects; Osteoarthritic knees were more extended during the radiography than controls; and osteoarthritic subjects had an elevated lateral tibial plateau, which was associated with pain. In conclusion, these results show that the shape of the knee plays a definite role in osteoarthritis, which might lead to novel imaging biomarkers to monitor or predict knee OA.

Chapter 10 reflects on the main findings of this thesis, as well as on the limitation of the studies and the implication for practice and future research.

Samenvatting

Artrose is een progressieve gewrichtsziekte, die kan leiden tot beperkingen in bewegingen. Het is een van de meest voorkomende gezondheidsproblemen bij mensen van middelbare en oudere leeftijd. Artrose kan voorkomen in alle gewrichten, maar het vaakst komt het voor in handen, rug, heupen en knieën. In dit proefschrift zal de focus liggen op artrose in de knieën.

Als een persoon met klachten zich presenteert met symptomen van knieartrose, is het zeer waarschijnlijk dat er al schade is opgetreden in het gewricht, misschien zelfs al voor lange periode (**Hoofdstuk 1**). De behandeling bestaat momenteel vooral uit symptoombestrijding, door bijvoorbeeld oefeningen en mechanische interventies zoals het dragen van zooltjes. De behandeling zou effectiever kunnen zijn in een eerder stadium van de ziekte. In een preklinisch stadium met vroege pathologische schade van het kniegewricht zou een ziektemodificerende behandeling veelbelovend kunnen zijn. Het is alleen nog niet mogelijk om een studiepopulatie in dit preklinisch of vroeg klinisch stadium te definiëren. Voorbeelden van zo'n studiepopulatie zijn: een populatie met extreem hoog risico op het ontwikkelen van artrose of een populatie met vroege kenmerken of symptomen van artrose. Om deze populaties te definiëren moet er bekend zijn wat artrose is. Verder moet er eerst worden onderzocht wat de eerste voorspellende kenmerken zijn voor klinische artrose. Het is waarschijnlijk het meest makkelijk om deze eerste voorspellende kenmerken te onderzoeken in een populatie met al bekende risicofactoren voor artrose in de knie. Voor dat onderzocht kan worden wat de voorspellende waarde van de mogelijke eerste kenmerken van artrose is, moeten deze eerste kenmerken geïdentificeerd worden in een cross-sectionele studie. De algemene doelstelling van dit proefschrift is om de verschillende classificatie criteria van knieartrose te evalueren, en radiologische kenmerken en kenmerken van de MRI te identificeren die gerelateerd zijn aan verschillende aspecten van klinische symptomen en risicofactoren van (vroege) knieartrose. In dit proefschrift is gebruikt gemaakt van data van cohorten van het ERGO onderzoek (the Rotterdam Study (RS)). Het ERGO-onderzoek is een prospectief cohortonderzoek onder mensen van 45 jaar en ouder die wonen in de Rotterdamse wijk Ommoord. In het onderzoek worden incidentie en risicofactoren van invaliderende ziektes onderzocht in verschillende cohorten (RS-I, RS-II en RS-III). Van het laatst geincludeerde cohort zijn vrouwen uitgenodigd om deel te nemen aan een substudie naar de eerste kenmerken van vroege knieartrose. Daarbij is de data uitgebreid met een kniespecifieke vragenlijst, een kniespecifiek lichamelijk onderzoek en een MRI van beide knieën. **Hoofdstuk 4** is gebaseerd op baseline data van het RS-III-1 cohort, **Hoofdstuk 5** is gebaseerd op baseline data van het RS-I-1 cohort en de **Hoofdstukken 6 tot en met 9** zijn gebaseerd op de baseline data van de substudie naar eerste kenmerken van vroege knieartrose.

