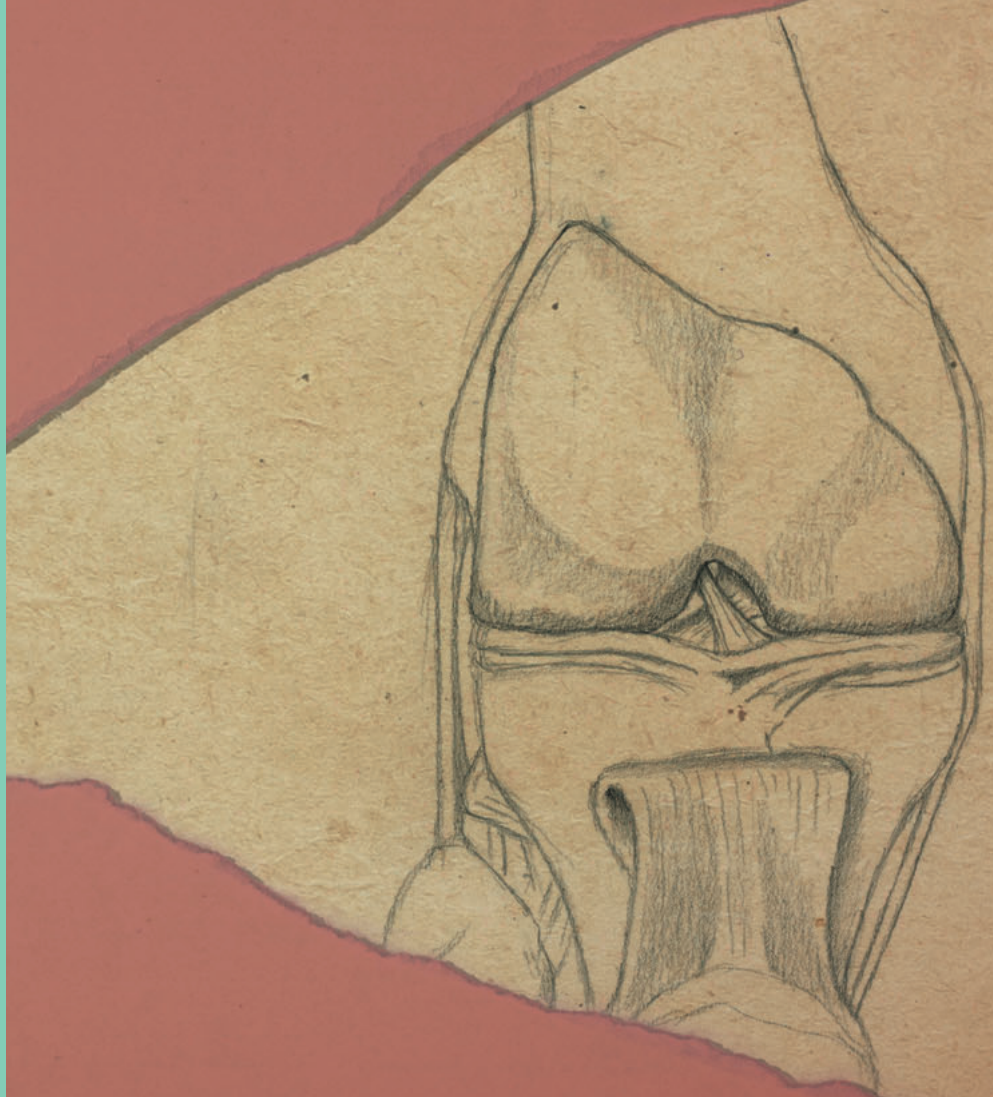
Different perspectives on diagnosis and prognosis of hip and knee osteoarthritis in primary care.



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Different Perspectives on Diagnosis and Prognosis of Hip and Knee Osteoarthritis in Primary Care

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Printing of this thesis was kindly supported by the SBOH, employer of GP trainees, and the department of General Practice, Eramus MC, Rotterdam.

ISBN 978-94-6375-292-3

Cover design and layout: © evelienjagtman.com
Printing: Ridderprint

Different Perspectives on Diagnosis and Prognosis of Hip and Knee Osteoarthritis in Primary Care

Verschillende perspectieven op de diagnose en
prognose van heup- en knieartrose in de huisartspraktijk

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. R.C.M.E. Engels
and in accordance with the decision of the Doctorate Board.

The public defence shall be held on
Wednesday 5 June 2019 13:30

by

Jurgen Damen

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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ReumaNederland
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The research in this thesis was supported by a grant of the Dutch Arthtritis Foundation.

Madelief is haar fiets kwijt. Roos ziet hem in een garage staan. “Voorzichtig!” fluistert Madelief, “Daar woont een dief!”. “Echt?”, vraagt Roos. “Tuurlijk!,” zegt Madelief, “Hoe komt mijn fiets daar anders?” De meneer die hem later teruggeeft had de fiets even binnen gelegd voor Madelief. “Dat was helemaal geen dief,’ zegt Roos, “dat was een aardige meneer.” Madelief haalt haar schouders op: “Misschien was het een goeie dief.”

Vrij naar Guus Kuijer, het grote boek van Madelief.

“Under Bayes theorem no theory is perfect. Rather, it is a work in progress, always subject to further refinement and testing.”

Nate Silver

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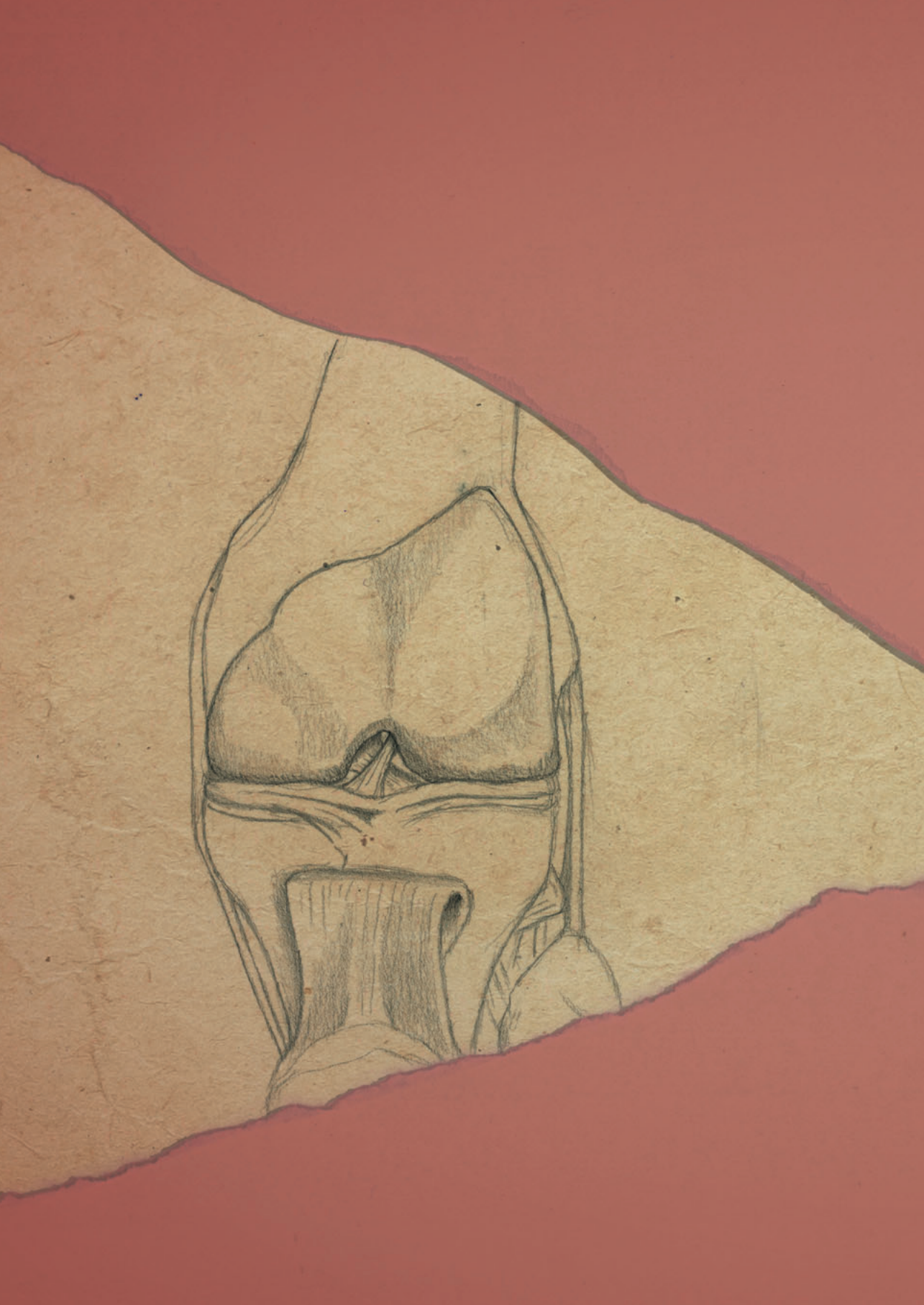

CHAPTER 1

General introduction

EPIDEMIOLOGY

Osteoarthritis (OA) is the most common form of arthritic disease, affecting approximately 9.6% of men and 18% of women aged ≥ 60 years worldwide.[1] The prevalence of hip and knee OA increases with age, with a female-to-male ratio of around 1 in the age category of 45-50 years for both hip and knee increasing to a ratio of 1.5 in the hip, and a ratio of 2 in the knee in the age category 70-75 years.[2] A similar pattern can be seen in the Netherlands, based on registration in general practice of the diagnosis peripheral OA (i.e. hip, knee, hand or foot). For example, in 2016, 1,251,000 persons were registered with OA (432,300 men, 818,700 women) which corresponds to 51.2 patients with OA per 1,000 men, and 95.4 patients with OA per 1,000 women (Figure 1). (https://www.volksgezondheidenzorg.info/onderwerp/artrose 2018)

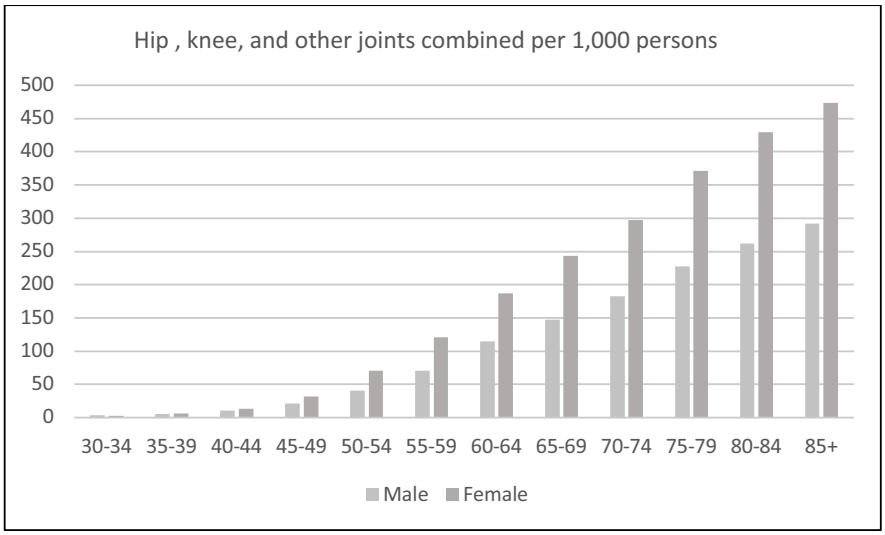

Figure 1. Data on yearly prevalence of osteoarthritis in the Netherlands (2016), displayed according to 5-year age bands. (Volksgezondheidenzorg.info 2018)

With the aging of the population, OA is an increasing challenge for health care worldwide. OA is already a major burden for medical practice and is also one of the most common diagnoses in general practice.[3] The National Institute for Public Health and Environment (in the Netherlands) estimates that OA will become the most prevalent disease by the year 2040 (Table 1).

Etiology

OA is characterized by structural damage to articular cartilage, subchondral bone alterations, meniscal degeneration and extrusion, synovial inflammatory response, and bone overgrowth.[4] Although now outdated, for a long time it was believed that OA was a 'wear and tear' degenerative

disease; however, the etiology is far more complicated and is still not entirely understood. Whereas in population-based studies high levels of repetitive joint movements during physical activity are reported to increase the risk of developing knee and hip OA [5,6] there is no evidence (once sporting injuries are accounted for) to support an effect of normal physical activity on normal joints in developing OA.[7,8] Nevertheless, knee trauma has the highest odds ratios for developing knee OA.[9] This suggests that wear and tear is not the sole cause of OA.

Table 1. Numbers of patients with specific conditions in the Netherlands: as at 2015 and projected to 2040 (https://www.vtv2018.nl/aandoeningen 2018).

Disease	2015	2040	Increase (%)
Osteoarthritis	1199100	2281900	190.3
Spine complaints	1982300	2256700	113.8
Diabetes	1111000	1491600	134.3
Vision impairment	749500	1139800	152.1
Coronary heart disease	732200	1093800	149.4
Anxiety disorder	1046300	1088800	104.1
Eczema	961700	1084100	112.7
Hearing impairment	624600	927000	148.4
COPD	607300	828400	136.4
Respiratory infections	619300	788600	127.3

To help elucidate the complex etiology, risk factors involved in the development of OA can be investigated; the diversity of these risk factors may provide insight into the complex etiology of OA. The prevalence of OA is higher in women. and they are also more likely to develop more severe radiographic knee OA (particularly during menopause). These differences between men and women (besides hormonal causes) may also be due to differences in bone strength, alignment, ligament laxity, number of pregnancies, and neuromuscular strength.[10] Obesity is another strong risk for OA, in particular for knee OA. Besides being a risk factor for developing OA,[11] obesity also increases the risk of progression of ROA.[13] This can be attributed to not only structural changes due to an individual's weight, but also to hormonal, metabolic and inflammatory responses of the body due to obesity.[13] In addition, it has been shown in various OA cohorts that a family history of OA is a risk factor, e.g. in 20-30% of the participants with knee OA, familial OA occurs.[14] However, it is not known whether these suspected genetic traits involve metabolic changes, pain sensitivity, or a combination of these factors, as well as (perhaps) behavioral traits.[15]

Signs and symptoms

The main symptoms of OA are pain, stiffness and loss of function. However, these symptoms are not continuously present, especially in an early stage of the disease when symptoms tend to fluctuate. Nevertheless, the symptoms tend to increase over time and can result in a very disabling condition. To monitor pain, stiffness and disability in OA, most researchers use disease-specific scores like the Western Ontario MacMaster questionnaire (WOMAC), the Knee Osteoarthritis Outcome Score (KOOS), the Hip Osteoarthritis Outcome Score (HOOS), and scores on a pain numeric rating scale. However, the fluctuating condition is a challenge when analyzing predictors for the course of pain. Generally, multiple assessments of pain over a longer period of time give a better indication of the course of pain than one single assessment and, therefore, it is necessary to determine pain trajectories.

Despite efforts to study pain in OA, until now the pathophysiology of pain in OA remains unclear. Nociceptive pain is a part of OA and clear associations exist between pain and synovial inflammation and bone marrow lesions.[16] However OA pain cannot be attributed only to structural change or damage of the joint, loss of cartilage, bone overgrowth, inflammatory causes, or bone marrow lesions. This conclusion is best demonstrated in the knee, where total knee replacement is considered the treatment option of choice in advanced OA. Post-surgery, a subgroup of 20% still suffers from pain, even when the surgical procedure is considered to be highly successful.[17] This could be due to pain sensitization, where (amongst other mechanisms) nociceptive pain stimuli may lead to overactivation of the central nervous system causing pain sensitization, leading to hyperalgesia.[18] Moreover, these pain mechanisms are influenced by the coping style of patients and their psychological health. For example, anxiety levels are known to be related to levels of knee pain.[19]

Diagnosis and radiography of OA in clinical care

The diagnosis of OA in general practice is hampered by a lack of uniform primary care guidelines and diagnostic criteria. However, most guidelines and experts agree that, in clinical practice, a diagnosis should be made on the basis of clinical history and a comprehensive physical examination.[20] More uniform and early diagnosis of OA provides a better window of opportunity for interventions and a clear diagnosis may also motivate patients to make (often difficult) lifestyle changes related to their diagnosis. The role of radiography, if any, is to rule out other disorders like rheumatoid arthritis, fractures, and bone metastasis.

Nevertheless, in major rheumatology textbooks, plain radiography is routinely discussed as a standard imaging modality for OA.[21] Currently in clinical practice, imaging is still probably an overused modality to arrive at a diagnosis of OA, i.e. a diagnosis that can be made clinically.[22,23]

Several groups have demonstrated that radiography is *not* required to diagnose OA. For example, one group that aimed to define the American College of Rheumatology (ACR) criteria for classification of hand OA, found that radiographs are less sensitive and less specific than physical examination in the diagnosis of symptomatic hand OA.[24] Another group found that, for all joints, radiographs were more useful to exclude other diagnostic possibilities than to confirm OA.[25]

The ACR criteria were developed in secondary care populations and three different sets emerged with clinical, radiological and combined criteria. However, there may be limitations to their application in general practice. For example, the ACR criteria were developed in a population from a rheumatology practice and are useful to distinguish between OA and more inflammatory arthritis in a population with more advanced OA disease than is normally seen in clinical practice.[26]

MRI and laboratory testing have, if any, only a minor role in the diagnosis of OA.[27] Although MRI studies are more sensitive to radiographic OA (ROA) than radiography, the association between pain and MRI findings is the same as the association between pain and radiographic findings.[28] The current proliferation of MRI in clinical practice may well be premature in the diagnosis of OA. Therefore, in clinical practice, radiography remains the most frequently used imaging technique, mainly because of its widespread availability and low costs.[29]

Various studies have indicated the discordance between pain in hip and knee diagnosed as OA and the resemblance of pathology on the plain posterior anterior (PA) radiograph.[30,31] One study found that in patients with ROA 47% reported knee pain, whereas in patients with knee pain only 15% had ROA.[32] Nevertheless, the absence of positive radiographic findings should not be interpreted as confirming the absence of symptomatic OA, and the presence of positive radiographic findings does not confirm that OA is the cause of pain in a symptomatic person.[32.]

Over the years, proposals have been made to improve the diagnostic and/or prognostic value of radiographic findings, mainly by changing or adapting the grading systems most commonly used.[33] Some groups employed new grading techniques in which actual measurements are used.[31,34] One possible reason for the discordance between pain and radiological features could be the wrong choice of radiological view(s). Although most ROA studies have focused on the tibiofemoral joint in the knee, radiographic evidence of early OA has also been found in the patellofemoral joint.[26] Also in the hip, specific radiographic views (e.g. the mediolateral view) are suggested to be more suitable to find radiographic evidence of early OA.[35] Furthermore, although some researchers suggest that MRI data are more sensitive, evaluation of such data remains debatable.

Course of OA

Pain and functional limitation are the hallmarks of OA; moreover, since OA is a chronic and deteriorating condition, a substantial proportion of the hip and knee OA population eventually receives surgical joint replacement therapy.[36] Although most studies report slow deterioration in participants over time, the course in early OA is difficult to reproduce since, in cohort studies, pain and function remain relatively stable or may even decrease in the first years.[37] These discrepancies might be explained by relatively large individual differences between persons who can be analyzed by identifying distinct pain trajectories.[38]

Study population

CHECK study

To study the prevalence and prognosis of OA in first presenters in primary care, the Cohort Knee and Cohort Hip (CHECK) was formed. The CHECK cohort is a prospective multicenter study among persons with knee and hip pain; it was initiated in 2002 and designed to investigate early OA. Persons with incident knee and or hip complaints were invited to participate in the CHECK study; in total, 1002 participants were included at baseline. Individuals were eligible to participate if they had pain and/or stiffness of the knee and/or hip, were aged between 45 and 65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry.

For our studies on i) the prevalence of OA, ii) radiographic reproducibility, iii) assessment of ROA features on multiple radiographs, and iv) the prognostic value of these ROA features, we used the baseline CHECK study data, as well as data from the 2 and 5-year follow-ups. All patients underwent radiographic assessment of hips and knees using various radiographic views, a standardized physical examination, and also filled out an extensive questionnaire at baseline and at the 2 and 5-year follow-up[39]

The Rotterdam Study

Data from the Rotterdam Study were used were used for our investigations on i) hereditary traits in hip, knee and hand pain, and on ii) OA in the lumbar spine causing hip pain and degeneration. This is an ongoing prospective cohort study among persons living in Ommoord (a neighborhood in the northern part of Rotterdam). Starting in 1990, inhabitants of Ommoord aged 55 years and older were invited to participate in the Rotterdam Study to examine risk factors for chronic disabling diseases. A total of 10,275 individuals were invited to participate (response rate 78%). Of the 7,983 participants who had a first interview, 6,494 visited the research center for baseline examination (including radiography of the knees, hips and hand). [40] Our studies included individuals for whom both radiography and genotyping were available.

Study aims and outline of thesis

The overall aim of the work in this thesis was to i) identify early OA criteria for epidemiological research in primary care, and ii) establish the usefulness of radiographic signs widely used in epidemiological research and clinical practice. An additional goal was to establish criteria for the prognosis of early OA.