Ondanks uitgebreid epidemiologisch en klinisch onderzoek is er geen consensus over welke classificatie criteria gebruikt moeten worden om knieartrose te definiëren. Er is geen gouden standaard beschikbaar en er zijn veel verschillende definities die gebruikt worden om knieartrose te definiëren. Voor toekomstig onderzoek en interpretatie van epidemiologische studies hebben we in **Hoofdstuk 2** de betrouwbaarheid en validiteit van gebruikelijke classificatie criteria geëvalueerd. De databases Medline en Embase zijn systematisch doorzocht naar artikelen die de betrouwbaarheid, constructvaliditeit

en inhoudsvaliditeit van classificatie criteria van knieartrose beschrijven. We vonden 18 artikelen, met daarin 25 verschillende classificatie criteria beschreven. Deze 25 verschillende classificatie criteria kunnen samengevat worden in 3 categorieën: radiologische classificatie criteria, klinische classificatie criteria en gecombineerde radiologische en klinische criteria. Classificatie criteria gebaseerd op MRI kenmerken konden niet geïncludeerd worden. Over het algemeen genomen zijn intra- en inter-beoordelaar betrouwbaarheid van de verschillende criteria goed. Constructvaliditeit is laag als een radiologisch criterium vergeleken worden met een klinisch criterium. Associaties tussen classificatie criteria en symptomen en risicofactoren zoals pijn en overgewicht zijn matig. Om uniformiteit te creëren in epidemiologisch onderzoek adviseren wij een aparte score van de radiologische kenmerken, een overall score en een pijnregistratie om knieartrose te definieren.

De Kellgren en Lawrence classificatie criteria (K&L) zijn de meest gebruikte classificatie criteria. Hiervan hebben we in **Hoofdstuk 3** alle verschillende beschrijvingen die gebruikt werden in epidemiologisch onderzoek samengevat en bekeken of er bewijs was voor de impact van die variaties van beschrijvingen op de classificatie van knieartrose in epidemiologisch onderzoek. We hebben 5 verschillende beschrijvingen gevonden. We concludeerden dat grote artrosestudies niet gelijke beschrijvingen gebruiken en zelfs soms binnen een cohort verschillende beschrijvingen rapporteren. In geen van de studies werd de impact van de verschillende beschrijvingen beschreven. Daarom hebben we in **Hoofdstuk 4** de impact van het gebruik van verschillende beschrijvingen van de K&L criteria geïdentificeerd en geëvalueerd welke beschrijving de grootste associatie vertoont met knieklachten passende bij knieartrose. Twee beoordeelaars hebben 3071 röntgenfoto's van de knieën van deelnemers van het RS-III-1 cohort gescoord met de originele K&L beschrijving. Daarbij hebben we met ieder alternatieve beschrijving (4 in totaal) ongeveer 20% van de röntgenfoto's gescoord. We hebben de reproduceerbaarheid van alle beschrijvingen berekend en de sensitiviteit en specificiteit van de alternatieve beschrijvingen voor 3 afkappunten (K&L≥1, K&L≥2 en K&L≥3) vergeleken met de originele beschrijving. Met kappa statistiek is de overeenkomst tussen de originele en de alternatieve beschrijvingen berekend en de associatie met knieklachten geëvalueerd. Bij afkappunt K&L≥1 hebben alle vier alternatieve beschrijvingen meer mensen geclassificeerd als hebbende knieartrose dan de originele beschrijving. De kappa was laag en sensitiviteit en specificiteit waren matig tot goed. Bij de afkappunten K&L≥2 en K&L≥3 was er minder verschil in aantal cases en de kappa, sensitiviteit en specificiteit waren goed tot perfect. De originele beschrijving en alternatief 3 lieten de sterkste associatie met knieklachten zien. De conclusie was dat de verschillende beschrijvingen van de K&L criteria impact hebben op de classificatie van knieartrose in de laagste graad (K&L≥1). Het is afhankelijk van het doel welke beschrijving het best gebruikt kan worden.