Chapter 2 describes the prevalence of OA in first presenters using the criteria of the American College of Rheumatology (ACR). Then we investigated whether first presenters who do not fulfil the ACR criteria develop OA within 5 years of follow-up and which factors may predict this. **Chapter 3** examines whether radiographic OA is detected more frequently when visualizing multiple compartments of the joint in individuals with early symptomatic OA. This study explored which combination of radiographs is most useful to detect early radiographic OA in different components of the hip and knee. **Chapter 4** aimed to elucidate the reliability of radiographic scoring in the CHECK cohort. Since assessment of large numbers of radiographs is time consuming and costly, we evaluated whether radiographic OA scoring performed by well-trained medical students was adequate. Historically, most research on knee OA has focused on the tibiofemoral joint. **Chapter 5** deals with a different knee joint and presents data on patellofemoral OA in the CHECK cohort. In this population, we examined the proportion of isolated patellofemoral osteoarthritis (PFOA) compared to tibiofemoral osteoarthritis (TFOA) and described the natural course of PFOA compared with that of TFOA. **Chapter 6** investigated whether these combinations of radiographic OA are related to pain trajectories, in order to advise whether or not these radiographs would be useful in daily practice to predict symptomatic progression.

Hip pain is often reported in patients in whom no radiographic OA of the hip can be distinguished. In **Chapter 7** we examined potential alternative causes of hip pain, e.g. the presence of OA in the lumbar spine which can cause pain to radiate to the hip. **Chapter 8** explores the question of hereditary pain traits within the Rotterdam Study: more specifically, whether common genetic variation in the GCH1 gene and its promoter is associated with self-reported pain in the hip, knee and hand. In **Chapter 9** we aimed to demonstrate risk factors for rapid progression of OA symptoms ultimately leading to undergoing total joint replacement surgery in the hip or knee in the first 6 years of follow up in the CHECK cohort. Finally, **Chapter 10** presents a summary of the main findings, discusses these in relation to earlier studies, considers implications for clinical practice, and makes some recommendations for future research.

REFERENCES

1 Wolf AD, Pfleger B. Burden of Major Musculoskeletal Conditions. Policy and Practice. Special Theme-Bone and Joint Decade 2000-2010. Bulletin of the World Health Organization 2003, 81 (9): 646-656.

2 Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis. 2014 Sep;73(9):1659-64.

3 Hsiao CJ, Cherry DK, Beatty PC, et al. National ambulatory medical care survey: 2007 summary. Natl Health Stat Report 2010;27:1-32.

4 Bijlsma JW1, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice.Lancet. 2011 Jun 18;377(9783):2115-26.

5 Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 1989;32(11):1396-1405

6 Vingård E, Alfredsson L, Goldie I, Hogstedt C. Sports and osteo- arthrosis of the hip. An epidemiologic study. Am J Sports Med 1993;21(2):195-200

7 Hunter DJ, Eckstein F. Exercise and osteoarthritis. J Anat 2009; 214(2):197-207

8 Buckwalter, J. A., & Martin, J. A. (2004). Sports and osteoarthritis. Current Opinion in Rheumatology, 16(5), 634–639.

9 J Driban, G Lo, C Eaton, L Price, B Lu, T McAlindon. Knee Pain and a Prior Injury Are Associated With Increased Risk of a New Knee Injury: Data from the Osteoarthritis Initiative. J Rheumatol 2015 Aug;42(8):1463-9

10 Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005;13(9):769-781

11 Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther. 2015 Jun 8;17:152.

12 Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the d isease and its risk factors. Ann Intern Med 2000;133(8):635-646

13 Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., Netter, P., & Pottie, P. (2003). Evidence for a key role of leptin in osteoarthritis. Arthritis & Rheumatism, 48(11), 3118–3129.

14 JBJ van Meurs. Osteoarthritis year in review 2016: genetics, genomics and epigenetics. Osteoarthritis Cartilage. 2017;25(2):181-9)

15 Zhang W, McWilliams DF, Ingham SL, Doherty SA, Muthuri S, Muir KR, Doherty M. Nottingham knee osteoarthritis risk prediction models.Ann Rheum Dis. 2011 Sep;70(9):1599-604.

16 de Lange-Brokaar BJ, Ioan-Facsinay A, Yusuf E, Visser AW, Kroon HM, van Osch GJ, Zuurmond AM, Stojanovic-Susulic V, Bloem JL, Nelissen RG, Huizinga TW, Kloppenburg M. Association of pain in knee osteoarthritis with distinct patterns of synovitis. Arthritis Rheumatol. 2015 Mar;67(3):733-40.

17 Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Facilitation of pain sensitization in knee osteoarthritis and persistent post-operative pain: a cross-sectional study. Eur J Pain. 2014 Aug;18(7):1024-31.

18 Xu YM, Ge HY, Arendt-Nielsen L. J Sustained nociceptive mechanical stimulation of latent myofascial trigger point induces central sensitization in healthy subjects. Pain. 2010 Dec;11(12):1348-55.

19 Creamer P, Lethbridge-Cejku M, Costa P, Tobin JD, Herbst JH, Hochberg MC The relationship

of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging.. Arthritis Care Res. 1999 Feb;12(1):3-7.

20 Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M. A., Arden, N. K., Bresnihan, B., et al. (2010). EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Annals of the Rheumatic Diseases, 69(3), 483–489.

21 Buckland-Wright C.Imaging.InHochber gMC,SilmanAJ,SmolenJS, Weinblatt ME&WeismanMH(eds.) Rheumatology, 3rd edn. Edinburgh: Mosby, 2003, pp. 1823–1833.

22 Henley MB, Turkelson C, Jacobs JJ, Haralson RH. AOA symposium. Evidence-based medicine, the quality initiative, and P4P: Performance or paperwork? J Bone Joint Surg Am 2008;90:2781-2790.

23 Bedson J, Jordan K, Croft P. How do GPs use x rays to manage chronic knee pain in the elderly? A case study. Annals of the Rheumatic Diseases 2003;62:450–454.

24 Altman, R., Alarcón, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., et al. (1991). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis & Rheumatism, 34(5), 505–514.

25 Cibere J Do we need radiogrpahs to diagnose OA Best prac clin res rheumatol 2006:20,27-38

26 G. Peat, E. Thomas, R. Duncan, L. Wood, E. Hay, P. Croft Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care Ann Rheum Dis, 65 (10) (2006 Oct), pp. 1363–1367

27 American College of Rheumatology Extremity Magnetic Resonance Imaging Task Force. Extremity magnetic reso- nance imaging in rheumatoid arthritis: Report of the American College of Rheumatology Extremity Magnetic Resonance Imaging Task Force Arthritis Rheum 2006;54:1034-1047

28 Schiphof D, Oei EH, Hofman A, Waarsing JH, Weinans H, Bierma-Zeinstra SM. Sensitivity and associations with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic Kellgren and Lawrence criteria: a population-based study in middle-aged females. Osteoarthritis Cartilage. 2014 Mar;22(3):440-6.

29 Dieppe PA, Cushnaghan J, Shepstone L. The Bristol "OA500" study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthr Cartil 1997;5:87–97.

30 Bedson J, Croft P. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.

31 Kinds MB, Welsing PMJ, Vignon EP, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis and Cartilage 2011;1–30.

32 Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic c hanges and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27:1513-1517.

33 Schiphof D, de Klerk BM, Kerkhof HJM, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Annals of the Rheumatic Diseases 2011;70:1422–1427.

34 Felson DT, Niu J, Guermazi A, et al. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Annals of the Rheumatic Diseases 2011;70:1884–1886.

35 Lequesne MG & Laredo J. The faux profil (oblique view) of the hip in the standing position. Contribution to the evaluation of osteoarthritis of the adult hip. Annals of the Rheumatic Diseases 1998; 57: 676–681.

36 Tuhina Neogi, Yuqing Zhang. Epidemiology of Osteoarthritis. Rheumatic Disease Clinics of NA,2013,39(1),1-19.

37 Wesseling J, Bierma-Zeinstra SM, Kloppenburg M, Meijer R, Bijlsma JW Worsening of pain and function over 5 years in individuals with 'early' OA is related to structural damage: data from the Osteoarthritis Initiative and CHECK (Cohort Hip & Cohort Knee) study. Ann Rheum Dis. 2015 Feb;74(2):347-53.

38 Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, Bierma-Zeinstra SM. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis. 2012 Apr 4

39 Wesseling J, Dekker J, van den Berg WB, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Annals of the Rheumatic Diseases 2009;68:1413–1419.

40 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur. J. Epidemiol. 1991 Jul.;7(4):403-422.

CHAPTER 2

Prevalence and development of hip and knee osteoarthritis according to ACR criteria in the CHECK cohort

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Arthritis Research & Therapy. (2019) Jan;21(1)

ABSTRACT

Background

We aimed to evaluate the prevalence of hip and knee osteoarthritis (HOA, KOA) according to American College of Rheumatology (ACR) criteria among participants with suspected early symptomatic osteoarthritis (OA) in the CHECK cohort. We also assessed whether participants not fulfilling ACR criteria at baseline develop ACR defined OA at 2 and/or 5-years follow-up, and which baseline factors are associated with this development.

Methods

The CHECK cohort included 1,002 subjects with first presentation of knee and/or hip complaints. Primary outcome was onset of HOA and/or KOA according to the ACR criteria: the clinical classification criteria as well as the combined clinical and radiographic classification criteria at 2 and/or 5-years follow-up.

Results

Of the participants with hip complaints 63% (n=370) were classified as having HOA at baseline according to the ACR criteria. Of those not classified with HOA at baseline, 40% developed HOA according to the clinical or combined clinical/radiographic ACR criteria after 2 and/or 5 years. As many as 92% (n=829) of participants with knee complaints were classified as having KOA at baseline; of those not classified with KOA at baseline, 55% developed KOA according to the clinical ACR criteria or the clinical/radiographic ACR criteria after 2 and/or 5 years. The following factors were associated with development of HOA: morning stiffness (OR 2.39; 95% CI 1.14-4.98), painful internal rotation (OR 2.53; 95% CI 1.23-5.19), hip flexion <115° (OR 2.33; 95% CI 1.17-4.64) and ESR<20mm/h (OR 2.94; 95% CI 1.13-7.61). No variables were associated with development of KOA at 2 and/or 5-years follow-up.

Conclusions

A large proportion of persons with hip complaints not fulfilling the ACR criteria at baseline develop HOA after 2 and/or 5-years follow-up. Almost all persons with knee complaints already fulfill the clinical and/or radiographic ACR criteria for OA, and half of the persons not fulfilling criteria at baseline will do so after 5 years of follow up. Several individual ACR criteria for HOA at baseline were associated with the development of HOA at follow-up. This association was not proven for KOA, probably because of the small number of subjects developing KOA in this study.

INTRODUCTION

Osteoarthritis (OA) is associated with joint pain and functional limitation and is a leading cause of disability among elderly. OA is considered the most common form of arthritis from which 15- 18% of the population suffers.[1] Approximately 22% of the general population suffers from knee pain, and knee and hip pain are even more common in the elderly.[2,3] This generally leads to consultation with a physician: e.g., in primary care in the United Kingdom 33% of the population with knee pain consults a general practitioner (GP).[4] One reason for consultation is that patients with knee pain are looking for a definite diagnosis.[5] However, no clear clinical diagnostic primary care tools are available. Diagnosis of OA is often based on radiological evidence and/or on recommendations formulated by OA experts active in secondary care. [6]

The diagnosis of OA in patients suffering from knee or hip pain in primary care would become easier if well-defined criteria were used. The American College of Rheumatology (ACR) has developed different criteria for the classification of OA of the knee and hip in order to promote uniformity in reporting OA in epidemiological and intervention studies. These criteria were developed using combinations of clinical, clinical/laboratory, and clinical, laboratory and radiographic criteria.[7,8] Although these criteria were developed primarily for epidemiological purposes rather than for clinical use, the ACR criteria are commonly used as a diagnostic tool in secondary care. Because the criteria were developed in secondary care with patients with (mostly) rheumatoid arthritis in the control group, these criteria might primarily distinguish OA patients from RA patients. Furthermore, it has been suggested that the criteria are probably mainly diagnostic for late stage OA.[9] More uniform and early diagnosis of OA would provide a better window of opportunity for interventions and a clear diagnosis could also help to motivate patients for often difficult lifestyle changes involved with such a diagnosis.

The present study aims to evaluate the prevalence of ACR criteria in subjects with knee and hip complaints and whether they will develop evident OA according to the ACR criteria for hip and knee OA. Besides, this study aims to determine predictive factors for the development of knee/hip OA according to the ACR criteria, during 5-year follow up. These predictive factors may help to diagnose OA at an earlier stage in primary care and thereby promote earlier treatment according to established guidelines.

PATIENTS AND METHODS

Study design

The CHECK (cohort hip and cohort knee) study is a prospective cohort study of 1,002 individuals who first presented with knee and/or hip pain. Details of the protocol are published elsewhere and a summary is presented below.[10] No ethical approval is required for a prognostic cohort without interventions in the Netherlands.

Study population

Patients that potentially fulfilled the inclusion criteria were invited to join the study when they visited their GP. In addition, participants were recruited through advertisements, articles in local newspapers, and via the website of the Dutch Arthritis Association. Individuals were eligible to participate if they had pain and/or stiffness of the knee and/or hip, were aged between 45 and 65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within the preceding 6 months.

First presenters with pathological, previously diagnosed, conditions that obviously explained the existing symptoms (e.g. other rheumatic disease, isolated tendinitis/bursitis, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome or Bakers' cysts (sign of more advanced OA)) were excluded. Other exclusion criteria where: a co-morbidity that precluded physical evaluation and/or follow-up for at least 10 years, malignancy in the last 5 years, and inability to understand the Dutch language.[10] Physicians at the participating centers checked whether referred patients, as well as patients from their outpatient clinic, fulfilled the inclusion criteria. All patients underwent radiographic assessment, a physical examination, and filled out an extensive questionnaire at baseline, and at 2 and 5-years follow-up.

Outcome measures

OA of the hip/knee was determined using the ACR criteria for hip and knee OA.[7,8] We determined the clinical classification criteria, and the combined clinical and radiographic classification criteria. The clinical classification for OA of the hip was determined using hip flexion measured during physical examination instead of the erythrocyte sedimentation rate (ESR), as ESR was only available at baseline. Therefore, we followed the alternative proposed by the ACR when the ESR is not available; these alternative criteria were reported to be equally sensitive and specific.[8]

For the classification of knee OA, the clinical criteria, and the combined clinical and radiographic criteria, were determined. The criteria were first defined per joint (i.e. left and right hip/knee) separately. A participant was classified as having hip or knee OA when at least one of the two joints fulfilled one of the ACR criteria at 2 and/or at 5-year follow-up for the hip and the knee

separately, e.g. patients fulfilling ACR criteria at 2 years and not at 5 years of follow up would be included as OA patient.

Predictors

The predictors assessed were factors available at consultation with the GP, and consisted of demographic factors (age, gender and BMI), anamnestic factors (site of pain, pain score in the last week and morning stiffness), co-morbidity (lower back pain, previous surgery in the knee or hip, use of analgetics, uni- or bilateral hip or knee pain), factors from physical examination (pain at hip/knee flexion, pain and reduced range of motion (ROM) at internal rotation (ROM < 15 vs. >=15 degrees) and hip flexion (ROM >115 vs.<=115 degrees), presence of Heberden's nodules, palpable warmth of the knee, patellofemoral grinding, joint line tenderness, bony enlargement of the knee) and simple diagnostic tests such as plain radiography Kellgren & Lawrence grade (K&L 0 vs. ≥1) and ESR (< 20 mm/h). An overview of all tested variables (19 in the hip-cohort and 21 in the knee cohort) is presented in Supplementary Table 1.

Data analysis

To reduce bias and improve efficiency, we performed multiple imputation of missing values at baseline. We generated 10 imputed datasets using chained equations implemented in the R routine MICE. All analyses were done separately on the 10 imputation sets. A weighted mean outcome (as proposed by Rubin) was calculated.[11] Separate logistic regression models were constructed for participants with hip or knee complaints at baseline, but who were not classified at baseline as having OA according to the ACR classification criteria for hip and knee OA. Predictors used are described in Supplementary Table 1. Because of the large number of measured predictors a data reduction method was used. Predictors related to the outcome ($p < 0.2$) were divided into 5 categories (i.e. demographics; complaints and symptoms; co-morbidities; physical examination; and diagnostic interventions). Per category of participants with knee or hip complaints a multiple logistic or linear regression (enter method) analysis was performed with predictors that were univariately associated with the outcome ($p < 0.2$). All predictors selected in the different categories were again entered into the final logistic or linear regression analysis to build the final model ($p < 0.05$). The results are presented as odds ratios (OR) with 95% confidence intervals (CI). Predictive values and likelihood ratios were calculated.[12] All analyses were performed with the SPSS software package (version 22.0.0.0).

RESULTS

The baseline characteristics of the study population are presented in Table 1.
Of the 1,002 participants in the CHECK cohort, 79.0% was female and mean age was 55.9 years. Of the total study population, 58.7% (n=588) had hip complaints, either stiffness or pain, at baseline. Of these, which 27.6% (n=162) were classified as having hip OA at baseline according to the ACR clinical criteria,50.0% (n=295) according to the combined clinical/radiographic criteria for hip OA, and 62.9% (n=370) met either one or the other of these criteria. 82.7% (n=829) had knee complaints at baseline, of which, 81.3% (n=674) were classified as having knee OA at baseline according to the ACR clinical criteria,73.1% (n=606) according to the combined clinical/radiographic criteria for knee OA, and 91.7% (n=760) met either one or the other of these criteria.

Table 1 Baseline characteristics of the CHECK study population at baseline.

Characteristics	**Participants (n=1002)**	**Knee complaints* (n=829)**	**Hip complaints# (n=588)**
Women, %	79.0	79.6	80.8
Age in years (SD)	55.9 (5.2)	56.0 (5.1)	55.8 (5.3)
BMI (SD)	26.2 (4.1)	26.4 (4.1)	26.1 (4.1)
WOMAC Pain (SD)	25.4 (17.2)	25.6 (17.3)	27.2 (17.1)
WOMAC Function	23.5 (17.1)	24 (17.3)	25.3 (17.6)
WOMAC Stiffness	33.2 (21.1)	33.8 (21.1)	34.8 (21.2)
NRS (0-10) (SD)	3.6 (2.1)	3.6 (2.1)	3.7 (2.1)
Hip pain, %	58.7	50.1	100.0
Knee pain, %	83.0	100.0	71.1
ACR clinical knee OA, (%)		674 (81.3)	
ACR combined knee OA (%)		606 (73.1)	
Clinical / combined knee OA (%)		760 (91.7)	
ACR clinical hip OA (%)			162 (27.6)
ACR combined hip OA (%)			322 (54.7)
Clinical or combined hip OA (%)			370 (62.9)

*Participant with either knee, or knee and hip pain; #Participant with either hip, or hip and knee pain; SD standard deviation. NRS numeric ratig scale 0-10 WOMAC scores 0-100

Predictive factors in participants with hip complaints and development of OA according to the ACR criteria
Of the 198 participants with hip complaints that were not classified as having hip OA at baseline according to the ACR clinical and/or combined criteria and were not lost to follow-up, 80 fulfilled the ACR criteria at 2 and/or 5-year follow-up. Based on the 19 potential predictive factors measured at baseline, 8 univariately significant factors were included in the final multivariate logistic regression model. This model identified the following baseline factors: morning stiffness (OR 2.39; 95% CI 1.14-4.98, LR+ 1.56), painful internal rotation (OR 2.53; 95% CI 1.23-5.19, LR+ 1.71), hip flexion < 115 degrees (OR 2.33 95% CI 1.17-4.64, LR+ 1.47) and ESR < 20 mm/h (OR 2.94; 95% CI 1.13-7.61, LR+ 0.77) (Table 2).

Combinations of these factors provided even higher likelihood ratios. Individuals with both morning stiffness and painful internal rotation had a positive likelihood ratio (LR +) of 4.03 (PPV 0.73, NPV 0.64, LR- 0.83). When individuals presented with morning stiffness, painful internal rotation and hip flexion < 115 degrees the positive likelihood ratio (LR+) was 15 (PPV 0.91, NPV 0.63, LR- 0.88). Addition of ESR < 20 mm/h as a predictor did not enhance the predictive value (LR+ 12,66, LR- 0.89, PPV 0.9,NPV 0.61).

Predictive factors in participants with knee complaints
A total of 64 participants with knee pain were not classified as having knee OA at baseline according to the ACR clinical and/or combined criteria and were not lost to follow-up. Of these, 35 fulfilled the ACR criteria at 2 and/or 5-year follow-up. In this group, 21 potential predictive factors were measured at baseline (Supplemental Table 1). Age, morning stiffness, joint line tenderness and ESR < 20 mm/h were included in the final multivariate logistic regression model. In this small sample no variable reached statistical significance. Morning stiffness in the knee < 30 minutes had a positive likelihood ratio (LR+) of 4.97 (PPV 0.86, NPV 0.49, LR- 0.08). (Table 3).

Table 2 Multivariate regression analysis for hip OA at 2 and/or 5-year follow-up according to the ACR classification criteria (n=198, 80 cases, a priori risk= 0.40).

Baseline characteristics	Analysis per category OR (95% CI)
Demographics	
Age (<=50 vs. >50)	0.53(0.28-1.01)
Complaints and symptoms	
Pain last week, NRS	1.15(0.99-1.33)
Morning stiffness hip (yes=1/no=0)	**2.60 (1.14-3.71)**
Comorbidities and interventions	
Knee pain (yes=1/no=0)	0.63 (0.33-1.20)
Painkillers (yes=1/no=0)	2.01 (1.12-3.59)
Physical examination	
Painful hip internal rotation (yes=1/no=0)	**2.59 (1.43-4.67)**
Hip flexion ROM (0= >115 vs. 1= <=115)	**2.00 (1.12-3.67)**
Diagnostic tests	
ESR < 20	**3.54 (1.30-7.13)**

OR=odds ratio; PPV=positive predictive value; NPV=negative predictive value; NRS=numeric rating scale; ROM=range of motion; Bold values indicate significant values (p< 0.05) in final model; LR+=positive likelihood ratio; LR- =negative likelihood ratio; na=not applicable (continuous variable).

Table 3 Multivariate regression analysis for knee OA at 2 and/or 5-year follow-up according to the ACR classification criteria (n=64, 35 cases, a priori risk = 0.55).

	Analysis per category OR (95% CI)
Demographics	
Age (<=50 vs. >50)	0.37 (0.13-1.36)
Complaints and symptoms	
Morning stiffness knee (yes=1/no=0)	6.79 (0.65-51.23)
Physical examination	
Joint line tenderness	1.05 (0.21-5.14)
Diagnostic tests	
ESR < 20	0.94 (0.87-1.02)

OR=odds ratio; PPV=positive predictive value; NPV=negative predictive value; NRS=numeric rating scale; ROM=range of motion; p< 0.05; LR+=positive likelihood ratio; LR- =negative likelihood ratio; na=not applicable (continuous variable).

Multivariate analysis OR(95% CI)	PPV	NPV	LR+	LR-
0.90(0.41-1.99)	0.36	0.48	0.84	1.6
1.04(0.87-1.26)	na	na	na	na
2.39 (1.14-4.98)	**0.51**	**0.66**	**1.56**	**0.75**
0.71 (0.32-1.55)	0.37	0.51	0.89	1.42
1.60 (0.75-3.41)	0.5	0.67	1.47	0.73
2.53 (1.23-5.19)	**0.53**	**0.69**	**1.71**	**0.66**
2.33 (1.17-4.64)	**0.5**	**0.67**	**1.47**	**0.73**
2.94 (1.13-7.61)	**0.46**	**0.77**	**1.22**	**0.4**

Multivariate analysis OR (95% CI)	PPV	NPV	LR+	LR-
0.42 (0.14-1.06)	0.39	0.37	0.53	1.44
6.08 (0.53-69.93)	0.86	0.49	4.97	0.08
1.92 (0.34-10.79)	0.73	0.5	2.2	0.8
0.94 (0.85-1.03)	na	na	na	na

DISCUSSION

This study demonstrates that the majority of patients presenting for the first time with hip pain fulfill the combined ACR hip OA criteria, both clinical or combined ACR criteria, and that 40% of patients not fulfilling those ACR criteria will develop evident OA according to the clinical or combined ACR criteria for hip after 5 years. For this last subgroup we identified the following predictive factors: morning stiffness, painful internal rotation, hip flexion < 115° and an ESR < 20 mm/h. Combinations of these signs and symptoms have an even higher predictive value. In first presenters with knee pain as many as 92% do fulfill ACR criteria, both clinical or combined ACR criteria, at baseline. For this reason, the number of participants with knee symptoms not fulfilling the ACR criteria was, in fact, too small to assess predictors for OA development. This study is unique in having such a large group of first presenters. We would like to argue that the CHECK cohort represents the first presenters with hip and knee complaints suspected for early OA in (Dutch) primary care.

We were surprised by the large percentage of participants fulfilling ACR criteria at baseline in participants with hip complaints, and that this was even more pronounced in participants with knee complaints.

In a previous open population-based knee pain cohort that included persons with chronic knee pain, 47% were not diagnosed with OA at baseline.[16] This proportion is larger than our proportion of participants without OA at baseline. This difference could be due to the lower age (mean age 45) and lower BMI in that cohort. In that same study, the majority 86% of persons developed OA during the 12-year follow-up.[16] In our study, a smaller proportion of participants with pain in the hip (40%) and knee (55%) were diagnosed with either hip or knee OA according to the ACR criteria during follow-up. However, this result could be related to the shorter follow-up period in our study.

The predictive factors we identified to be associated with the development to hip OA are consistent with the previous literature. Morning stiffness and limited internal rotation are known predictors for total hip replacement in primary care.[19,20] Age and pain levels, however, were not statistically significant in the final model in the current study whereas other studies found these to be predictive.[19,20] This could be explained by our relatively young cohort with generally quite low pain levels (WOMAC pain score 27.2 on a scale of 0-100, NRS 3.7 , table 1) such as can be expected in an early OA cohort. Limited hip flexion and ESR < 20 mm/h were not identified previously as risk factors for development but reached significance in our final model. A possible explanation could be that higher ESR was related to inflammatory diseases at baseline which were not evident at the time of inclusion.

In contrast to previous studies we were unable to identify predictors for development of knee pain into knee OA,[17,18] even when we performed a separate analysis for the clinical and the combined ACR criteria. Also, in these subgroup analyses, no variables were significantly associated with development of knee OA, except for borderline significant results for morning stiffness. The high percentage of knee patients fulfilling the ACR criteria at baseline is probably the main reason for not finding significant predictive factors based on OR. However the predictive values show that morning stiffness would probably a good prognostic value if we had more power.

As expected, the criteria found to be associated with fulfilling the ACR criteria at follow-up in either the combined or separate analysis for the clinical and the combined ACR criteria, were all sub-items of the ACR criteria. This indicates that pain in combination with one or more of these sub-items of the ACR criteria might be indicative of future OA.

No clear diagnostic criteria for OA currently exist in primary care, e.g. the ACR criteria are widely used in epidemiologic research but not validated in primary care. Most discussions focus on the use of radiographic outcomes.[21] For example, the Kellgren and Lawrence (K&L) grade of 2 or higher is accepted as a cut-off for OA in epidemiological studies and (possibly) in secondary care. The cut-off of K&L grade 1 and higher is useful in epidemiologic studies to predict progression, but its use is not advised in primary care since the knee radiography has no additional value in the assessment of individual patients with knee pain.[22-25] However, in the present study we chose to examine not only clinical features but also radiographic features, because of the availability and still frequent use of radiography in primary care. Our study clearly showed that radiographic features do not predict fulfilling ACR criteria, also not when assessed in subgroups of clinical or combined ACR criteria (data not shown.)

The prevalence, incidence and the predictors for the incidence of OA are clinically important findings, because it implicates that most persons aged 45 to 65 years of age presenting to a GP with no other hip or knee disease could already be diagnosed with clinical OA or are prone to develop clinical OA within the following years. This could help to provide a clear diagnosis, which contributes to early treatment according to guidelines which are available for both hip and knee, whereas undiagnosed knee and/or hip pain is usually treated according to the best insight of the individual physician.[13,14,15] For patients diagnosed with OA, first-step treatments (e.g. education, lifestyle advice, and acetaminophen) should be started, due to their beneficial effects in an early stage of the disease process.[26]

Our study offers a unique population to study hip and knee pain in first presenters, since the included patients are comparable with patients who would present to a primary care physician and therefore this study helps in addressing the diagnostic challenge of hip and knee pain in

primary care. A limitation of our study is that a substantial number of variables were tested in the analysis. Due to the limited number of OA cases found, we could justify testing only 2-5 variables per analysis per category when building the explorative models. However, clinically relevant variables were used (defined prior to our analyses) that were previously applied in epidemiological/clinical research and no new predictors were introduced. Further, data reduction methods were used by means of restrictions based on p-values by pre-analyzing the predictors in their categories. Due to this lack of power other predictors of OA could remain unexposed.

Conclusion

The majority of first presenters with hip pain fulfill the clinical or combined ACR criteria and 40% of the patients not fulfilling those ACR criteria will develop OA according to the clinical or combined ACR criteria for hip after 5 years. Predictive factors for the development of HOA are morning stiffness, painful internal rotation, hip flexion < 115° and an ESR < 20 mm/h. In first presenters with knee pain as many as 92% already fulfill the clinical or combined ACR criteria . No predictive characteristics for the development of knee OA in those not fulfilling ACR criteria could be identified.

Recommendations

We would suggest that future studies validate whether patients with hip complaints aged above 45 with the following characteristics: morning stiffness, painful internal rotation, hip flexion < 115° and an ESR < 20 mm/h are indeed early OA patients. It also needs to be validated whether first presenters with knee complaints aged above 45 are indeed early KOA patients.

REFERENCES

1 Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. Curr Opin Rheum 2006;18:147–56.

2 Linsell L, Dawson J, Zondervan K, Rose P, Carr A, Randall T, Fitzpatrick R. Population survey comparing older adults with hip versus knee pain in primary care. Br J Gen Pract 2005;55:192–8.

3 Odding E, Valkenburg HA, Algra D, Vandenouweland F, Grobbee D, Hofman A. Association of locomotor complaints and disability in the Rotterdam study. Ann Rheum Dis 1995;54:721–5.

4 Jinks C, Jordan K, Ong B, Croft P. A brief screening tool for knee pain in primary care (KNEST). 2. Results from a survey in the general population aged 50 and over. Rheum 2004;43:55–61.

5 Mann C, Gooberman-Hill R. Health care provision for osteoarthritis: Concordance between what patients would like and what health professionals think they should have. Arthritis Care Res (Hoboken) 2011;63:963–72.

6 Zhang W, Doherty M, Peat G, Bierma-Zeinstra S, Arden N, Bresnihan B, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheumatic Dis 2010;69:483–9.

7 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29:1039–49.

8 Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.

9 Peat G, Thomas E, Duncan R, Wood L, Hay E, Croft P. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. Ann Rheum Dis 2006;65:1363–7.

10 Wesseling J, Dekker J, van den Berg W, Bierma-Zeinstra S, Boers M, Cats H, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009;68:1413–9.

11 Multiple Imputation for Nonresponse in Surveys. New York: J. Wiley & Sons

12 Altman D, Bland J. Diagnostic tests 2: Predictive values. BMJ 1994;309:102–2.

13 Zhang W, Moskowitz M, Nuki G, Abramson S, Altman R, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669–81.

14 Jordan K, Arden N, Doherty M, Bannwarth B, Bijlsma J, Dieppe P, et al.. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145–55.

15 Zhang W, Nuki G, Moskowitz W, Abramson S, Altman R, Arden N, et al. OARSI r ecommendations for the management of hip and knee osteoarthritis. Osteoarthritis Cartilage 2010;18:476–99.

16 Thorstensson C, Andersson M, Jonsson H, Saxne T, Petersson I. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. Ann Rheum Dis 2009;68:1890–3.

17 Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, Dieppe, P. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.

18 Belo J, Berger M, Reijman M, Koes B, Bierma-Zeinstra S. Prognostic factors of progression of osteoarthritis of the knee: A systematic review of observational studies. Arthritis Rheum 2007;57:13–26.

19 Lievense A, Bierma-Zeinstra S, Verhagen A, Verhaar J, Koes B. Prognostic factors of progress of hip osteoarthritis: A systematic review. Arthritis & Rheumatism, 2002;47(5):556–562.

20 Birrell F, Lunt M, Macfarlane, G, Silman A. Association between pain in the hip region and radiographic changes of osteoarthritis: results from a population-based study. Rheumatology, 2005;44(3):337–341.

21 Kinds M, Welsing P, Vignon E, Bijlsma J, Viergever M, Marijnissen A, Lafeber F. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis Cartilage 2011;19:168-78.

22 Schiphof D, Boers M, Bierma-Zeinstra SMA. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis 2007;67:1034–6.

23 Schiphof D, de Klerk B, Koes B, Bierma-Zeinstra, S. Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal. J Clin Epidemiol 2008;61:1205-1225

24 Reijman M, Hazes J, Pols H, Bernsen R, Koes B, Bierma-Zeinstra, S. Validity and reliability of three definitions of hip osteoarthritis: cross sectional and longitudinal approach. Ann Rheum Dis 2004;63:1427–33.

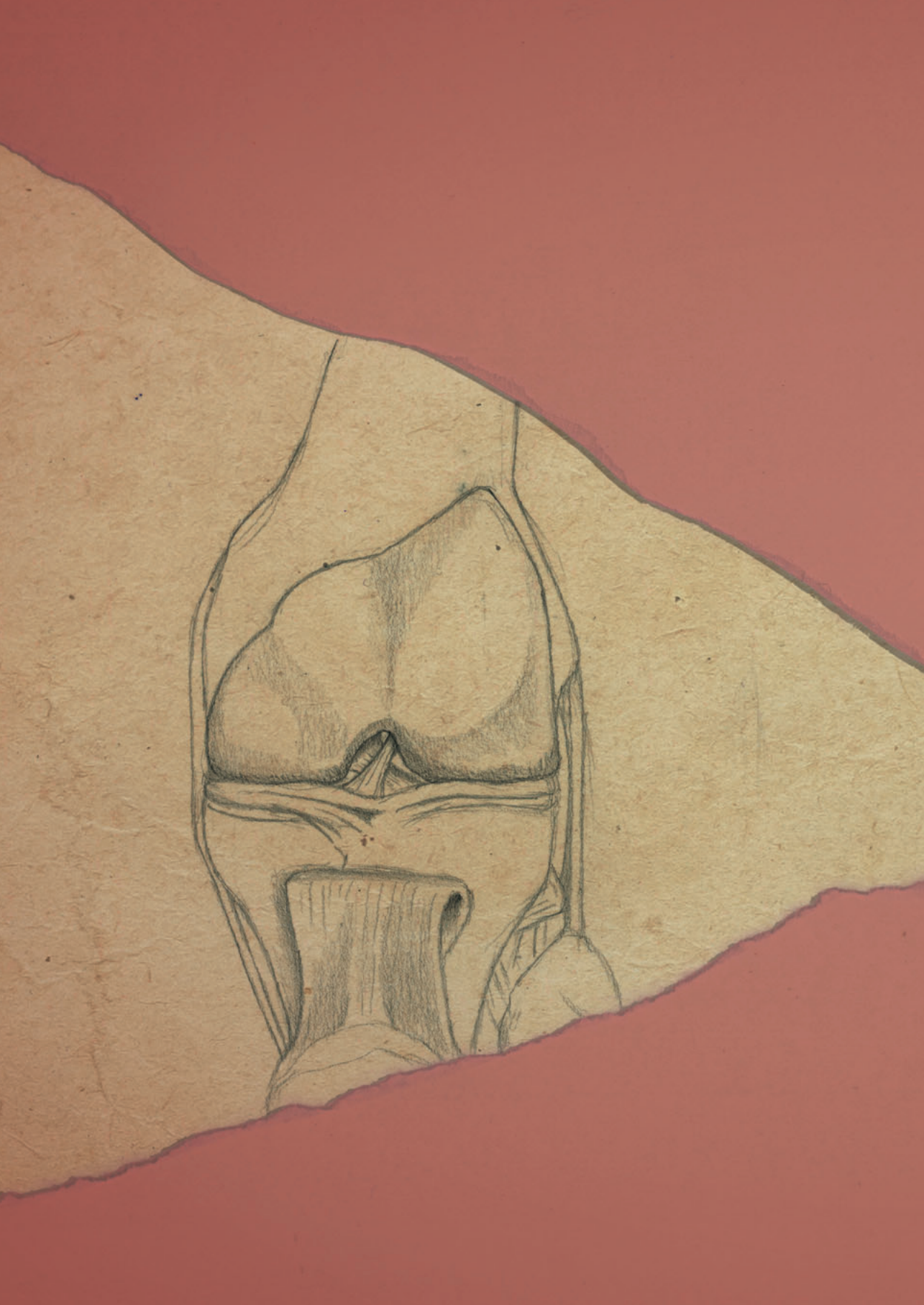
25 Bedson J, Croft P. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.

26 Smink A, Ende C, Vliet Vlieland T, Swierstra B, Kortland J, Bijlsma J et al. 'Beating osteoARThritis': Development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. Clin Rheumatol 2011;30:1623–9.

Supplemental table 1

Hip	p-value	OR	CI-	CI+
Demographics				
Age (<=50 vs. >50 years)	0.05	0.53	0.28	1.00
Gender (men vs. woman)	0.44	0.71	0.30	1.70
Complaints and symptoms				
Knee (pain yes/no)	0.16	0.63	0.33	1.20
Pain last week, NRS	0.06	1.15	0.99	1.33
Morning stiffness hip (yes=1/no=0)	0.02	2.06	1.14	3.71
resting pain	0.22	2.24	0.61	8.26
Comorbidities and interventions				
Complaints in lower spine	0.26	1.53	0.73	3.19
BMI (continuous)	0.96	1.00	0.93	1.08
Surgery knee or hip (yes vs.no)	na			
Analgesics (yes=1/no=0)	0.02	2.01	1.12	3.59
Bilateral complaints (yes=0 vs. no=1)	0.25	1.47	0.77	2.80
Physical examination				
Painful hip flexion (yes vs. no)	0.61	1.28	0.49	3.36
Painful hip internal rotation (yes vs. no)	0.00	2.59	1.43	4.67
Painful hip external rotation (yes vs. no)	0.33	1.99	0.47	8.37
Internal rotation ROM (<15 vs.>=15)	0.80	1.36	0.12	15.28
Hip flexion ROM (>115 vs.<=115)	0.02	2.00	1.12	3.57
Heberden's nodes (yes vs. no)	0.45	0.80	0.46	1.42
Diagnostic investigation				
Kellgren & Lawrence (0 vs ≥1)	0.71	1.19	0.47	3.00
ESR <20 vs > 20	0.01	3.05	1.30	7.13

Supplemental table 1 (Continued)				
Knee				
Demographics				
Age (<=50 vs. >50 years)	0.06	0.37	0.13	1.06
Gender (men vs. woman)	0.32	2.02	0.51	8.00
Complaints and symptoms				
Hip (pain yes/no)	0.91	1.06	0.39	2.88
Pain last week, NRS	0.62	1.08	0.80	1.46
Morning stiffness knee	0.11	5.79	0.66	51.24
resting pain	na			
Crepitus while squatting	0.53	1.98	0.24	16.64
Comorbidities and interventions				
Complaints in lower spine	0.54	1.74	0.30	10.27
BMI (continuous)	0.50	1.05	0.91	1.23
Surgery knee or hip (yes vs. no)	na			
Analgesics (yes=1/no=0)	0.30	2.17	0.51	9.27
Bilateral complaints (yes=0 vs. no=1)	0.27	0.54	0.18	1.61
Physical examination				
painful knee flexion yes vs. no	na			
painful knee extension yes vs. No	na			
palpable warmth knee	na			
Patellofemoral grinding	0.19	3.22	0.55	18.76
Heberden's nodes yes vs. No	0.74	1.20	0.41	3.55
Joint line tenderness	0.12	2.75	0.77	9.86
Bony enlargement knee				
Diagnostic investigation				
Kellgren & Lawrence (0=0 / 1=1/2)	0.95	1.05	0.21	5.14
ESR <20 vs > 20	0.86	1.16	0.22	6.27



CHAPTER 3

Additional Value of Different Radiographic Views on the Identification of Early Radiographic Hip and Knee Osteoarthritis and Its Progression: A Cohort Study

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Arthritis Care Res (Hoboken). 2017 Nov;69(11):1644-1650

ABSTRACT

Objective

To investigate the prevalence and progression of early radiographic osteoarthritis (ROA) of the hip and knee on different radiographic views, to determine whether different radiographic views have additional value in detecting early hip and knee ROA cases, or progression.

Methods

In the CHECK cohort (N=1002) five different radiographs were obtained: an anteroposterior (AP) and faux profile view of the hips and a posteroanterior (PA), mediolateral (ML) and skyline view of the knees. Prevalence of ROA was estimated based on each view separately and in combinations. We determined whether different radiographic views have additional value in detecting and determining progression of ROA cases compared to standard projections.

Results

In the hip we found 22.9% more cases when we combined both views. In the knee, we detected 79.7% more ROA cases when we combined information from all three different radiographic views than when using only the PA view. Progression was demonstrated in 33.1% more cases when using 2 hip radiographs, and in 65.1% more cases when using three knee radiographs.

Conclusion

Different radiographic views increase the number of participants with ROA in an early osteoarthritis cohort both at baseline and follow up. Progression of early ROA is demonstrated more frequently when multiple different radiographic views are used.

INTRODUCTION

A large number of studies have indicated the discordance between pain in hips and knees diagnosed with osteoarthritis (OA) and findings on radiographs.[1,2] In a study by Hannan et al., only 47% of subjects with radiographic OA (ROA) of the knee reported knee pain, and only 15% of subjects with knee pain had ROA.[3] Despite this well-reported discordance, radiography of the hips and knees is still commonly used in clinical practice to diagnose OA and to assess OA progression, although most guidelines recommend advise no radiographic assessment.[4,5]

Several suggestions have been made to improve the diagnostic and prognostic value of radiographic findings by adapting the most commonly used existing radiographic OA grading systems.[5] Some authors have suggested using new grading techniques with actual quantitative measurements of JSW, or using different radiographic views.[2,6,7] Others have suggested that magnetic resonance imaging (MRI) may be more sensitive for the diagnosis and follow-up of OA (8). Radiography, though, remains the most important imaging technique because of its widespread availability and low costs.[9]

Previous research has shown that symptomatic knee OA may be associated with patellofemoral OA that is not revealed by PA (posteroanterior) knee radiographs. When the radiography protocol also consisted of (lateral and/or skyline) views that enable assessment of the patellofemoral joint (PFJ), positive associations between knee pain and radiographic joint damage were found in several studies. [1,10,11,12,13]

In the hip, it has been suggested that the faux profile (FP) view is more sensitive than the AP (anteroposterior) view for detecting early OA. Lequesne et al. introduced the FP view as a useful aid for detecting posterior or anterosuperior joint space narrowing (JSN) when no JSN is visible on the AP view.[13] They also demonstrated that this technique helps in detecting OA at an earlier stage compared to the AP view.[13]

The primary purpose of this study was, therefore, to investigate the prevalence and progression of radiographic hip and knee OA features when different radiographic views are used in an early OA cohort. We also aimed to determine whether different view radiographs, single or in combination, have additional value in detecting early hip and knee ROA cases compared to standard AP/PA projections.