In **Hoofdstuk 2** hebben we de strijdigheid tussen klinisch gedefinieerde artrose en radiologisch gedefinieerde artrose bevestigd. Er wordt gesuggereerd dat dit vooral waar is voor de minder ernstige graden van artrose. Maar er zijn mensen met een K&L-graad 3 of 4 van artrose die geen pijn hebben. Het doel van **Hoofdstuk 5** was daarom het identificeren welke determinanten en verschillen in determinanten er zijn en welke

associëren met pijn in mensen met verschillende graden van knieartrose. In meer dan 5000 deelnemers van het RS-I-1 cohort hebben we de knieën van de deelnemers onderverdeeld in de graad van knieartrose. Multivariate GEE (General Estimating Equations) logistische regressie analyses zijn gebruikt om de associatie met kniepijn te analyseren. Zoals verwacht was er een toename in percentage van deelnemers die geen pijn rapporteerde met een minder ernstige knieartrose: 25.8% van de deelnemers rapporteerde geen kniepijn bij graad 3/4 knieartrose, 84.5% van de deelnemers rapporteerde geen pijn als ze ook geen knieartrose hadden. We concludeerden dat: vrouwen, het hebben van wijdverspreide pijn, het rapporteren van algemene gezondheidsklachten, familiare artrose en ochtendstijfheid determinanten zijn voor het hebben van kniepijn, maar deze determinanten zijn niet specifiek voor een bepaalde graad van radiologische knieartrose. Depressie en heupartrose zijn determinanten die geassocieerd zijn met kniepijn in de knieën zonder tekenen van artrose (K&L=0).
MRI is een opkomend instrument dat gebruikt wordt in artrose onderzoek. Er is nog weinig data beschikbaar over de associatie tussen de verschillende risicofactoren en de eerste tekenen van artrose op de MRI. We weten nog niet of risicofactoren leiden tot verschillende eerste tekenen van schade (verschillende MRI kenmerken) of dat de risicofactoren leiden tot verschil in schade in een bepaald compartiment van de knie. Verder willen we ook weten welke eerste tekenen van vroege MRI artrose gerelateerd zijn aan kniepijn. Om in te schatten hoe verschillende risicofactoren geassocieerd zijn met vroege MRI artrose kenmerken in vrouwen zonder radiologische knieartrose en om te onderzoeken welke kenmerken geassocieerd zijn met pijn in de knie beschrijven we in **Hoofdstuk 6** hoe deze risicofactoren geassociëerd zijn met vroege artrose gerelateerde kenmerken zichtbaar op de MRI. Leeftijd en overgewicht zijn risicofactoren voor osteophyten en kraakbeen schade. Overgewicht is ook geassocieerd met vocht in het gewricht. Een knieblessure in het verleden is geassocieerd met artrose gerelateerde schade in het mediale tibiofemoralegewricht. Kniepijn op dit moment is geassocieerd met vocht in het gewricht en persisterende kniepijn met botschade in het patellofemoralegewricht. De conclusie van dit hoofdstuk is dat twee risicofactoren geassocieerd zijn met vroege MRI artrose kenmerken op een specifieke locatie in de knie (een knieblessure in het verleden met schade in de laterale kant van de knie en Heberden's nodes met schade in de mediale kant van de knie) en dat geen van de risicofactoren het verschil maakt voor een specifiek type schade. Leeftijd en overgewicht zijn de meest belangrijke risicofactoren voor artrotische schade in de knie.
In **Hoofdstuk 7** hebben we de relatie tussen de klinische bevindingen en MRI artrose kenmerken van het patellofemorale gewricht onderzocht in vrouwen tussen de 45 en 60 jaar met en zonder knieartrose. Dit hebben we gedaan omdat er weinig bekend is over deze relatie en het patellofemorale gewricht een belangrijk compartiment is in vroege herkenning van knieartrose. We hebben hiervoor röntgenfoto's en MRIs van de knieën van vrouwen van een substudie van de Rotterdam Studie (Ergo studie; RS-III-1) gebruikt, welke met een semikwantitatieve score gescoord waren. Data van specifieke patellatesten, uitgevoerd in een lichamelijk onderzoek, was beschikbaar. Verder zijn pijn in de knie op dit moment en pijn aan de patella in het verleden uitgevraagd. We vonden significante associaties tussen crepitatie en alle MRI artrose kenmerken van het patellofemorale