METHODS

We used data from the CHECK study; CHECK (Cohort Hip and Cohort Knee) is an ongoing prospective multicenter cohort study of 1,002 individuals with early symptomatic OA of the hip or knee aimed to study progression of OA. Details of the protocol have been published earlier, and a summary is presented below.[14]

Study population

Participants that potentially fulfilled the inclusion criteria were invited to join the study when they visited their general practitioner (GP). In addition, participants were recruited through advertisements, articles in local newspapers, and via the website of the Dutch Arthritis Foundation. Individuals were eligible to participate if they had pain and/or stiffness of the hip and/or knee, were aged between 45 and 65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before inclusion.

Exclusion criteria were: any pathological condition other than OA that could explain the present symptoms (e.g. other rheumatic disease, isolated tendinitis/bursitis, previous hip or knee joint replacement, congenital dysplasia of the hip, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome or Baker's cysts), or a co-morbidity that precluded physical evaluation and/or follow-up for at least 10 years, malignancy in the last 5 years, and inability to understand the Dutch language. Physicians at the participating centers ascertained whether participants fulfilled the inclusion criteria.

All participants underwent radiographic assessment of hips and knees, standardized physical examination, and filled out an extensive questionnaire at baseline and after two and five years of follow-up, including the Western Ontario McMaster questionnaire (WOMAC) pain subscale which ranges from 0 (no pain) to 20 (severe pain). [14,15]

Radiography

All radiographs obtained at baseline and during follow-up in the CHECK study were acquired according to a standardized radiography protocol. For the hips, weight-bearing anteroposterior radiographs of the pelvis were acquired, as well as weight-bearing faux profile radiographs of both hips taken according to Lequesne and Laredo.[13] The faux profile view provides a lateral projection of the femoral head and neck, and an oblique view of the acetabulum tangential to its superoanteromedial edge (13). For the knee, semi-flexed (7–10 degrees) weight-bearing posteroanterior radiographs of the tibiofemoral joints were made, followed by standing mediolateral views in 30 degrees flexion for assessment of the tibiofemoral and patellofemoral joints. Skyline (inferior to superior) views of the patellofemoral joints (with 30 degrees' flexion of the tibiofemoral joint) were also performed.

Only subjects of which both baseline and 5 year follow up radiographs were available were used in this study resulting in a study population of 894 participants.

Radiographic scoring

Five trained observers independently scored all radiographs. The inter-reader observer reliability (prevalence-adjusted and bias-adjusted kappa; PABAK) across a range or radiographic OA features was 0.80 (K&L 0 vs K&L≥ 1) for the hip and 0.62 (K&L 0 vs K&L≥ 1) for the knee. More detailed inter-reader reliability scores have been published previously (16).

The anteroposterior (AP) radiographs of the hip were scored for individual radiographic OA features according to Altman et al..[17] For grading the severity of hip OA, the Kellgren & Lawrence definition was used and assessed on the AP radiograph.[18] Superior and medial hip JSN, superior acetabular osteophytes, and superior and inferior femoral osteophytes were scored on a 0-3 scale. Inferior acetabular osteophytes, femoral subchondral sclerosis, acetabular subchondral cysts, flattening of the femoral head and buttressing were scored on a 0 -1 scale (19). On the faux profile radiographs, superior and posterior JSN was scored using the aforementioned 0-3 scale. [13].

The posteroanterior (PA) radiographs of the knee were scored for individual OA features according to Altman et al..[17] For grading the severity of knee OA, the Kellgren & Lawrence definition was used, as determined on the PA radiograph (18). Medial and lateral femorotibial JSN, medial and lateral femoral osteophytes, and medial and lateral tibial osteophytes were scored on a 0-3 scale, (0 = normal; 1 = mild; 2 = moderate; and 3 = severe). Tibial bone attrition, tibial sclerosis and femoral sclerosis were scored both medially and laterally on a 0–1 scale (0= absent; 1 = present). Spiking of the tibial spines was scored on a 0-1 scale according to the atlas of Burnett et al.[19] The mediolateral and skyline radiographs of the knee were assessed for patellar osteophytes on a 0-3 scale according to Burnett et al., as was patellofemoral sclerosis (only on the skyline view).[19]

Outcomes

To study the presence of ROA in our cohort, we used different radiographic views at baseline. Hip ROA on the faux profile radiograph was defined as JSN ≥ 1 of at least the superior or posterior joint space (13). Femorotibial ROA of the knee on the PA view and ROA of the hip on the AP view were defined as K&L grade ≥ 1 graded according to Altman et al. Patellofemoral ROA on the skyline radiographs was defined in three ways: either only JSN ≥ 1, either only osteophytes ≥ 1, or any sign (either JSN or osteophytes) of ROA scored according to Altman et al.

Patellofemoral ROA on the mediolateral radiographs was also defined as osteophytes ≥ 1 according to the atlas of Burnett et al. Progression was defined when there was an increase of the K&L score or in increase in any osteophyte or JSN score between baseline and 5 year follow up.

Statistical analysis

We used descriptive statistics per hip and knee to calculate prevalence of K&L score, ROA features, ROA definitions at baseline and 5 year of follow-up, as well as to determine ROA progression. All analyses were performed with the SPSS software package (IBM corporation, version 22.0.0.0).

RESULTS

At baseline, mean age of the participants was 55.9 years (SD 5.2), 79% was female, average body mass index (BMI) was 26.2 kg/m^2 (SD 4.1), and mean WOMAC pain score was 5.07 (SD 3.1). 411 (41%) Participants reported pain in the knee only, 170 (17%) only reported pain in the hip, and 421 (42%) reported pain in both knee and hip. Prevalence of radiographic OA features visualized on each radiographic view are described in Table 1. The lost to follow-up rate from baseline to 5-years follow-up was 10.9%

All results described are those of the right hip and the right knee at baseline. For the left hip and knee similar numbers were found.

Table 1 Prevalence of early radiographic OA features for the hip and the knee per radiographic view at baseline (N = 894)

	Baseline				**Progression T0-T5**		
	Left/Right	**No OA**	**OA ≥ 1**	**NI**	**No**	**Yes**	**NI**
Hip							
Anteroposterior view							
K&L score	L	649	212	33	697	139	58
	R	651	210	33	688	150	56
Superior joint space narrowing	L	675	186	33	768	69	57
	R	673	188	33	766	72	56
Medial joint space narrowing	L	747	114	33	753	84	57
	R	747	114	33	769	69	56
Superior acetabulum osteophytes	L	744	114	36	697	137	60
	R	752	108	34	712	124	58
Superior femoral head osteophytes	L	691	166	37	716	117	61
	R	704	156	34	714	123	57
Inferior acetabulum osteophytes	L	793	68	33	771	66	57
	R	796	66	32	773	66	55
Inferior femoral head osteophytes	L	766	95	33	759	78	57
	R	765	96	33	751	87	56
Faux Profile view							
Superior joint space narrowing	L	810	62	22	793	55	51
	R	796	68	30	779	58	62
Inferior joint space narrowing	L	825	46	23	783	64	47
	R	815	49	30	801	37	56

Table 1. Continued

	Baseline				Progression T0-T5		
	Left/Right	**No OA**	**OA ≥ 1**	**NI**	**No**	**Yes**	**NI**
Knee							
Posteroanterior view							
K&L Score Knee	L	535	343	16	549	297	48
	R	544	330	20	524	318	52
Medial joint space narrowing	L	399	480	15	653	194	47
	R	446	429	19	656	188	50
Lateral joint space narrowing	L	652	227	15	763	84	47
	R	643	232	19	754	90	50
Medial femoral osteophytes	L	837	41	16	784	62	48
	R	830	44	20	769	74	51
Lateral femoral osteophytes	L	816	62	16	748	98	48
	R	806	66	22	749	92	53
Medial tibial osteophytes	L	640	237	17	633	212	49
	R	628	244	22	622	219	53
Lateral tibial osteophytes	L	646	229	19	637	206	51
	R	628	242	24	619	219	56
Mediolateral view							
Patellofemoral osteophytes	L	525	339	30	610	223	61
	R	504	363	27	600	229	65
Skyline view							
Patellofemoral osteophytes	L	489	366	39	627	195	72
	R	464	396	34	716	117	61
Patellofemoral joint space narrowing	L	785	73	36	727	100	67
	R	779	85	30	806	26	62

NI: Radiograph not available or interpretable; progression: progression of at least one grade

Hip

K&L ≥1 on the AP view vs JSN ≥1 on the faux profile view. On the AP view we detected 210 (23.4%) hip ROA cases in our population with a K&L grade ≥1. On the faux profile view we observed JSN ≥1 in 112 (12.5%) of the hips. When we combined these views we found ROA in 258 hips (28.8%) (Table 2), an increase of 48 (22.9%) ROA cases in the cohort compared to the K&L score on the AP view alone.

Table 2. Prevalence of ROA on different views, hips, baseline, 5 year follow up, and progression after 5 years of follow up.

Radiographic view obtained (features assessed)	**ROA visible on radiograph**			
Left hip Baseline	AP only	FP only	AP + FP	Any
AP +FP (JSN)	158	46	53	257
Left hip 5 year follow up	AP only	FP only	AP + FP	Any
AP +FP (JSN)	198	52	84	334
Progression after 5 years, L	AP only	FP only	AP + FP	Any
AP + JSN (FP)	105	29	32	166
Right hip Baseline	AP only	FP only	AP + FP	Any
AP +FP (JSN)	146	53	59	258
Right hip 5 year follow up	AP only	FP only	AP + FP	Any
AP +FP (JSN)	201	57	94	352
Progression after 5 years, R	AP only	FP only	AP + FP	Any
AP + JSN (FP)	107	39	39	185

AP: anteroposterior hip (K&L), JSN: joint space narrowing, FP: faux profile, L: left, R:right

Progression

After five years of follow up an increase of at least 1 grade on the K&L score on the AP view was seen on 139 (15.5%) of the hips. When we combined the AP and faux profile view we identified 185 hips with progression, an increase 46 (33.1%) hip ROA cases compared to the K&L score on the AP view alone (Table 2).

Knee

K&L ≥1 ROA on the PA view vs Osteophytes ≥1 on the PA, mediolateral and skyline view. We found ROA of K&L ≥1 severity on the PA view in 330 out of 894 knees (36.9%). The prevalence of osteophytes ≥ 1 on the mediolateral view and skyline view was 363 (40.6%), and 396 (44.3%), respectively (Table 1). When we combined these views we found ROA in 585 knees (65.4%), an increase of 255 (77.3.5%) ROA cases compared to the K&L score on the AP view (Table 3).

K&L ≥1 ROA vs JSN ≥1 on the skyline view.

On the skyline view we observed 85 (9.5%) of knees with JSN ≥1. (Table 1) When we combined the skyline and AP view we found ROA in 354 knees (65.4%), an increase of 24 (7.3%) ROA cases compared to the K&L score on the AP view alone. Moreover, when we combined all views: either K&L ≥1 on the PA view, osteophytes ≥ 1 on the mediolateral and osteophytes ≥ 1 and/or JSN ≥ 1 on the skyline view, we demonstrated 593 knees with ROA equaling 263 additonal (79.7%) ROA cases in the cohort compared to the K&L score on the AP view alone (Table 3 and Figure 1).

Table 3. Prevalence of ROA on different views, right knee, baseline, 5years of follow up and progression after 5 years of follow up.

Radiographic view (features assessed)	**ROA visible on radiograph**							
Baseline, N=894	PA only	Sky only	ML only	PA+ SKY	PA+ ML	SKY + ML	PA + SKY + MLL	Any
PA & SKY (osteophytes)	108	174	na	218	na	na	na	500
PA & ML (osteophytes)	150	na	182	na	178	na	na	510
PA & SKY & ML (osteophytes)	70	84	87	77	36	90	141	585
PA & SKY (JSN)	269	28	na	57	na	na	na	354
PA & SKY (osteophytes & JSN)	103	184	na	223	na	na	na	510
PA & SKY & ML (osteophytes/JSN)	68	92	86	79	33	91	144	593
5 years of follow up								
PA & SKY (osteophytes)	112	152	na	376	na	na	na	640
PA & ML (osteophytes)	131	na	173	na	361	na	na	665
PA & SKY & ML (osteophytes)	44	47	70	85	66	101	291	704
PA & SKY (JSN)	351	33	na	137	na	na	na	521
PA & SKY (osteophytes & JSN)	91	162	na	396	na	na	na	649
PA & SKY & ML (osteophytes/JSN)	36	51	64	92	53	107	304	707
Progression after 5 years								
PA & SKY (osteophytes)	202	118	na	106	na	na	na	426
PA & ML (osteophytes)	183	na	125	na	131	na	na	439
PA & SKY & ML (osteophytes)	123	76	83	53	78	39	52	504
PA & SKY (JSN)	246	51	na	63	na	na	na	360
PA & SKY (osteophytes & JSN)	169	154	na	139	na	na	na	462
PA & SKY & ML (osteophytes/JSN)	105	97	69	71	63	53	67	525

PA: posteroanterior knee (K&L), SKY: skyline view, ML: mediolateral view, JSN: joint space narrowing, na; not applicable

Progression

After five years of follow up an increase of at least 1 grade of the K&L score on the PA view was seen in 318 (35.6%) of the knees. When we combined all views, we demonstrated 525 (58.7%) knees with progression, an additional 207 (65.1%) knee ROA cases (Table 3 and Figure 2).

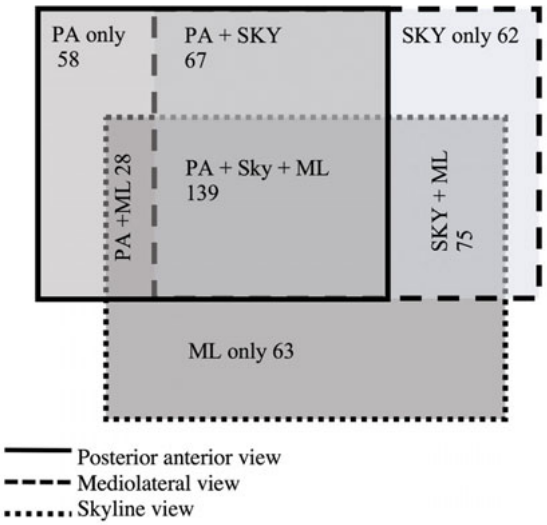

Figure 1. Venn diagram of radiographic osteoarthritis features of the knee, showing overlap between views. (Right knee, N = 593) prevalence at 5 year follow up

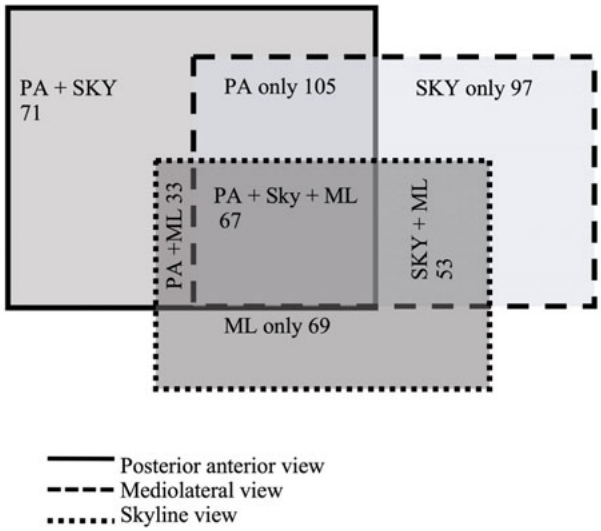

Figure 2. Venn diagram of progression of radiographic osteoarthritis features of the knee, showing overlap between views, progression (Right knee, N = 318)

DISCUSSION

In this study we determined the prevalence of radiographic OA features on different radiographic views of the knee and hip in an early OA cohort. We showed that the use of a combination of different radiographic views, e.g. skyline, mediolateral and faux profile radiographs leads to the detection of more early knee and hip ROA cases compared to the currently commonly used method of defining ROA based on single radiographic projections in general practice and most imaging studies. Furthermore, we demonstrated that the same combination of different views resulted in the identification of more cases of ROA progression over a period of 5 years. These additional cases could provide us with more cases in which research could be done, and also target different phenotypes of ROA.

Our study demonstrated that the number of knee ROA cases increases when using multiple radiographic views compared to single views. This could be explained by the fact that it is possible to assess both the tibiofemoral and patellofemoral joints when using multiple views. This is consistent with the study by Duncan et al. who previously demonstrated a three-fold increase of mild ROA when combining tibiofemoral and patellofemoral ROA in a population-based study. McAlindon et al. also found an increase of ROA prevalence when combining tibiofemoral and patellofemoral imaging. [12, 20]

The mediolateral radiograph was used to assess osteophytes at the superior and inferior margins of the patellofemoral joint, but presence of these osteophytes did not result in many additional cases because of their low prevalence. This is in line with previous findings by Cicuttini et al. who found that skyline views are more useful than mediolateral views for assessment of the PFJ. [21] In our study the number of ROA cases based on osteophytes was equal for the skyline and mediolateral view, although these osteophytes are anatomically in a different location. This indicates that the use of both views is needed, for although the number of cases identified with both separate views would be equal, both views represent other individuals and therefore the use of both views adds to the total number of identified cases.

We also identified more ROA cases of the hip when using combined information from different radiographic views. It has been suggested previously that hip ROA is detected more sensitively by determining joint space narrowing on the faux profile radiograph than by applying the traditional K&L score on the AP view.[13] Our findings add to this previous report, suggesting that the faux profile is a relevant view in early hip OA.

Remarkably not much previous research has been performed to assess whether different radiographic views have additional value in determining progression of ROA. However, Felson et al. did show that different views help demonstrate 50% more progression of knee ROA in 30 months.[7] Likewise, we demonstrated 68% more progression in 5 years. To our knowledge we are the first to demonstrate a similar trend for the hip in a large population. Although Maheu et al. have reported an increased sensitivity for the detection of JSN on the faux profile view over the pelvic view in a subgroup (n=50) of a hip OA intervention study.[22]

Our study offers a unique population and presents opportunities to study onset and progression of OA in an early stage of disease with participants who are comparable with those presenting in primary care. However, the same early OA population also proposes some challenges in determining OA. For example, we did not observe many participants with established ROA (K&L≥2) and therefore chose a lower ROA threshold in this study (K&L≥1 and similarly used a lower threshold for separate ROA features. Because no clear ROA definitions exist for some of the radiographic views studied, we defined several cut-offs ourselves. This also applied to the ROA definition when we combined several radiographs. As in all cohort studies we also had dropouts occurring between baseline and five years of follow-up, although our dropout rate was low. Still, there were only few radiographs that were missing or uninterpretable.

No clear guidelines exist stating which radiograph should be obtained for the assessment of radiographic OA. The American College of Rheumatism only recommends the use of the PA view of the hip only when radiography is performed. For the knee, PA and lateral views are recommended and skyline views are optional. The European League Against Rheumatism (EULAR) has formulated similar guidelines only for the radiographic assessment of knee OA, recommending a PA view plus ML and skyline views.[23,24,25] Our study supports these guidelines: when radiographic assessment for early OA is indicated different radiographs should be performed.

Based on these findings we would recommend the use of different view radiographs in assessing ROA in early OA patients. The added prognostic value of performing different radiographic views should be assessed in future research.

In conclusion, the use of different radiographic views increases the number of ROA cases in a symptomatic early OA cohort, both on baseline, as well as at 5 years of follow up. Moreover, the use of multiple different radiographic views leads to more frequent detection of progression during five years of follow-up.

Acknowledgements

The authors would like to thank all participants of the CHECK cohort and all collaborators of the different sites for their efforts. CHECK is funded by the Dutch Arthritis Association on the lead of a steering committee comprising 16 members with expertise in different fields of osteoarthritis chaired by Prof. J.W.J. Bijlsma and coordinated by J. Wesseling. Involved are: Erasmus MC University Medical Center Rotterdam; Academic Hospital Maastricht; Jan van Breemen Institute/VU Medical Center Amsterdam; Kennemer Gasthuis Haarlem; Martini Hospital Groningen/Allied Health Care Center for Rheumatology and Rehabilitation Groningen; Medical Spectrum Twente Enschede/Twenteborg Hospital Almelo; St Maartenskliniek Nijmegen; Leiden University Medical Center; University Medical Center Utrecht and Wilhelmina Hospital Assen.

REFERENCES

1 Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.

2 Kinds MB, Welsing PMJ, Vignon EP, Bijlsma JW, Viergever MA, Marijnissen AC, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis and Cartilage 2011;19:1-30.

3 Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000 Jun;27:1513-1517

4 Dieppe PA, Cushnaghan J, Shepstone L. The Bristol "OA500" study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthr Cartil 1997;5:87–97.

5 Bedson J, Jordan K, Croft P. How do GPs use x rays to manage chronic knee pain in the elderly? A case study. Annals of the Rheumatic Diseases 2003;62:450–454.

6 Schiphof D, de Klerk BM, Kerkhof HJM, Hofman A, Koes BW, Boers M, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Annals of the Rheumatic Diseases 2011;70:1422–1427.

7 Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Annals of the Rheumatic Diseases 2011;70:1884–1886.

8 Guermazi A, Roemer FW, Burstein D, Hayashi D. Why radiography should no longer be considered a surrogate outcome measure for longitudinal assessment of cartilage in knee osteoarthritis. Arthritis Res Ther 2011;13:247.

9 Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C,et al. Comparison of radiographic joint space width with magneticresonance imaging cartilage morphometry: Analysis of longitudinaldata from the Osteoarthritis Initiative. Arthritis Care Res, 2010;62:932-7.

10 Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? Osteoarthr Cartil 2009;17:1151–1155.

11 Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. How do pain and function vary with compartmental distribution and severity of radiographic knee osteoarthritis? Rheumatology 2008;47:1704–1707.

12 Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis--it all depends on your point of view. Rheumatology 2006;45:757–760.

13 Lequesne MG, Laredo JD. The faux profil (oblique view) of the hip in the standing position. Contribution to the evaluation of osteoarthritis of the adult hip. Annals of the Rheumatic Diseases 1998;57:676–681.

14 Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Annals of the Rheumatic Diseases 2009;68:1413–1419.

15 Roorda, L. D. (2004). Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis, 63(1), 36–42.

16 Damen J, Schiphof D, Wolde ST, Cats HA, Bierma-Zeinstra SM, Oei EH. Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (cohort hip and cohort knee) study. Osteoarthritis Cartilage 2014;22:969-74.

17 Altman R, Gold G. Atlas of individual radiographic features in osteoarthritis,

revised1. Osteoarthritis and Cartilage 2007;15:A1–A56.
18 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases 1957;16:494–502.
19 A Radiographic Atlas of Osteoarthritis. S Burnett, DJ Hart, C Cooper TD Spector. London: Springer Verlag; 1994.
20 McAlindon T E, Snow S, Cooper C, Dieppe P A. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992;51: 844–849.
21 Cicuttini FM, Baker J, Hart DJ, Spector TD. Association of pain with radiological changes in different compartments and views of the knee joint. Osteoarthr. Cartil. 1996;4:143–147.
22 Maheu E, Cadet C, Marty M, Dougados M, Ghabri S, Kerloch I, et al. Reproducibility and sensitivity to change of various methods to measure joint space width in osteoarthritis of the hip: a double reading of three different radiographic views taken with a three-year interval. Arthritis Res. Ther. 2005;7:1375-1385
23 Zhang, M Doherty, G Peat, S M A Bierma-Zeinstra, N K Arden, B Bresnihan, G Herrero-Beaumont, S Kirschner, B F Leeb, L S Lohmander, B Mazières, K Pavelka, L Punzi, A K So, T Tuncer, I Watt, J W Bijlsma . EULAR evidence-based recommendations for the diagnosis of knee. Ann rheum diss 2010;69:483-489
24 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29:1039-1049.
25 Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, , et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum. 1991;34:505-14.

CHAPTER 4

Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (cohort hip and cohort knee) study

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Osteoarthritis Cartilage.2014 Jul;22(7):969-74

ABSTRACT

Objective

To calculate inter-observer reliability between four different trained readers and an experienced reader on early radiographic osteoarthritis (OA) features in our early OA CHECK cohort (cohort hip and cohort knee).

Methods

Four readers were trained by a radiologist and experienced reader to score radiographic OA features. After this training they scored the CHECK cohort. Of the 1002 participants, 38 were scored by all readers. Five different angle radiographs (three for the knee, two for the hip) at three different time points were scored and compared. Inter-observer reliability was evaluated between each of the four trained readers and the experienced reader. Separate radiographic OA features and of overall Kellgren and Lawrence (K&L) scores. In addition, reliability of progression of radiographic was determined in K&L scores and joint space narrowing (JSN).

Results

For hip and knee there was substantial inter-observer reliability on overall K&L scores. In the knee, JSN was scored with fair to moderate reliability, osteophytes with moderate to nearly perfect reliability, and other features with fair to substantial reliability. In the hip, reliability ranged from substantial to nearly perfect. Moderate inter-observer reliability was found for progression of OA in both knee and hip, with slightly better reliability for progression based on K&L scores than on separate features.

Conclusion

Good inter-observer reliability can be achieved between trained readers and an experienced reader. Although JSN in the knee is scored with lower inter-observer reliability than osteophytes, this does not seem to influence overall K&L scoring. In the hip all features showed good reliability.

INTRODUCTION

Radiographic assessment of osteoarthritis (OA) is very important, as findings on radiography are used for both diagnosis and staging of OA and as a tool for measuring progression of disease. Despite limitations of radiography and the emergent role of magnetic resonance imaging (MRI) for OA, radiography is still the most widely applied imaging tool for OA in clinical and research settings. This is mainly because of the wide availability of the technique, low costs, and relatively easy interpretation of the images.[1]

Many studies have indicated the discordance between radiological findings and symptoms pertaining to OA.[2,3] Several approaches have been suggested to improve the diagnostic and prognostic value of radiographic findings, including redefinition of existing grading systems, implementing new quantitative grading methods with actual measurements, and performing additional angled radiographic views to find relationships between pain and radiographic joint damage. [4,5,6]

A common problem in all these approaches is the difficulty of standardized classification of OA. While standardized acquisition of radiography is commonly applied, the method of grading of OA features, OA definition varies by study and training of readers. These factors make it even more difficult to relate OA signs to clinical outcomes, because data from different studies cannot easily be combined.

Assessment and improvement of inter-observer reliability might contribute to solving this problem as it leads to more uniformity in radiographic scoring both between and within studies. However, compared to the large number of studies performed using radiological outcomes, not all studies have reported on their inter reliability of OA grading. We found only one review article on inter-observer reliability for radiographic grading of hip and knee OA, which indicated that only few data exist on this issue, especially for separate radiological OA features; therefore, the authors advised that in larger cohort studies inter-observer reliability should be reported.[7]

The purpose of the present study was to assess various aspects of inter-observer reliability for radiographic hip and knee OA assessment within the longitudinal Cohort Hip and Cohort Knee (CHECK) study. First, we aimed at evaluating inter-observer reliability between four trained readers and one experienced reader for grading of radiographic OA, including analyses per separate OA feature. Second, we aimed to determine the inter-observer reliability for assessing progression of OA, which is relevant for longitudinal studies on OA.

METHODS

CHECK is an ongoing prospective multicentre cohort study of 1,002 individuals with early symptomatic OA of the knee or hip. Details of the protocol have been published earlier, and a summary is presented below.[8]

Study population
Participants that potentially fulfilled the inclusion criteria were invited to join the study when they visited their general practitioner (GP). In addition, participants were recruited through advertisements, articles in local newspapers, and via the website of the Dutch Arthritis Association. Individuals were eligible to participate if they had pain and/or stiffness of the knee and/or hip, were aged between 45 and 65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry.

Exclusion criteria were: any other pathological condition that could explain the existing symptoms (e.g. other rheumatic disease, isolated tendinitis/bursitis, previous hip or knee joint replacement, congenital dysplasia of the hip, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome or Bakers' cysts), or a co-morbidity that precluded physical evaluation and/or follow-up for at least 10 years, malignancy in the last 5 years, and inability to understand the Dutch language.

Physicians at the participating centres checked whether referred participants and participants reacting to advertisements, as well as participants from their own outpatient clinic, fulfilled the inclusion criteria.

All patients underwent radiographic assessment of both hips and knees, standardised physical examination, and filled out an extensive questionnaire at baseline, and at 2 and 5 years follow-up, including the Western Ontario McMaster questionnaire (WOMAC) pain subscale. [8,9]

Radiography
All radiographs in the CHECK study were obtained according to a standardized protocol:
Semi-flexed (7-10 degrees) weight-bearing posteroanterior (PA) radiographs of the tibiofemoral joints were made, followed by standing mediolateral views in 30 degrees flexion for assessment of the tibiofemoral and patellofemoral joints. Skyline (infero-superior) non-weight bearing views of the patellofemoral joints were also acquired (with 30 degrees flexion of the femorotibial joints). For the hip, weight-bearing anteroposterior (AP) radiographs of the pelvis were made, as well as weight-bearing faux profile radiographs of both hips taken according to Lequesne and Loredo.[10] The faux profile view provides a lateral projection of the femoral head and neck, and an oblique view of the acetabulum tangential to its superoanteromedial edge.[10]

Radiographic OA scoring and training

When readers scored approximately 75 participants each, a subset of 38 participants from different centres was scored by five readers for the purpose of this study on inter-observer reliability. Radiographic OA scoring of this subset was performed independently by five trained observers (four research assistants and one experienced GP reader). For these random selected participants no selection criteria were used other than having no missing data. Of each participant, we scored right and left radiographs at three different points in time. Radiographs at baseline, and at 2 and 5-years follow-up were all scored at the same time and the readers were aware of their sequence in time.

Before scoring, the four research assistants were extensively trained by an experienced musculoskeletal radiologist and the experienced GP reader in four separate training sessions of 2.5 hours each, using training radiographs from the CHECK cohort. At the end of this training program the assistants' performance was assessed by scoring a set of radiographs of 12 participants with differing OA severity in the presence of the GP reader. When the assistants reached good reliability compared to the GP reader they were allowed to score radiographs in the CHECK cohort.

The PA radiographs of the knee were scored for individual OA features according to Altman et al.[11] For grading of OA, the Kellgren & Lawrence (K&L) definition was used for the patellofemoral joint, as determined on the PA radiograph.[12] Medial and lateral joint space narrowing (JSN), femoral medial and lateral osteophytes, and tibial medial and lateral osteophytes were scored on a 0-3 scale (0=normal; 1=mild; 2=moderate; and 3=severe). Tibial bone attrition, tibial sclerosis and femoral sclerosis were scored both medial and lateral on a 0-1 scale (0=absent; 1=present). Spiking of the tibial spines was scored according to the atlas of Burnett et al. on a 0-1scale. [13] The mediolateral and skyline radiographs of the knee were also scored for patellofemoral JSN and osteophytes on a 0-3 scale, as well as patello-femoral sclerosis (only on the skyline view) according to Burnett et al..[13] For these random selected participants no selection criteria were used other than having no missing data

The AP radiographs of the hip were scored for individual radiographic OA features according to Altman et al.[11] For grading of OA, the K&L definition was used and assessed on the AP radiograph.[12] Superior and medial hip JSN, superior acetabular osteophytes, and superior and inferior femoral osteophytes were scored on a 0-3 scale. Inferior acetabular osteophytes, femoral subchondral sclerosis, acetabular subchondral cysts, flattening of the femoral head and buttressing were scored on a 0-1 scale.[13] On the faux profile radiographs superior and posterior JSN were scored on a 0-3 scale.

For measuring reliability on progression we defined progression as an increase of at least one K&L grade. For JSN we defined progression as an increase of at least one point on the 0-3 scale in one of the sites. When calculating inter-observer reliability for JSN and osteophytes we used the maximum JSN and largest osteophyte scored at one of the subsites where JSN or osteophytes were scored. Progression was determined during the time intervals: baseline to 2-years follow-up, baseline to 5-years follow-up, as well as 2-5 years follow-up.

Statistical analysis

The inter-observer reliability was calculated for all the above-mentioned separate OA features, for OA grade, and for OA progression between each of the four research assistants individually and the experienced GP reader.

Because radiographic OA findings in our early OA cohort were sparse we dichotomized the original variables, including K&L grades that ranged from 0-3 to 0 vs ≥ 1.

Reliability of categorical data is commonly quantified by the kappa coefficient, which indicates the beyond chance agreement and ranges from 0 (indicating no agreement beyond chance) to 1 (when agreement is perfect). A kappa of 0-0.2 is considered poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 substantial, and 0.81-1 almost perfect.[14] A major disadvantage of the kappa statistic is the fact that it not only measures agreement but is also affected in complex ways by the presence of bias between observers and by the frequencies and distributions of data. Because the prevalence of the radiographic features is low in our early OA cohort, we used the prevalence adjusted bias adjusted kappa (PABAK). The PABAK is calculated as 2po – 1, where po is the observed proportion of agreement and takes into account the effects of bias and prevalence. [15] In addition we calculated percentage agreement of all features studied. All analyses were performed with the SPSS software package (version 20.0.0.1, 2011)

RESULTS

Mean age of this subgroup of CHECK participants was 56.05 (SD 4.26) years, 74% was female, average body mass index was 25.35 (SD 3.31), and their mean WOMAC pain score (0 indicating no pain, 20 indicating severe pain) was 4.76 (SD 3.23) Table 1 presents the frequencies of their OA features at baseline, and at 2 and 5-years follow-up.

Table 1. Frequency of radiographic features at baseline, and at 2 and 5-year follow-up (data from experienced GP reader).

	Baseline (n=76)		2-year follow-up (n=76)		5-year follow-up (n=76)	
	≥1	%	≥1	%	≥1	%
Knee						
K&L Knee grade						
0	43	56.6%	34	45%	28	37%
1	33	43.4%	36	47%	38	50%
2	0	0%	6	8%	6	8%
3	0	0%	0	0%	4	5%
4	0	0%	0	0%	0	0%
JSN lateral	31	40.7%	38	36.8%	50	51.3%
JSN medial	14	18.4%	18	23.7%	28	36.8%
JSN (SKY)	6	7.9%	10	13.2%	11	14.5%
Ost femoral med	5	6.6%	6	7.9%	6	7.9%
Ost femoral lateral	5	6.6%	10	13.2%	21	27.6%
Ost tibial medial	23	30.3%	28	36.8%	33	43.4%
Ost tibial lateral	19	25.0%	24	31.6%	30	39.5%
Ost patella (ML)	22*	29.3%	37	48.7%	43**	58.1%
Ost (SKY)	29	38.2%	40	52.6%	40	52.6%
Attrition	0	0.0%	0	0.0%	0	0.0%
Sclerosis	0	0.0%	0	0.0%	1*	1.3%
Sclerosis (SKY)	0	0.0%	0	0.0%	1	1.3%
Tibial spiking	7	9.2%	12	15.8%	13	17.1%

Table 1. Continued.

	Baseline (n=76)		2-year follow-up (n=76)		5-year follow-up (n=76)	
	≥1	%	≥1	%	≥1	%
Hip						
K&L Hip grade						
0	64	84%	63	83%	62	82%
1	12	16%	12	16%	12	16%
2	0	0%	1	1%	2	3%
3	0	0%	0	0%	0	0%
4	0	0%	0	0%	0	0%
JSN superior	5	6.6%	7	9.2%	8	10.5%
JSN medial	3	3.9%	4	5.3%	5	6.6%
JSN superior (FP)	2	2.6%	2	2.6%	3	3.9%
JSN posterior (FP)	0	0.0%	0	0.0%	0	0.0%
Ost superior acetabelum	3	3.9%	6	7.9%	7	9.2%
Ost superior femoral	12	15.8%	14	18.4%	14	18.4%
Ost inferior acetebelum	1	1.3%	3	3.9%	3	3.9%
Ost inferior femoral	5	6.6%	5	6.6%	6	7.9%
AP sclerosis	0	0.0%	0	0.0%	0	0.0%
Cysts	0	0.0%	0	0.0%	0	0.0%
Flattening femoral head	0	0.0%	0	0.0%	0	0.0%
Buttressing	2	2.6%	3	3.9%	4	5.3%

K&L: Kellgren and Lawrence criteria; JSN: joint space narrowing; Ost: osteophyte; ML: medio-lateral radiograph; SKY: skyline radiograph; FP: faux profile radiograph; 1 radiograph missing; **2 radiographs missing

Inter-observer reliability for knee OA

The average PABAK between the research assistants and the experienced GP reader regarding K&L scores of the knee joint ranged from 0.28-0.79, indicating fair to near perfect inter-observer reliability (Table 2). PABAK values on JSN on the AP view ranged from fair to moderate. On the skyline view, patellofemoral JSN was scored with fair to substantial inter-observer reliability. Osteophytes were scored with moderate to near perfect reliability on the AP view and with substantial reliability on the mediolateral radiograph. On the skyline radiograph osteophytes were scored with moderate to near perfect reliability.

Inter-observer reliability for spiking was fair to moderate. We were not able to calculate inter-observer reliability statistics on all radiographic features. In the tibiofemoral joint we did not find any attrition or sclerosis in this subset of participants. On the skyline radiograph sclerosis was not seen in any of the participants (Table 1).

Inter-observer reliability for hip OA

The average PABAK between the research assistants and the experienced GP reader regarding K&L scores of the hip joint ranged from 0.71-0.91, indicating substantial to almost perfect inter-observer reliability (Table 3). On the PA view, JSN was scored with substantial to almost perfect reliability; on the faux profile superior JSN was also scored with almost perfect reliability. on the PA view, osteophytes were scored with substantial to almost perfect reliability, and buttressing with almost perfect reliability (Table 3). Features indicating more advanced hip OA, such as flattening of the femoral head, cysts and sclerosis, were not seen in any of these individuals. On the faux profile radiographs posterior, JSN was not encountered.

Progression

Reliability on progression of OA (K&L score) in the knee ranged from substantial to almost perfect and was almost perfect in the hip (Table 4). For progression of JSN, reliability ranged from substantial to almost perfect in both the knee and the hip (Table 4).

Table 2. Inter-observer reliability for individual ROA features of the features of the knee 38 participants.

Feature	PABAK research assistant vs GP reader				
	1	2	3	4	Average
K&L Knee ≥1	0.79	0.23	0.75	0.53	0.58
95% CI	0.70-0.87	0.10-0.35	0.66-0.83	0.42-0.64	
JSN lateral	0.65	0.31	0.29	0.26	0.38
95% CI	0.55-0.75	0.18-0.43	0.16-0.41	0.14-0.39	
JSN medial	0.59	0.52	0.60	0.36	0.52
95% CI	0.48-0.69	0.41-0.63	0.50-0.70	0.23-0.48	
Ost femoral medial	0.89	0.91	0.90	0.82	0.88
95% CI	0.83-0.95	0.85-0.96	0.84-0.95	0.74-0.89	
Ost femoral lateral	0.81	0.77	0.91	0.90	0.85
95% CI	0.73-0.88	0.69-0.85	0.86-0.97	0.85-0.96	
Ost tibial medial	0.72	0.74	0.79	0.54	0.70
95% CI	0.63-0.92	0.66-0.83	0.71-0.87	0.43-0.65	
Ost tibial lateral	0.82	0.82	0.78	0.63	0.77
95% CI	0.75-0.90	0.74-0.89	0.70-0.86	0.53-0.73	
Tibial spiking	0.87	0.77	0.73	0.35	0.68
95% CI	0.80-0.93	0.69-0.85	0.64-0.82	0.23-0.47	
ML ost	0.86	0.65	0.61	0.59	0.68
95% CI	0.79-0.92	0.55-0.75	0.50-0.71	0.48-0.70	
SKY ost	0.80	0.63	0.62	0.71	0.69
95% CI	0.72-0.88	0.53-0.73	0.52-0.72	0.62-0.80	
SKY JSN	0.78	0.78	0.78	0.50	0.71
95% CI	0.70-0.86	0.70-0.86	0.70-0.86	0.38-0.49	

PABAK: prevalence adjusted bias adjusted kappa; K&L: Kellgren and Lawrence criteria; JSN: joint space narrowing; Ost: osteophyte; ML: medio-lateral radiograph; SKY: skyline radiograph. Left and right hip, three points in time

% agreement research assistant vs GP reader					Cohen's kappa research assistant vs GP reader				
1	**2**	**3**	**4**	**Average**	**1**	**2**	**3**	**4**	**Average**
0.90	0.55	0.87	0.82	0.79	0,79	0,27	0,74	0,52	0,58
					0.71-0.87	0.15-0.39	0.65-0.83	0.41-0.63	
0.80	0.66	0.65	0.63	0.68	0,65	0,32	0,30	0,25	0,38
					0.55-0.75	0.19-0.44	0.17-0.42	0.13-0.38	
0.79	0.72	0.80	0.64	0.74	0,39	0,12	0,43	0,39	0,33
					0.23-0.54	0-00-0.32	0.28-0.58	0.28-0.51	
0.95	0.93	0.95	0.91	0.93	0,45	0,59	0,60	0,56	0,55
					0.17-0.74	0.36-0.83	0.37-0.82	0.38-0.74	
0.83	0.93	0.95	0.95	0.91	0,59	0,47	0,74	0,76	0,64
					0.43-0.75	0.28-0.66	0.58-0.90	0.63-0.90	
0.86	0.87	0.86	0.77	0.84	0,69	0,71	0,76	0,55	0,68
					0.60-0.80	0.62-0.81	0.68-0.85	0.44-0.66	
0.91	0.91	0.88	0.77	0.87	0,80	0,78	0,75	0,61	0,73
					0.71-0.88	0.69-0.87	0.66-0.85	0.50-0.71	
0.93	0.88	0.87	0.68	0.84	0,74	0,43	0,22	0,29	0,42
					0.61-0.87	0.21-0.63	0.00-0.48	0.15-0.42	
0.92	0.83	0.83	0.79	0.84	0,85	0,65	0,60	0,59	0,66
					0.79-0.92	0.55-0.75	0.49-071	0.59-0.49	
0.90	0.82	0.81	0.85	0.84	0,79	0,62	0,62	0,71	0,69
					0.72-0.88	0.52-0.73	0.51-0.72	0.62-080	
0.89	0.66	0.89	0.75	0.80	0,34	0,17	0,41	0,34	0,32
					0.09-0.58	0.00-0.48	0.19-0.63	0.19-0.49	

Table 3. Inter-observer reliability for individual ROA features of the hip 38 participants.