gewricht (odds ratios varieerde van 2,77 tot 4,58). Ook een verleden van pijn aan de patella is significant geassocieerd met alle MRI artrose kenmerken van het patellofemorale gewricht (odds ratios varieerde van 1,62 tot 2,07). In vrouwen zonder knieartrose zijn de odds ratios vergelijkbaar. Onze conclusie is daarom dat de klinische bevindingen crepitatie en een verleden van pijn in de patella kunnen aangeven dat er artrotische schade is (zichtbaar op de MRI) in het patellofemorale gewricht. Vervolgmetingen zijn nodig om te bevestigen dat deze testen een additionele diagnostische waarde hebben voor vroege knieartrose.

Naast semikwantitatieve scores kunnen kwantitatieve metingen uitgevoerd worden aan de MRI. Een volautomatische methode voor het kwantificeren van het kraakbeenvolume van de knieën is ontwikkeld en gevalideerd op een MRI met een laag magnetische veld. In **Hoofdstuk 8** hebben we met deze volautomatische methode het kraakbeenvolume van alle knieën van de vrouwen van onze substudie van de Rotterdam studie gemeten op MRIs met een hoogmagnetisch veld. De volumes hebben we vergeleken met radiologische scores en semikwantitatieve scores van de MRI. Een totaal van 859 vrouwen (1709 knieën) zijn geincludeerd in de analyses. Zoals verwacht was het kraakbeenvolume minder bij vrouwen met een hogere leeftijd en met een ernstigere graad van degeneratie van het kraakbeen en gewrichtsspleetversmalling. Dat meer kraakbeenvolume is geassocieerd met een hoger BMI en een ernstigere graad van osteofyten was niet verwacht. Geen significante trends werden gezien met pijn, K&L graden, botschade of subchondrale cystes.

Alle weefsel van het gewricht zijn betrokken bij de ziekte artrose, waarbij bot minstens zo belangrijk is als het kraakbeen. Daarom hebben we in **Hoofdstuk 9** een nieuwe potentiële indicator beschreven, namelijk de vorm van het bot. We hebben bepaald welke aspecten van de vorm van het bot verschillend zijn in knieën met artrose in vergelijking met knieën zonder artrose. We hebben gevonden dat er 3 verschillende vormen te onderscheiden zijn, die refereren naar 3 aspecten van de knie die associeren met de aanwezigheid van radiologische artrose. De breedte van het femur en de tibia zijn groter bij deelnemers met artrose. Knieën met artrose stonden meer in extensie gedurende de röntgenfoto dan de knieën zonder artrose, en knieën met artrose hadden een verhoogd lateraal tibia plateau, welke geassocieerd is met pijn. Concluderend zeggen deze resultaten dat de vorm van de knie een zekere rol speelt in artrose, en dit kan leiden tot nieuwe indicatoren om knieartrose te voorspellen en verder te onderzoeken.

Hoofdstuk 10 bediscussieert de belangrijkste bevindingen van dit proefschrift, evenals de beperkingen van de onderzoeken en de implicatie voor de praktijk en toekomstig onderzoek.

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CURRICULUM VITAE

Dieuwke Schiphof is op 27 november 1978 geboren in Kimswerd. Na het behalen van haar VWO diploma aan de RSG Simon Vestdijk te Harlingen is zij in 1997 begonnen aan de studie Bewegingswetenschappen aan de Vrije Universiteit in Amsterdam. Tijdens haar afstudeeronderzoek onderzocht zij het effect van de duikreflex op de hartslag, en of het niveau van training (vastgesteld via de hartslag) voldoende was voor de wedstrijden van onderwaterhockeyers. In mei 2003 studeerde zij af in de richting Bewegingssyteem. Na haar studie Bewegingswetenschappen heeft zij de verkorte opleiding Fysiotherapie aan de Avans Hogeschool in Breda afgerond in 2006. Tijdens en na haar studies werkte zij gedurende 2 jaar als onderzoeksassistent bij Longitudinal Ageing Study Amsterdam (LASA) en Nederlands Studie naar Depressie en Angst (NESDA) in Amsterdam. In 2005 werd zij coördinator biologie bij NESDA. In maart 2006 begon zij aan haar promotie traject als aio bij de afdeling Huisartsgeneeskunde van het Erasmus MC in Rotterdam, waarbij zij werkt aan de in dit proefschrift beschreven project.