Feature	PABAK research assistant vs GP reader				
	1	2	3	4	Average
K&L Hip ≥1	0.91	0.77	0.71	0.82	0.80
95% CI	0.86-0.96	0.69-0.85	0.62-0.80	0.74-0.89	
JSN superior	0.82	0.90	0.84	0.61	0.79
95% CI	0.74-0.89	0.85-0.95	0.77-0.91	0.51-0.72	
JSN medial	0.87	0.95	0.78	0.89	0.87
95% CI	0.83-0.95	0.91-0.99	0.69-0.86	0.84-0.95	
Ost superior acetabelum	0.89	0.85	0.85	0.82	0.87
95% CI	0.84-0.95	0.78-0.92	0.78-0.92	0.75-0.90	
Ost superior femoral	0.87	0.73	0.84	0.82	0.81
95% CI	0.84-093	0.64-0.82	0.77-0.91	0.75-0.90	
Ost inferior acetabelum	0.95	0.86	0.92	0.86	0.91
95% CI	0.91-0.99	0.79-0.93	0.87-0.97	0.79-0.93	
Ost inferior femoral	0.89	0.85	0.92	0.82	0.87
95% CI	0.82-0.95	0.78-0.92	0.87-0.97	0.75-0.90	
Buttressing	0.98	0.92	0.97	0.92	0.95
95% CI	0.96-1.00	0.87-0.97	0.94-1.00	0.87-0.97	
FP JSN superior	0.97	0.93	0.93	0.96	0.95
95% CI	0.94-1.00	0.88-0.98	0.88-0.98	0.93-1.00	

PABAK: prevalence adjusted bias adjusted kappa; K&L: Kellgren and Lawrence criteria; JSN: joint space narrowing; Ost: osteophyte; FP: faux profile radiograph Left and right hip, three points in time

% agreement research assistant vs GP reader					Cohen's kappa research assistant vs GP reader				
1	**2**	**3**	**4**	**Average**	**1**	**2**	**3**	**4**	**Average**
0.95	0.89	0.84	0.91	0.90	0,84 0.75-0.94	0,53 0.36-0.70	0,62 0.13-0.66	0,73 0.62-0.84	0,68
0.92	0.95	0.92	0.78	0.89	0,44 0.21-.67	0,66 0.46-0.86	0,40 0.13-0.66	0,38 0.22-0.55	0,47
0.93	0.97	0.89	0.94	0.93	0,35 0.01-0.69	0,65 0.38-0.93	0,40 0.17-0.62	0,51 0.24-0.78	0,48
0.95	0.93	0.92	0.91	0.93	0,60 0.37-0.82	0,62 0.44-0.79	0,28 0.00-0.61	0,52 0.32-0.72	0,51
0.94	0.85	0.92	0.91	0.90	0,77 0.66-0.88	0,49 0.33-0.66	0,75 0.64-0.86	0,69 0.56-0.82	0,67
0.97	0.94	0.96	0.94	0.95	0,65 0.38-0.93	0,47 0.22-0.72	0,55 0.26-0.84	0,30 0.00-0.63	0,49
0.94	0.92	0.96	0.89	0.93	0,52 0.27-0.77	0,37 0.09-0.66	0,62 0.38-0.86	0,48 0.26-0.70	0,50
0.99	0.96	0.98	0.96	0.97	0,88 0.72-1.04	0,65 0.42-0.87	0,79 0.56-1.03	0,65 0.42-0.87	0,74
0.99	0.96	0.96	0.99	0.97	0,82 0.61-1.02	0,18 0.00-0.74	0,62 0.36-0.88	0,59 0.19-0.99	0,55

Table 4. Inter-observer reliability for the progression of knee OA and hip OA.

Feature	PABAK research assistant vs GP reader				
	1	2	3	4	average
Knee					
K&L 0 to 2 years	0.82	0.81	0.82	0.79	0.81
K&L 2 to 5 years	0.82	0.68	0.74	0.68	0.73
K&L 0 to 5 years	0.90	0.80	0.74	0.87	0.82
JSN 0 to 2 years	0.79	0.88	0.89	0.74	0.82
JSN 2 to 5 years	0.74	0.83	0.87	0.71	0.79
JSN 0 to 5 years	0.89	0.92	0.74	0.87	0.85
HIP					
K&L 0 to 2 years	0.95	0.91	0.95	0.92	0.93
K&L 2 to 5 years	0.90	0.86	0.92	0.95	0.90
K&L 0 to 5 years	0.92	0.95	0.95	0.92	0.93
JSN 0 to 2 years	0.74	0.87	0.90	0.89	0.85
JSN 2 to 5 years	0.74	0.88	0.79	0.87	0.82

K&L: Kellgren and Lawrence criteria; JSN: joint space narrowing; 0-2 years: the progression score between baseline and 2-yea
score between baseline and 5-year measurements.

	% agreement research assistant vs GP reader					Cohen's kappa research assistant vs GP reader				
	1	2	3	4	Average	1	2	3	4	Average
	0.91	0.85	0.87	0.88	0.88	0,55	-0,02	0,48	0,31	0,33
	0.91	0.70	0.87	0.84	0.83	0,66	0,06	0,38	0,54	0,41
	0.95	0.83	0.87	0.94	0.90	0,70	0,06	0,47	0,47	0,43
	0.90	0.95	0.95	0.87	0.92	0,05	-0,03	-0,02	0,49	0,12
	0.87	0.91	0.93	0.86	0.89	-0,04	0,13	-0,05	0,48	0,13
	0.95	0.95	0.87	0.94	0.93	0,01	-0,06	-0,06	0,13	0,01
	0.97	0.96	0.98	0.96	0.97	0,65	0,00	0,19	0,15	0,25
	0.95	0.95	0.96	0.98	0.96	0,66	0,00	0,49	-0,02	0,28
	0.96	0.97	0.98	0.96	0.97	0,00	0,48	0,19	0,27	0,23
	0.87	0.94	0.95	0.95	0.92	0,37	0,00	0,00	-0,07	0,08
	0.87	0.88	0.89	0.94	0.89	0,39	0,22	0,00	0,22	0,21

ar measurements; 2-5 years: the progression score between the 2-year and 5-year measurements; 0-5 years: the progression

DISCUSSION

This study was performed to assess inter-observer reliability for early radiographic hip and knee OA across 4 trained readers and 1 experienced GP reader for grading of radiographic OA. Furthermore, we determined the inter-observer reliability for assessing progression of OA.

Overall reliability

For the knee K&L grading we found substantial reliability, which is in line with recent studies reporting kappa coefficients of 0.51-0.8, including our own group (Schiphof et al.[6] reporting a kappa of 0.62, in the Rotterdam study) as well as the original paper by Kellgren and Lawrence reporting a Pearson's r of 0.83.[11,12]

In the hip, the inter-observer reliability of the K&L grade as determined in the present study, was similar to that of a previous report from our group.[17] The original study of Kellgren and Lawrence showed a relatively low inter-observer reliability for the hip with a Pearson's r value of 0.75.[12]

Inter-observer reliability for individual knee OA features and their implications for K&L grading

In the knee we noticed a trend towards higher reliability for osteophytes than for JSN between readers for all three different radiographic views studied; this is in agreement with previous findings.[7] This is an interesting result considering that progression of the K&L score from grade 1 to grade 2 (the threshold for the diagnosis of OA in many studies) is primarily based on the detection of definite osteophytes. This is in concordance with previous findings in the CHECK cohort that there is a high correlation between the K&L grade and osteophytes.[17] Others did not find conclusive evidence for this correlation.[18]

The low reliability for JSN is surprising as joint space width (JSW) is regarded as a better predictor for outcomes in knee OA than the K&L grade. It is important to note, however, that JSW is a quantitative feature (i.e. measured by a ruler of computerized) whereas JSN is determined visually on a 0-3 scale and is, therefore, subjective. [19,20]

Inter-observer reliability for individual hip OA features and their implications for K&L grading

In the hip we found high inter-observer reliability for all OA features, while we observed no large differences between the different features; all PABAK values were ≥ 0.8. A previous review reported slightly better ICCs for JSN (0.58-0.79) than for osteophytes (0.45-0.78). [7] The interobserver reliability on buttressing was comparable to previous findings. [7]

Inter-observer reliability for ROA progression

Using the overall K&L score, the inter-observer reliability for progression was high. The K&L score is considered to be insensitive to progression of OA because a combination of different OA features has to deteriorate to progress on the K&L scale, while it has been estimated that progression on an ordinal scale for one feature takes about 2 years. [4] Therefore, it has been suggested that progression might best be defined by deterioration of single OA features.[21] Although these changes are probably of low clinical interest. However, in the hip we found that reliability was slightly lower when we looked at progression based on JSN alone. This could be due to the low prevalence of progression in the hip, and due to low reliability based on JSN in the knee.

Few studies have reported on the quality of OA grading; assessment of the reporting of inter-observer reliability could lead to more uniformity in radiographic scoring both between and within studies. The present study offered a unique opportunity to train four readers and evaluate how they agreed on radiological outcomes. Because we used bilateral radiographs of three different time points with three different radiographic projections of the knee, and two different views of the hip, we were able to assess inter-observer reliability based on a considerable number of radiographs.

Limitations

The present study has several limitations, the most important being that we did not have large radiographic diversity in OA severity. This is because the CHECK cohort consists of participants with early symptomatic OA who have not yet developed many radiographic OA features.[8] This may (in particular) have influenced our results on features indicating more advanced OA and progression of OA, and probably more so for hip than knee OA because far fewer participants in our cohort have hip symptoms than knee symptoms. More disease variability could hypothetically lead to lower inter observer agreement, however we think we adjourned this by dichotomizing our features. Although our readers were relatively inexperienced in the beginning, they underwent a simple yet thorough structured training program and received supervision from an experienced GP and musculoskeletal radiologist. We believe that this situation is common in OA research settings, especially in large studies, in which trained research assistants score the radiographs because of the lack of enough experienced readers (such as radiologists) to score large datasets. We believe our study confirms that this strategy is indeed possible after a simple yet thorough training program, such as the one we implemented.

Therefore, our results on inter-observer reliability are mainly generalizable to OA research settings and may not be directly generalizable to clinical practice where radiographs are usually assessed by radiologists, orthopaedic surgeons, or rheumatologists.

Conclusion

The results of our study show that with a simple yet thorough training we could achieve good inter-observer reliability between trained readers and an experienced reader for the assessment of early OA features, OA grading and OA progression. Although JSN in the knee is scored with lower inter-observer reliability than osteophytes, this does not appear to influence overall K&L scoring. Reliability for radiographic OA progression is higher for K&L scores than for JSN.

REFERENCES

1 Bucklandwright C. Which radiographic techniques should we use for research and clinical practice? Best Practice & Research Clinical Rheumatology 2006;20:39–55.

2 Bedson J, Croft P. The discordance between clinical and radiographic knee osteoarthritis: A Systematic search and summary of the literature. BMC Musc Dis 2008;9:116-127

3 Duncan R., Peat G., Thomas E., Wood L., Hay E., Croft P. How do pain and function vary with compartimental distribution and severity of radiographic knee osteoarthritis? Rheum 2008;47(11)1704-1707.

4 Kinds MB, Welsing PMJ, Vignon EP, Bijlsma JWJ, Viergever MA, Marijnissen ACA, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis and Cartilage 2011:1–30.

5 Schiphof D, Boers M, Bierma-Zeinstra SMA. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Annals of the Rheumatic Diseases 2007;67:1034–1036.

6 D Schiphof, B de Klerk, H Kerkhof, A Hofman, B Koes, M Boers, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Annals of the Rheumatic Diseases 2011;70 (8):1422-1427

7 Sun Y, Günther KP, Brenner H. Reliability of radiographic grading of osteoarthritis of the hip and knee. Scand J Rheumatol 1997;26:155–165.

8 Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SMA, Boers M, Cats HA, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Annals of the Rheumatic Diseases 2009;68:1413–1419.

9 Roorda, LD. (2004). Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis, 63(1), 36–42.

10 Lequesne MG, Laredo JD. The faux profil (oblique view) of the hip in the standing position. Contribution to the evaluation of osteoarthritis of the adult hip. Annals of the Rheumatic Diseases 1998;57:676–681.

11 Altman R, Gold G. Atlas of individual radiographic features in osteoarthritis, revised1. Osteoarthritis and Cartilage 2007;15:A1–A56.

12 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases 1957;16:494–502.

13 A Radiographic Atlas of Osteoarthritis. S Burnett, DJ Hart, C Cooper, TD Spector. London: Springer Verlag; 1994.

14 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.

15 Byrt, T., Bishop, J., & Carlin, J. B. (1993). Bias, prevalence and kappa. Journal of Clinical Epidemiology, 46(5), 423–429.

16 Reijman M, Hazes JM, Pols HA, Bernsen RM, Koes BW, Bierma-Zeinstra SM. Validity and reliability of three definitions of hip osteoarthritis: cross sectional and longitudinal approach. Annals of the Rheumatic Diseases 2004;63:1427–1433.

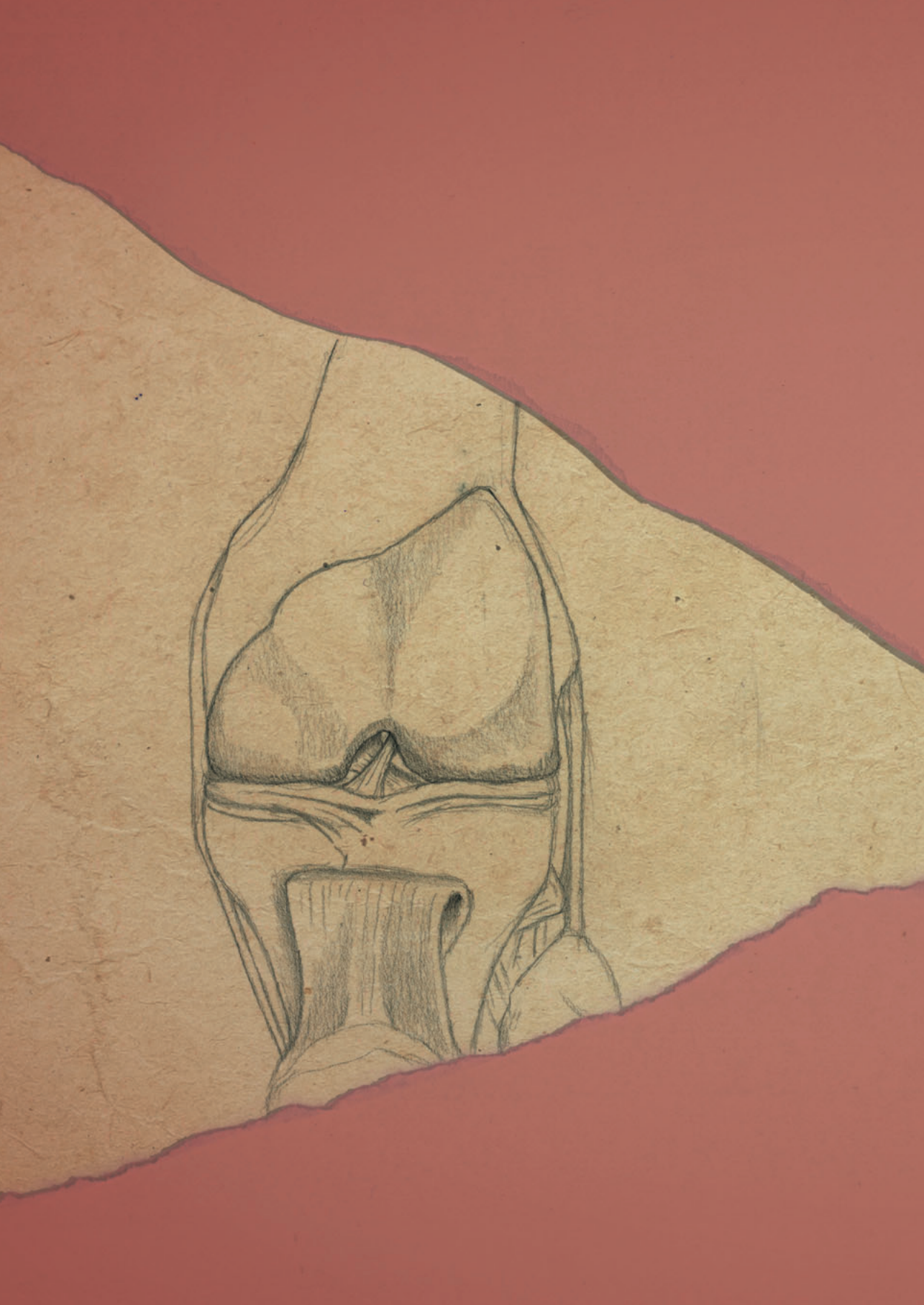
17 Kinds MB, Vincken KL, Vignon EP, Wolde ST, Bijlsma J, Welsing P, et al. Radiographic features of knee and hip osteoarthritis represent characteristics of an individual, in addition to severity of osteoarthritis. Scand J Rheumatol 2012;41:141–149.

18 Kessler S, Guenther KP, Puhl W. Scoring prevalence and severity in gonarthritis: the suitability of the Kellgren & Lawrence scale. Clin Rheumatol 1998;17:205–209.

19 Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Annals of the Rheumatic Diseases 2011;70:1884–1886.

20 Gossec L, Jordan JM, Mazzuca SA, Lam MA, Suarez-Almazor ME, Renner JB, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the OARSI–OMERACT task force. Osteoarthritis and Cartilage 2008;16:742–748.

21 Scott WW, Lethbridge-Cejku M, Reichle R, Wigley FM, Tobin JD, Hochberg MC. Reliability of grading scales for individual radiographic features of osteoarthritis of the knee. The Baltimore longitudinal study of aging atlas of knee osteoarthritis. Invest Radiol 1993;28:497–501.



CHAPTER 5

Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study

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Osteoarthritis Cartilage 2017 May;25(5):647-653

ABSTRACT

Objective

To examine the proportion of isolated patellofemoral osteoarthritis (PFOA) compared to tibiofemoral OA (TFOA) in middle-aged participants with early OA symptoms of the knee; to describe the natural course of PFOA compared with that of TFOA and to identify whether patients with PFOA have a different phenotype compared to patients with TFOA, or with combined PFOA and TFOA (COA).

Design

Participants with early OA symptoms of the knee were selected, completed questionnaires, underwent physical examination, and had knee radiographs at baseline, and at 2 and 5 years follow-up. Based on radiographs, participants were classified as having isolated TFOA, isolated PFOA, COA, or no radiographic OA. Multivariate logistic regression was used to identify participant characteristics associated with a specific group of OA at 2 years follow-up.

Results

The cohort comprised 845 participants (mean age 55.9 years). At baseline, 116 had PFOA, none had TFOA or COA. Of these 116 participants, 66.3% had developed COA at 5 years follow-up. At 2 years follow-up, PFOA, TFOA and COA were present in 77 (10.8%), 39 (5.5%) and 83 (11.6%) participants, respectively. Multivariate regression analyses at 2 years follow-up showed that participants with radiographic PFOA or TFOA were not significantly different from each other with respect to signs and symptoms.

Conclusions

These results suggest that OA is more likely to start in the patellofemoral joint and then progress to COA in individuals with symptoms of early knee OA. No differences in TFOA and PFOA phenotypes were determined with respect to signs and symptoms.

Keywords

Osteoarthritis, patellofemoral joint, tibiofemoral joint, cohort, knee

INTRODUCTION

The most common condition to affect the knee joint is osteoarthritis (OA)[1, 2]. The knee joint consists of two compartments the tibiofemoral (TF) and the patellofemoral (PF) compartment. OA in the knee can occur solely in the TF joint [isolated tibiofemoral osteoarthritis (TFOA)] or in the PF joint [isolated patellofemoral osteoarthritis (PFOA)] or can be present in both joints [combined TFOA and PFOA (COA)]. Most research on OA has focused on the TF joint, although the prevalence of isolated PFOA might be higher than isolated TFOA[3-6]. Furthermore, radiographic signs of PFOA are associated with symptoms such as pain and disability[7-10].

Although the main goal of treatment for OA is pain relief, not every participant responds equally well to treatment[11, 12]. One possible reason for this difference is that the heterogeneous OA population consists of persons with different phenotypes of OA[12-14]. Identification of the distinct phenotypes in OA may help classify which preventive measures are suitable for an individual[14]. Therefore, it is suggested to target interventions to different OA phenotypes[15-18]. However, Mills and Hunter stated: '*due to the inclusion of homogenous study groups based on TFOA in clinical trials, the phenotype specific effects of OA can be masked*'[19]. Therefore, large cohort studies that include participants with COA and isolated TFOA and PFOA are needed to determine whether participants with PFOA have a different phenotype compared to those with TFOA or COA.

Additionally, evidence from a study including participants aged ≥ 50 years with knee complaints suggests that OA in the knee starts in the PF joint and subsequently progresses to the TF joint[20]. This was recently strengthened by Stefanik et al. (2016) who found that knees with structural damage in one compartment of the knee do not develop structural damage in another compartment. Moreover, knees that developed mixed structural damage were more likely to start with isolated to the PF joint[21]. Therefore, more insight is required in the natural course of PFOA and how its natural course differs from TFOA. The few studies describing the prevalence and natural course of TFOA and PFOA included participants with severe signs of OA on radiographs [22] or studied a general population including individuals without knee complaints[9, 23]. Other studies focusing on TFOA and PFOA included participants with a relatively high age (mean age 68.4, 65.2 and 62.5 years, respectively)[20, 21, 24, 25]. Although two studies evaluated the prevalence of PFOA in a younger population (aged 34-55 years), these participants had chronic knee complaints [26] or no baseline X-ray data of the PF joint were available so that progression could not be evaluated[27]. Thus, most research has focused on older participants with a longer symptom duration of knee pain, or on the general population and therefore little is known on the incidence and prevalence rates, as well as the natural course of PFOA and TFOA, in relatively young subjects with a recent onset of knee complaints.

Therefore, the aim of this study is to 1) determine the proportion PFOA compared to TFOA in individuals with early knee OA symptoms; 2) describe the natural course of PFOA at 2 and 5 years follow-up compared with that of TFOA; and 3) identify whether participants with PFOA have a different phenotype of signs and symptoms compared to those with TFOA, and those with COA.

METHODS

Study population

The present study used baseline data, and data from 2 and 5 years follow-up of the Cohort Hip and Cohort Knee study (CHECK). A detailed description of this cohort is published elsewhere.[28,29] In brief, the cohort included 1002 participants recruited between October 2002 and September 2005. Inclusion criteria were: participants aged 45-65 years with hip and/or knee complaints (pain or stiffness) who had never visited a general practitioner (GP) for their complaints, or had visited a GP no longer than 6 months previously.

Participants were excluded if they had a pathologic disorder (based on medical history and physical examination) that also could explain the symptoms (e.g. for the knee; other rheumatic disease, ligament or meniscus injury, knee joint replacement, plica syndrome, Baker's cyst); had a serious comorbidity that did not allow physical evaluation/follow-up for up to 10 years; and did not have adequate understanding of the Dutch language[28].

For the current study only those participants that reported knee pain or knee stiffness at baseline were included (n=845). Ethical approval was obtained and participants provided informed consent prior to commencement of the study[28].

Questionnaires

Self-reported questionnaires were filled in yearly by all participants. At baseline and at follow-up the following domains were assessed by questionnaires: 1) Socio-demographic characteristics: age (in years), sex (male/female), body height (m) and weight (kg), 2) Knee symptoms: duration of complaints (only assessed at baseline), side of knee pain, number of subjects with hip and knee symptoms, and the Western Ontario and McMaster Universities Index (WOMAC) [30] for knee function (higher scores indicating worse function). Moreover, information on pain when going up/down upstairs and when walking on a flat surface was obtained by means of a five-point Likert scale ('none', 'slight', 'moderate', 'severe', 'extreme')[30].

Physical examination

All participants underwent a standardised physical examination at baseline, and at 2 and 5 years follow-up. For the present study, we used data of the physical examination at baseline and data of the 2-year follow-up of the index knee (i.e. the most affected knee) [31]. Of the 845 participants with knee pain, 384 (44.5%) had unilateral symptoms. For participants with bilateral symptoms the index knee was based on the following decision tree as described by Holla et al.[31] 1) highest Kellgren/Lawrence score, 2) lowest degree of active knee flexion, 3) highest pain during knee flexion, and 4) crepitus during knee flexion. In participants for whom we could not define an index knee based on these signs, we randomly assigned an index joint.

Range of joint motion was measured with a goniometer (in degrees). To assess knee effusion the refill test was used (present or absent), palpable warmth was determined by comparing both knees with each other (present or absent), and bony enlargement, joint line tenderness, crepitus (during squatting) and patellofemoral grinding test were all scored for presence or absence by palpation.

Radiographs

At baseline and at 2 and 5 years follow-up, weight-bearing posterior-anterior (PA), with 7-10°; knee flexion; lateral weight-bearing radiographs with 30° of knee flexion; and skyline view with the knees in 30° flexion were made of both knees separately. For the PA radiographs individual features of OA were scored according to the atlas of Altman et al. [32] The following features of OA were scored: joint space narrowing (none, doubtful, mild or moderate), femoral medial and lateral osteophytes, and tibial medial and lateral osteophytes (none to moderate). The original Kellgren & Lawrence (K&L) criteria were used to score the severity of TFOA of the involved knee on the PA radiographs[33]. On the lateral views osteophytes (none to moderate) were scored and on the skyline view osteophytes (none to moderate) and joint space narrowing (none to moderate) were scored according to Burnett et al.[34]. All the above-mentioned features were scored by five observers independently, according to a paired reading procedure (inter-reader reliability: 0.62)[35].

Definition of radiographic OA per compartment

The type of OA was defined for the index knee of the individual. Patients were classified having no OA, isolated PFOA, isolated TFOA or combined OA. Patients classified having isolated PFOA only had signs of OA in the PF joint, which was defined as; 1) a K&L score <2 on PA radiographs and osteophytes grade ≥2 on skyline or 2) K&L score <2 on PA radiographs and osteophytes grade ≥2 on lateral radiographs or 3) K&L <2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs. Patients with isolated TFOA only had signs of OA in the TF joint, and none in the PF joint. This was defined as a K&L score ≥2 on PA radiographs and osteophytes grade <2 on both skyline and lateral radiographs (or K&L score ≥2 on PA radiographs and narrowing grade <2 and osteophytes grade <1 for skyline radiographs). Patients with COA had signs of OA in both the TF and the PF joint. This was defined as a K&L score ≥2 on PA radiographs and skyline or lateral osteophytes grade ≥2 or K&L score ≥2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs. No radiographic OA was defined if none of the above-mentioned definitions was fulfilled. Incident cases at 2 or 5 years follow-up were defined as participants with radiographic signs of any type of OA at follow-up who did not have signs of OA at baseline or at 2 years follow-up[23 4].

Statistical analyses

To determine the proportion PFOA compared to TFOA in individuals with early knee OA symptoms, descriptive statistics (mean, standard deviations [SD] and proportions) were applied. Descriptive statistics were also applied to determine the natural course of PFOA and TFOA at 2 and 5 years follow-up. Differences in characteristics at baseline and at 2 years follow-up were analysed with independent t-tests and with ANOVA tests.

To identify whether participants with PFOA had a different phenotype of signs and symptoms compared to those with TFOA, and those with COA multivariate binary logistic regression (based on complete case analyses) ($p<0.01$) was used. For the analyses data at 2 years follow-up were used because none of the participants had TFOA or COA at baseline so that we were unable to test for differences in phenotypes at baseline. The following variables were included in the regression analyses: gender, age, body mass index (BMI), pain when walking up/down stairs and when walking on a flat surface [both dichotomised into no pain ('none' and 'slight') and painful ('moderate', 'severe' and 'extreme')], function score (WOMAC), bony tenderness during palpation, joint line tenderness, crepitus in the knee duration flexion, degrees of knee flexion and extension, and the patellar grinding test. This selection of characteristics was based on the literature and their practicability in general practice [20, 25, 36]. Significance level was set at $p< 0.01$, and a significant trend was defined as a p-value >0.01 and <0.05. Analyses were based on complete case analyses (i.e. no missing radiograph and physical examination). Analyses were performed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago IL, USA).

RESULTS

Study population

At baseline, the total cohort comprised 845 participants (80% females) who reported knee pain or stiffness. The mean age was 55.9 (5.18) years and mean BMI was 26.3 (4.15) kg/m^2. Due to missing data, the type of OA could not be determined for 139 (16.4%), 129 (15.3%) and 150 (17.8%) participants at baseline and at 2 and 5 years follow-up, respectively.

Incidence and prevalence of different types of OA

- Baseline

Of the 706 participants available at baseline, 116 (16.4%) had isolated PFOA and none had TFOA or COA; 590 participants had no radiographic defined OA at baseline. The presence of isolated PFOA in those with knee pain at baseline was associated with higher age, higher BMI, hip pain at baseline, crepitus, positive patellofemoral grinding test, palpable bony enlargement, lower knee flexion range of motion and a K&L score ≥1 (Table 1).

Table 1. Radiographic criteria for PFOA, TFOA and COA

Isolated PFOA	**Isolated TFOA**	**Combined OA**
K&L score <2 on PA radiographs and osteophytes grade ≥2 on skyline	K&L score ≥2 on PA radiographs and osteophytes grade <2 on both skyline and lateral radiographs	K&L score ≥2 on PA radiographs and skyline or lateral osteophytes grade ≥2
OR	OR	OR
K&L score <2 on PA radiographs and osteophytes grade ≥2 on lateral radiographs	K&L score ≥2 on PA radiographs and narrowing grade <2 and osteophytes grade <1 for skyline radiographs	K&L score ≥2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs
OR		
K&L <2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs		

- Two-year follow-up

Table 1 presents the characteristics of the participants at the 2-year follow-up. Isolated PFOA was found in 77 (10.8%) participants. Of those 77, 48 already had PFOA at baseline, 27 were new incident cases and 2 PFOA patients had missing data at baseline. Isolated TFOA was present in 39 (5.5%) participants, none of them had signs of OA at baseline. COA was present in 83 (11.6%) participants at two years follow-up; 63 (75.9%) had PFOA at baseline, 18 patients did not have signs of OA at baseline and 2 patients had missing data at baseline. (Figure 1.)

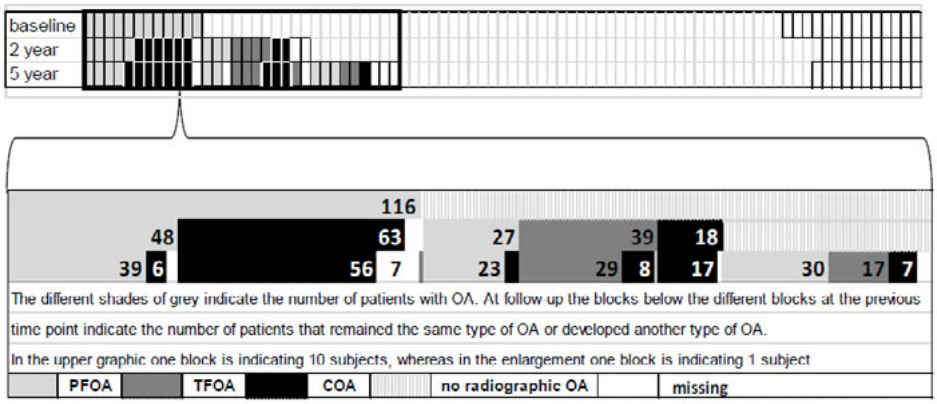

Figure 1. Natural course of different subgroups of OA
In the upper figure one block represents 10 patients, whereas in the lower figure one block represents 1 patient.

- Five-year follow-up

At the 5-year follow-up, 100 participants were diagnosed with isolated PFOA:.39 already had PFOA at baseline and 2-years follow-up, 23 had PFOA at 2-years and 30 did not have signs of OA neither at baseline and 2-years follow-up. Of the 129 participants with missing data at two years follow-up, 8 had PFOA at 5-year follow-up. A total of 54 patients had TFOA at 5-year follow-up: 29 already had TFOA at 2-years follow-up, 17 did not have signs of OA at baseline and 2-years follow-up and 7 patients had missing data at two-years follow-up. A total of 102 patients had COA: 56 54.9%) already had COA at two-years follow-up and PFOA at baseline, while 6 (5.9%) had PFOA at baseline and 2-year follow-up and progressed to COA. Five out of the 102 patients developed COA while they were diagnosed with PFOA at 2-years follow-up, and 8 progressed from TFOA at 2-year follow-up to COA. Seventeen patients had no signs of OA at baseline and already had COA at two years follow-up. Seven patients with COA at 5-year follow-up did not have signs of OA at baseline and 2-year follow-up and three patients with COA at 5 years follow-up had missing data at two-years follow-up. (Figure 1.)

Natural course of PFOA and TFOA

Of the 116 participants with isolated PFOA at baseline, 63 (54.3%) had developed COA at the 2-year follow-up and 62 (53.4%) had developed COA at the 5-year follow-up. The status of 5 participants with PFOA at baseline was unknown due to missing data at both 2 and 5 year follow-up. Seven of the 116 participants had already progressed to COA at 2-years follow-up, but had missing data at 5-years follow-up and three participants were diagnosed with PFOA at baseline and 2-years follow-up, but had missing data at 5-years follow-up (Figure 1). Of the 39 participants with isolated TFOA at the 2-year follow-up, 8 (20.5%) had developed COA at the 5-year follow-up (Figure 1).

Table 2. Patient characteristics and symptoms at baseline and at 2-year follow-up per group: variables are n [%] unless stated otherwise

Characteristics at baseline	**isolated TFOA**	**isolated PFOA n=116**
Age (years), mean [SD]		57.8 [4.82]
Sex (female)		89 [76.7%]
BMI (kg/m^2), mean [SD}		28.1 [4.55]
Bilateral complaints (yes)		61 [52.6%]
Hip and knee pain at baseline (yes)		42 [36.2%]
Pain when walking on flat surface (yes)		21 [18.1%]
Pain when going up or down stairs (yes)		61 [52.6%]
Baseline WOMAC function (0-68), mean [SD]		25.9 [17.2]
Crepitus (yes)		72 [62.1%]
Bony enlargement (yes)		12 [10.3%]
Patellofemoral grinding test (pos)		46 [39.7%]**
Knee flexion ROM (degrees), mean [SD]		130.8 [10.6]*
Knee extension ROM (degrees), mean [SD]		2.63 [2.68]*
Knee effusion (yes)		15 [12.9]
Morning stiffness knee < 30 minutes (yes)		85 [73.3%]
Joint line tenderness (yes)		49 [42.2%]
K&L score 1 (yes)		89 [76.7%]
Characteristics at 2-year follow-up	**n=39**	**n=77**
Age (years), mean [SD]	58.5 [5.54]	59.3 [5.39]
Sex (female)	33 [84.6]	58 [75.3]
BMI (kg/m^2), mean [SD]	26.7 [3.81]	26.4 [4.27]
Bilateral complaints (yes)	17 [43.6]	38 [49.4]
Pain when walking on flat surface (yes)	18 [46.2]	12 [15.6]
Pain when going up or down stairs (yes)	6 [15.4]	37 [48.1]
WOMAC function (0-68), mean [SD]	19.5 [16.2]	24.9 [20.1]
Crepitus (yes)	18 [46.2]	40 [51.9]
Bony enlargement (yes)	1 [2.6]	8 [10.4]
Patellofemoral grinding test (pos)	4 [10.3] ***	17 [22.1]**
Knee flexion ROM (degrees), mean [SD]	134.6 [8.02] *	136.9 [9.07]*
Knee extension ROM (degrees), mean [SD]	2.19 [2.23]*	2.52 [3.27]*
Knee effusion (yes)	4 [10.3]	2 [2.6]
Morning stiffness knee < 30 min (yes)	22 [56.4]	49 [63.3]
Joint line tenderness (yes)	6 [15.4]	15 [19.5]

SD: standard deviation, n: number, BMI: body mass index, m: meter, kg: kilogram, WOMAC: Western Ontario and McMaster Universities Arthritis Index, pos: positive, ROM: range of motion, OR: odds ratio, PFOA: patellofemoral osteoarthritis, TFOA: Tibiofemoral osteoarthritis, COA: combined osteoarthritis, OA: osteoarthritis

combined TFOA and PFOA	no radiographic OA n=590	OA status unknown n=139	total n=845	p-value between groups*
	55.5 [5.16]	56.4 [5.18]	55.9 [5.18]	**<0.01**
	473 [80.2%]	110 [79.1%]	672 [79.5%]	0.70
	26.1 [4.00]	26.0 [4.21]	26.3 [4.15]	**<0.01**
	324 [54.9%]	76 [54.7%]	461 [54.6%]	0.33
	324 [54.9%]	65 [46.8%]	431 [51.0%]	**0.06**
	96 [16.3%]	26 [18.7]	143 [16.9%]	0.72
	258 [43.7%]	68 [48.9]*	387 [45.8%]	0.13
	22.7 [16.9]	27.4 [18.4]	23.9 [17.3]	**<0.01**
	271 [45.9%]^	55 [39.6%]^	398 [47.1%]	**<0.01**
	21 [3.6%]^	4 [2.9%]^	37 [4.4%]	**<0.01**
	159 [26.9%]**^	32 [23.0%]***^	237 [28.0%]**	**<0.01**
	135.1 [8.88]*	133.4 [12.5]*	134.2 [9.92]	**<0.01**
	2.73 [2.77]*	2.28[2.46]*	2.64 [2.74]	0.24
	43 [7.3]	5 [3.6%]^	63 [7.5]	0.02
	356 [60.3%]^	92 [66.2%]	533 [63.1%]	0.02
	273 [46.3%]	53 [38.1%]	375 [44.4%]	0.22
	243 [41.2%]^	5 [3.6%]***^	343 [46.7%]***	**<0.01**
n=83	**n=517**	**n=129**	**n=845**	
59.7 [4.16]	57.5 [5.21]^	56.3 [5.15]	58.1 [5.17]	**<0.01**
68 [81.9]	407 [78.7]	106 [82.2%]	672 [79.5]	0.65
28.4 [4.67]^	25.7 [3.75]	26.3 [3.95]	26.2 [4.06]	**<0.01**
51 [61.4]	217 [42.0]	70 [54.3%]	367 [43.4]	0.03
21 [25.3]	75 [14.5]	29[22.5%]*	143 [16.9]	0.07
56 [67.5]	214 [21.4]	62 [48.1%]*	387 [45.8]	0.02
27.8 [17.7]	21.2 [17.1]	26.9 [18.8]	22.9 [17.8]	**<0.01**
49 [59.0]	201 [38.9]	54 [41.9%]	339 [40.1]	**0.03**
6 [7.2]	24 [4.6]	5 [3.9%]	43 [5.1]	0.23
20 [24.1]**	88 [17.0]**	30 [23.3%]***	142 [16.8]***	0.28
130.0 [10.4]^	136.1 [8.50]	133.4 [13.2]*	135.3 [9.09]*	**<0.01**
2.84 [2.99]	2.69 [2.63]	2.55 [2.78]*	2.64 [2.74]*	**<0.01**
11 [13.3]^	27 [5.2]	5 [3.9%]	50 [5.9]	0.03
56 [67.5]	288 [55.7]	83[64.3%]	464 [54.9]	0.23
28 [33.7]	164 [31.7]	53 [41.1%]	242 [28.6]	0.04

Bold indicates: p-value <0.01

* p-value between groups using ANOVA analyses, ^ Posthoc Bonferroni analysis: significant different compared to PFOA, * data missing in >5% to ≤10% cases, ** data missing in >10% to ≤20% cases, *** data missing in >20% cases

Multivariate regression analysis for different types of OA at 2-year follow-up

No significant differences in clinical signs and symptoms were found between participants with radiographic PFOA or TFOA. Compared with participants with PFOA, those with COA were more likely to have a lower knee flexion range of motion (OR 0.94, 95% CI 0.89-0.98). Participants without radiographic knee OA had better knee function (lower WOMAC scores) compared with those with isolated PFOA (OR 0.97, 95% CI 0.95-0.99) and reported more joint line tenderness compared with those with isolated PFOA (OR 3.13, 95% CI 1.47-6.69). Participants without radiographic OA tended to be younger, were less likely to have palpable bony enlargement and were less likely to have crepitus during knee flexion compared to those with isolated PFOA (Table 2).

DISCUSSION

The results of this study suggest that combined OA may start in the PF joint and then progresses to COA. At baseline, 16.4% of our participants with symptoms of early knee OA were diagnosed with radiographic isolated PFOA and none with isolated TFOA and at the 2-year follow-up, half of the participants with PFOA at baseline had developed COA, and at 5-year follow-up two thirds of the participants with isolated PFOA at baseline had developed COA. The incidence of COA and TFOA in patients that presented with symptoms of knee OA was low, i.e. 3.1-6.6%, respectively at the 2-year follow-up and 1.4-4.5%, respectively, at the 5-year follow-up.

Compared to the CAS(K) studies [20, 25, 37, 38], in the present study the prevalence of PFOA at baseline was lower (23.9% versus 16.4%, respectively) and this difference remained at follow-up (28.8% at 3 years follow-up in the CAS(K) study versus 4.6% at 2 years follow-up in the present study)[20]. These differences in prevalence and incidence are probably explained by the different populations in the studies. The CAS(K) studies [20, 25] comprised older patients with a higher BMI compared to our CHECK population. However, it was notable that, compared to Thorstensson et al. [27] who also included middle-aged participants (age range 35-54 years) with chronic knee complaints (>3 months), we found a lower prevalence of TFOA at baseline (47% versus 0%, respectively). Therefore, the differences in prevalence and incidence might not only be due to different populations but might also be attributed to the use of inconsistent definitions for knee OA[39]. The inconsistency in definitions of radiological OA in studies evaluating different OA types may have led to misclassification into the different OA groups[40]. This emphasises the need for consensus on the radiographic classification system used for OA[39].

It is noteworthy that in the present study, none of the participants had TFOA at baseline. This can probably be explained by our study population as most participants had not visit a GP or physician for their knee symptoms yet. However, the absence of TFOA in the present study might also be explained by detectability of the abnormalities of the different radiographs. It could be possible that on skyline radiographs osteophytes are earlier detectable than osteophytes on the PA radiograph, so that PFOA is earlier detectable with radiographs compared to TFOA. This may be strengthened by the findings of Stefanik et al. (2016) in which isolated PFOA was already seen at baseline, though in a relatively older population[21]. Though similar to our study, knees that developed OA in both the PFJ and TFJ started with damage isolated to the PFJ. It therefore seems important to get more insight in the patient population who develop combined knee OA and develop preventative and therapeutic strategies targeting the PFJ.