PHD PORTFOLIO

Courses	**Year**	**Workload**
NWO talentendag	2006	8 hours
NIHES clinical epidemiology,	2007 – 2008	70 ECTS
Biomedical English Writing and Communication	2009	40 hours
BROK (Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers)	2011	20 hours
Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2011	8 hours
Presentations		
International		
Eular Amsterdam	2006	
KARMA Amsterdam	2006	
Eular Barcelona, poster	2007	16 hours
OARSI Rome, 2 posters	2008	32 hours
OARSI Montreal, poster	2008	16 hours
OARSI Brussel	2010	
OARSI Imaging workshop Salzburg, oral	2011	20 hours
KARMA Keele, oral	2011	20 hours
OARSI San Diego, oral and poster	2011	36 hours
National		
KNGF Amsterdam, poster	2008	16 hours
NHG wetenschapsdag, poster	2009	16 hours
International collaboration		
Research visit at Nordic Bioscience, Denmark	2009	2 months
Teaching activities		
Supervising medical student	2011	80 hours

LIST OF PUBLICATIONS

This thesis:

Schiphof D, de Klerk BM, Koes BW, Bierma-Zeinstra SMA. Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal. *J Clin Epidemiol.* 2008;61:1205-15

Schiphof D, Boers M, Bierma-Zeinstra SMA. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Ann Rheum Dis.* 2008;67:1034-6

Schiphof D, De Klerk BM, Kerkhof HJM, Hofman A, Koes BW, Boers M, Bierma-Zeinstra SMA. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. *Ann Rheum Dis.* 2011;70:1422-7

Schiphof D, Kerkhof HJM, Damen J, De Klerk BM, Hofman A, Koes BW, Van Meurs JBJ, Bierma-Zeinstra SMA. Determinants for pain in patients with different grades of knee osteoarthritis. *Submitted*

Schiphof D, De Klerk BM, Waarsing JH, Hofman A, Ginai AZ, Oei EH, Weinans H, Bierma-Zeinstra SMA. Risk factors and their association with MRI osteoarthritic features in female knees without radiographic signs of osteoarthritis. *Submitted*

Schiphof D, Van Middelkoop M, De Klerk BM, Oei EH, Hofman A, Koes BW, Weinans H, Bierma-Zeinstra SMA. Crepitus is a First indication of patellofemoral osteoarthritis. *Submitted*

Schiphof D, Dam EB, De Klerk BM, Hofman A, Niessen WJ, Oei EH, Weinans H, Bierma- Zeinstra SMA, Waarsing JH. Cartilage volume associated with semi-quantitative radiographic and MRI measures in an open female population. *Submitted*

Haverkamp DJ, Schiphof D, Bierma-Zeinstra SMA, Weinans H, Waarsing JH. Variation in joint shape of osteoarthritic knees. *Arthritis Rheum.* 2011;63:3401-7.

Coauthor

De Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Biema-Zeinstra SM. No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review. *Rheumatology* 2009;48:1160-5.

De Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Bierma-Zeinstra SM. Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review. *Rheumatology*. 2009;48:104-12.

De Klerk BM, Willemsen S, Schiphof D, Koes BW, Hofman A, Bierma-Zeinstra SMA. Development of radiological knee osteoarthritis in people with knee complaints. *Ann Rheum Dis* 2011; Epub ahead of print

Vijfvinkel F, Schiphof D, Verhagen AP. Further questions remain concerning osteoarthritis risk and index finger-to-ring finger length ratios: Comment on the article by Haugen et al. *Arthritis Rheum* 2011;63:4038