In the literature, three main signs of OA that were determined on physical examination (i.e. crepitus, restricted movement, and bony enlargement) were found to be associated with the development of radiographic OA[2]. These positive physical examination findings increase the

risk of radiographic OA[2]. However, the present results indicate the difficulty of discriminating between the different types of OA using the measures from clinical history and physical examination. However, the results do indicate that participants with COA had a lower knee flexion ROM compared to those with isolated PFOA, and a trend was seen in participants with TFOA; i.e. they also had a lower knee flexion ROM compared to those with isolated PFOA. Consistent results were reported in another cross-sectional study on clinical features of symptomatic OA, showing that lower knee flexion ROM was an indicator for radiographic COA and not for radiographic PFOA[25]. Furthermore, this latter study also reported that lower knee flexion ROM was an indicator for TFOA[25]. It is proposed that knee flexion ROM is an important clinical finding in (especially) participants with severe radiological signs of OA[41]. In the present cohort, the majority of the participants with knee symptoms had PFOA at baseline and this was already associated with reduced knee flexion ROM. Therefore, reduced knee flexion ROM seems to be an early sign of knee OA. However, it is questionable whether the ROM can distinguish between those with isolated PFOA, and those with TFOA and COA, in middle aged persons with knee symptoms.

It is noteworthy that participants without radiographic signs of OA were more likely to have joint line tenderness compared to those with PFOA. It could be hypothesised that joint line tenderness might be associated with other intra-articular pathologies (e.g. meniscus) that are not seen on radiographs. This hypothesis is strengthened by the fact that, when the K&L grade ≥1 variable was added to the multivariate regression model to test differences in phenotype between patients without radiographic signs of OA and those with PFOA, the significant association between joint line tenderness remained (data not shown).

The strength of the present study is that we were able to analyse a large cohort of relatively young subjects with early knee symptoms so that the natural course of OA could be evaluated. However, the study also has some limitations. In this relatively young cohort of participants with symptoms of knee OA, X-rays may not be sufficiently sensitive to detect early OA features and changes that are detectable on MRI[42]. On the other hand, these participants were followed over five years, a period in which radiographic signs are expected to progress[43].

Due to the small number of participants with TFOA we were unable to test for differences in phenotype based on baseline characteristics; therefore, we performed a cross-sectional analysis with the 2-year follow-up data. Furthermore, a limited number of variables were included in the regression analysis. Additional variables measured in the CHECK study (including clinical hand OA, profession, and physical activity) and reported to be risk factors for knee OA, might also differ between patients with PFOA and TFOA[43].

The explained variance in the regression model was low, indicating that other factors not included in the present study (e.g. quadriceps strength, malalignment) might be able to differentiate between the different types of OA[19, 25, 43]. These biomechanical variables could be potential targets for specific treatments for PFOA[44].

Implications for future research

None of the participants in the present study had TFOA at baseline and 116 had PFOA. This suggests but does not prove that combined OA is more likely to start in the PF-joint. Furthermore, two-thirds of the participants that had PFOA at baseline progressed to COA at the 5-year follow-up (assuming that the status of the 7 participants with COA at 2-year follow-up but missing data at 5-year follow-up did not change), whereas only 20% of the participants that had TFOA at the 2-year follow-up progressed to COA at the 5-year follow-up. This indicates that, in those who have their first signs of radiographic OA in the PF joint, they are more likely to progress to COA compared to those with isolated radiographic signs of OA in the TF joint. This is in agreement with earlier studies[20, 38]. Additionally, this was recently strengthened by Stefanik et al (2016) showing that patients with isolated PFOA on MRI at baseline were 2.1 times more likely to develop combined OA compared to patients with isolated TFOA at baseline[21]. However, a longer follow-up period is needed to determine whether all participants with PFOA at baseline will develop COA, or whether there are more subgroups within the PFOA population (e.g. stable PFOA, progression to COA, and progressive PFOA).

Conclusion

The results of this study suggest that combined OA seems to start in the PF joint and then progress to COA. Differences in TFOA and PFOA phenotypes could not be determined with respect to signs and symptoms. A longer follow-up is necessary to determine whether all participants with PFOA will eventually develop COA.

Acknowledgements

The steering committee of CHECK comprises 16 members with expertise in different fields of osteoarthritis chaired by J.W.J. Bijlsma, coordinated by J. Wesseling and performed within Erasmus Medical Centre Rotterdam; Kennemer Gasthuis Haarlem; Leiden University Medical Centre; Maastricht University Medical Centre; Martini Hospital Groningen / Allied Health Care Centre for Rheumatology and Rehabilitation Groningen; Medical Spectrum Twente Enschede / Ziekenhuisgroep Twente Almelo; Reade/VU Medical Centre Amsterdam; St Maartens-kliniek Nijmegen; University Medical Centre Utrecht; and Wilhelmina Hospital Assen.

REFERENCES

1 Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995; 38: 1134-1141.

2 Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis 2010; 69: 483-489.

3 Szebenyi B, Hollander AP, Dieppe P, Quilty B, Duddy J, Clarke S, et al. Associations between pain, function, and radiographic features in osteoarthritis of the knee. Arthritis Rheum 2006; 54: 230-235.

4 Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis--it all depends on your point of view. Rheumatology (Oxford) 2006; 45: 757-760.

5 McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992; 51: 844-849.

6 Hinman RS, Lentzos J, Vicenzino B, Crossley KM. Patellofemoral osteoarthritis is common in middle-aged people with chronic patellofemoral pain. Arthritis Care Res (Hoboken) 2013.

7 Kornaat PR, Bloem JL, Ceulemans RY, Riyazi N, Rosendaal FR, Nelissen RG, et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 2006; 239: 811-817.

8 Hunter DJ, Zhang YQ, Niu JB, Felson DT, Kwoh K, Newman A, et al. Patella malalignment, pain and patellofemoral progression: the Health ABC Study. Osteoarthritis Cartilage 2007; 15: 1120-1127.

9 Cicuttini FM, Baker J, Hart DJ, Spector TD. Association of pain with radiological changes in different compartments and views of the knee joint. Osteoarthritis Cartilage 1996; 4: 143-147.

10 Hunter DJ, March L, Sambrook PN. The association of cartilage volume with knee pain. Osteoarthritis Cartilage 2003; 11: 725-729.

11 Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010; 18: 476-499.

12 Driban JB SM, Barbe MF. Is osteoarthritis a heterogeneous disease that can be stratified into subsets? Clin Rheumatol 2009; 29: 123-131.

13 Felson D. Identifying different osteoarthritis phenotypes through epidemiology. Osteoarthritis and Cartilage 2010; 18: 601-604.

14 Knoop J, van der Leeden M, Thorstensson CA, Roorda LD, Lems WF, Knol DL, et al. Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2011; 63: 1535-1542.

15 Kerkhof HJ, Meulenbelt I, Akune T, Arden NK, Aromaa A, Bierma-Zeinstra SM, et al. Recommendations for standardization and phenotype definitions in genetic studies of osteoarthritis: the TREAT-OA consortium. Osteoarthritis Cartilage 2011; 19: 254-264.

16 van Middelkoop M, Dziedzic KS, Doherty M, Zhang W, Bijlsma JW, McAlindon TE, et al. Individual patient data meta-analysis of trials investigating the effectiveness of intra-articular glucocorticoid injections in patients with knee or hip osteoarthritis: an OA Trial Bank protocol for a systematic review. Syst Rev 2013; 2: 54.

17 Eyles J, Lucas BR, Hunter DJ. Targeting care: tailoring nonsurgical management according to clinical presentation. Rheum Dis Clin North Am 2013; 39: 213-233.
18 Hinman RS, Crossley KM. Patellofemoral joint osteoarthritis: an important subgroup of knee osteoarthritis. Rheumatology (Oxford) 2007; 46: 1057-1062.
19 Mills K, Hunter DJ. Patellofemoral joint osteoarthritis: an individualised pathomechanical approach to management. Best Pract Res Clin Rheumatol 2014; 28: 73-91.
20 Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. Ann Rheum Dis 2011; 70: 1944-1948.
21 Stefanik JJ, Guermazi A, Roemer FW, Peat G, Niu J, Segal NA, et al. Changes in patellofemoral and tibiofemoral joint cartilage damage and bone marrow lesions over 7 years: the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage 2016.
22 Elahi S, Cahue S, Felson DT, Engelman L, Sharma L. The association between varus-valgus alignment and patellofemoral osteoarthritis. Arthritis Rheum 2000; 43: 1874-1880.
23 Baker KR, Xu L, Zhang Y, Nevitt M, Niu J, Aliabadi P, et al. Quadriceps weakness and its relationship to tibiofemoral and patellofemoral knee osteoarthritis in Chinese: the Beijing osteoarthritis study. Arthritis Rheum 2004; 50: 1815-1821.
24 Cahue S, Dunlop D, Hayes K, Song J, Torres L, Sharma L. Varus-valgus alignment in the progression of patellofemoral osteoarthritis. Arthritis Rheum 2004; 50: 2184-2190.
25 Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. Arthritis Res Ther 2012; 14: R63.
26 Kumm J, Tamm A, Lintrop M, Tamm A. The prevalence and progression of radiographic knee osteoarthritis over 6 years in a population-based cohort of middle-aged subjects. Rheumatol Int 2012; 32: 3545-3550.
27 Thorstensson CA, Andersson ML, Jonsson H, Saxne T, Petersson IF. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. Ann Rheum Dis 2009; 68: 1890-1893.
28 Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68: 1413-1419.
29 Wesseling J, Boers M, Viergever MA, Hilberdink WK, Lafeber FP, Dekker J, et al. Cohort Profile: Cohort Hip and Cohort Knee (CHECK) study. Int J Epidemiol 2014.
30 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
31 Holla JF, Steultjens MP, Roorda LD, Heymans MW, Ten Wolde S, Dekker J. Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee. Arthritis Care Res (Hoboken) 2010; 62: 1415-1425.
32 Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007; 15 Suppl A: A1-56.
33 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
34 Burnett S HD, Cooper C, Spector TD. A Radiographic Atlas of Osteoarthritis. London, Springer Verslag 1994.
35 Damen J, Schiphof D, Wolde ST, Cats HA, Bierma-Zeinstra SM, Oei EH. Inter-observer reliability for radiographic assessment of early

osteoarthritis features: the CHECK (cohort hip and cohort knee) study. Osteoarthritis Cartilage 2014; 22: 969-974.
36 Belo JN, Bierma-Zeinstra SMA, Raaijmakers AJ, Van der Wissel F, Opstelten W. NHG-Standaard Niet-traumatische knieproblemen bij volwassenen (Eerste herziening). Huisarts & Wetenschap 2008; 51: 229-240.
37 Peat G, Thomas E, Handy J, Wood L, Dziedzic K, Myers H, et al. The Knee Clinical Assessment Study--CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population. BMC Musculoskelet Disord 2004; 5: 4.
38 Seedhom BB, Takeda M, Tsuabuku M, Wright V. Mechanical factors and patellofemoral osteoarthrosis. Annals of Rheumatic Diseases 1979; 38: 307-316.
39 Schiphof D, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis 2008; 67: 1034-1036.
40 Schiphof D, de Klerk BM, Koes BW, Bierma-Zeinstra S. Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal. J Clin Epidemiol 2008; 61: 1205-1215.
41 Holla JF, van der Leeden M, Roorda LD, Bierma-Zeinstra SM, Damen J, Dekker J, et al. Diagnostic accuracy of range of motion measurements in early symptomatic hip and/or knee osteoarthritis. Arthritis Care Res (Hoboken) 2012; 64: 59-65.
42 Guermazi A, Hayashi D, Roemer FW, Felson DT. Osteoarthritis: a review of strengths and weaknesses of different imaging options. Rheum Dis Clin North Am 2013; 39: 567-591.
43 Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011; 377: 2115-2126.
44 Callaghan MJ, Parkes MJ, Hutchinson CE, Gait AD, Forsythe LM, Marjanovic EJ, et al. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. Ann Rheum Dis 2015.

CHAPTER 6

Multiple angle radiographs for prediction of complaints: added value in the longitudinal prospective cohort (CHECK) study

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ABSTRACT

Objective

To investigate whether radiologic osteoarthritis (ROA) phenotypes assessed with multiple view radiographs have predictive value with respect to pain patterns over a five-year period.

Methods

In the CHECK early OA cohort (n=1002) five radiographic views were obtained: an anteroposterior and faux profile view of the hips, and a posteroanterior, mediolateral and skyline view of the knees. For different ROA phenotypes and based on multiple views (5 for knee, 2 for hip) it was investigated whether they were predictive with respect to pain trajectories retrieved by latent class growth analysis. In a previously built multivariate model the seven combinations of ROA were assessed on their prognostic value with respect to longitudinal pain patterns, using a stable low pain trajectory as reference.

Results

In the hip, participants with an ROA phenotype assessed on both the anteroposterior and faux profile view had less chance of a decreasing pain trajectory when tested univariately [OR 0.51 (95% CI 0.30-0.88)]; in the multivariate model this association was not significant. In the knee, when using the ROA features from all views (Kellgren & Lawrence grade ≥1 on the posteroanterior view, ≥1 osteophytes on the mediolateral view, and ≥1 osteophytes and/or joint space narrowing ≥1 on the skyline view), participants with features of ROA had less chance of decreasing pain [OR 0.53 (95% CI 0.30-0.94)].

Conclusions

Although this study used sensitive methods to determine ROA features, no pattern emerged in these features that predicted pain trajectories. Therefore, at this moment, we cannot recommend the use of combinations of ROA views to predict future pain.

INTRODUCTION

The use of radiographic assessment in osteoarthritis (OA) is widely debated. In medical practice its main usefulness is the assessment of end-stage disease, and to rule out other conditions. In epidemiological research there is contradictory evidence for the diagnostic and prognostic value of radiographic features of OA. Despite this controversy, radiography remains the most important imaging technique due to its widespread availability and low cost.[1]

Previous research has shown that symptomatic knee OA may be associated with patellofemoral OA that is not revealed by posteroanterior (PA) knee radiographs. When the radiographic protocol also consisted of views that enable assessment of the patellofemoral joint (i.e., lateral and/or skyline views), more positive associations were found between knee pain and radiographic joint damage.[2,3,4,5,6]

In the hip, the faux profile (FP) view is suggested to be more sensitive than the anteroposterior (AP) view for detecting early OA. Lequesne and Laredo introduced the FP view as a useful aid for detecting posterior or anterosuperior joint space narrowing (JSN) when no JSN is visible on the AP view (Lequesne). They also showed that this technique helps to detect OA at an earlier stage compared to the AP view.[6] Our group contributed to this debate by showing in the CHECK cohort that different radiographic views indeed help to reveal radiologic OA (ROA) at an earlier stage compared with the use of one view alone.[7]

The clinically relevant question is whether such imaging helps to predict the prognosis of early symptomatic OA. However, one difficulty in research on the prognosis of symptomatic OA is the fluctuating symptoms in OA. Most studies determined risk factors (including ROA features) for the development and progression of symptomatic OA or pain, based on only one point in time. However, due to the fluctuating symptoms (especially in first presenters of hip/knee pain), multiple assessments of pain over a longer period of time give a better indication of the course of pain than one single assessment at baseline and at follow-up. Multiple assessments are useful to define a pain trajectory, e.g. increasing or decreasing pain.[8] These pain trajectories are related to denominators such as body mass index (BMI), and aspects of physical examination in first presenters of hip/knee pain; however, it is unknown whether ROA found on multiple-angle radiographs is related to distinct pain trajectories.[9,10]

Therefore, the aim of this investigation was to assess within the Cohort Hip and Cohort Knee (CHECK) study, whether multiple view radiographs in first presenters with hip/knee pain have predictive value with respect to longitudinal pain trajectories established with multiple pain assessment over a five-year period.

METHODS

Design

The CHECK is a 10-year prospective cohort study of 1,002 individuals with early symptomatic OA of the knee and/or hip. The present study used data from baseline up to the 5-year follow-up. Details of the protocol are already published and a summary is presented below.[11]

Study population

Participants who potentially fulfilled the inclusion criteria were invited to join the study when they visited their general practitioner. In addition, participants were recruited through advertisements, articles in local newspapers, and via the website of the Dutch Arthritis Foundation. Individuals were eligible to participate if they had pain and/or stiffness of the knee and/or hip, were aged between 45 and 65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry.

Exclusion criteria were: i) any other pathological condition that could explain the existing symptoms (e.g. other rheumatic disease, isolated tendinitis/bursitis, previous hip or knee joint replacement, congenital dysplasia of the hip, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome or Bakers' cysts), ii) or a co-morbidity that precluded physical evaluation and/or follow-up for at least 10 years, iii) malignancy in the last 5 years, and iv) inability to understand the Dutch language.

Physicians at the participating centers checked whether referred patients, as well as patients from their own outpatient clinic, fulfilled the inclusion criteria.

All patients underwent radiographic assessment, a physical examination, and filled out an extensive questionnaire at baseline and once a year during the follow-up.[11]

Radiography

All radiographs obtained in the CHECK study were made according to a standardized radiographic protocol.[11] Semi-flexed (7-10 degrees) weight-bearing PA radiographs of the tibiofemoral joints were made, followed by standing mediolateral (ML) views in 30 degrees flexion for assessment of the tibiofemoral and patellofemoral joints. Skyline (inferior superior) views in 30 degrees flexion of the patellofemoral joints were also made. For the hip, weight-bearing AP radiographs of the pelvis were made, as well as weight-bearing FP radiographs of both hips taken according to Lequesne and Loredo. The FP view provides a lateral projection of the femoral head and neck, and an oblique view of the acetabulum tangential to its superoanteromedial edge.[6]

Radiographic scoring

The inter-reader observer reliability (prevalence-adjusted and bias-adjusted kappa; PABAK) for Kellgren and Lawrence [K&L] 0 vs K&L ≥ 1 was 0.80 (range 0.62-0.95) for the hip and 0.58 (range 0.10-0.87) for the knee (K&L 0 vs K& L ≥ 1). More detailed inter-reader reliability scores are already published.[12]

In the present cohort, different radiographic views at baseline were used to examine the presence of ROA. On the FP radiograph, hip ROA was defined as JSN ≥1 of at least the superior or posterior joint space.[6] On the PA view, femorotibial ROA of the knee, and on the AP view, ROA of the hip, were defined as K/L grade ≥1, graded according to Kellgren & Lawrence.[14] On the skyline radiograph, patellofemoral ROA was defined in three ways: i) only JSN (≥ 1), ii) only osteophytes (≥1), or iii) any sign of ROA (either JSN or osteophytes) scored according to Altman and Gold. [15] On the ML radiographs, patellofemoral ROA was also defined as ≥1 osteophytes according to the atlas of Burnett et al.[16] In all scores, a cutoff ≥1 was used due to the early stage of the disease in this cohort.

Outcome variable

Pain was assessed annually by means of questionnaires using the Numeric Rating Scale (NRS); scores ranged from 0-10 with higher scores indicating more pain. Participants were asked to score the average pain they experienced during the previous week; if a participant missed more than two pain assessments they were excluded from the analysis.

These scores were interpreted with latent class growth analysis (LCGA). LCGA is a technique that reveals heterogeneity in a population and enables to distinguish groups of people who are similar in their growth trajectories longitudinally. This technique has been described by Verkleij et al. and was applied in our study population.[8] LCGA was used to test whether the course of pain was best described by linear, quadratic or cubic trajectories. The most optimal model was determined by a combination of indices of fit, the interpretability of the model (i.e., is each identified group sufficiently large to enable further analyses), and whether the trajectories were visually distinguishable from each other for the clinical physician, i.e., is it possible to identify groups with progressing/decreasing trajectories or trajectories with variable paths, i.e. are the trajectories truly distinct.

In the hip, the model identified sufficiently large groups of participants with highly distinct trajectories; these were considered to be highly informative and clinically relevant, i.e. constant mild pain (n=231), moderate pain regression during follow-up (n=94), moderate pain progression (n=132), and an 'always pain' group (n=88).[9]

In the knee, the following groups were distinguished: stable low pain (n=137), slight pain regression (n=157), severe pain regression (n=15), severe pain progression (n=31), slight pain progression (n=128), and stable high pain (n=52).[10]

Statistical analysis

Logistic regression models were used to determine the strength of the association between knee ROA and hip ROA, and the different pain trajectories. Furthermore, these ROA features were added to models previously built by our group to test whether they have added value in models where only commonly used K&L scores were applied. [8,9]

In short, the final multivariate hip model included the following variables: i) highest achieved education, ii) pain coping inventory subscale 'pain transformation', iii) the WOMAC 'physical functioning' subscale, and iv) painful internal rotation hip. The final multivariable knee model included the following variables: i) BMI, ii) highest achieved education, iii) presence of comorbidity, iv) the WOMAC 'physical functioning' subscale, v) joint space tenderness, and vi) pain with knee flexion.

Results are presented as odds ratios (OR) with 95% confidence intervals (CI). The area under the curve (AUC) was calculated to assess whether the ROA scores helped to optimize the models. The earlier LCGA was performed using Mplus 6.1 ed. 1998-2010. All other analyses were performed with the SPSS version 22.0.0.0 (IBM Corp., USA).

RESULTS

At baseline, mean age of the participants was 55.9 (SD 5.2) years, 79% was female, average BMI was 26.2 (SD 4.1) kg/m^2, and the mean WOMAC pain score was 5.07 (SD 3.1). Of all participants, 411 (41%) reported pain in the knee only, 170 (17%) reported pain in the hip only, and 421 (42%) reported pain in both knee and hip.

Hip

Table 1a presents associations between either only ROA at the AP radiograph, or ROA at either the AP or FP view, and the different pain trajectories. Table 1b shows the associations when adjusted for confounders in the defined multivariate model. In the unadjusted model there was a significant association with ROA phenotypes when using the AP and FP views; patients with these ROA features had less chance of a decreasing pain trajectory [OR 0.51 (95% CI 0.30-0.88)]. However, this association was attenuated in the full model. When the FP radiograph was added to the AP radiograph, the AUC did not differ and was 0.23 in both models.

Knee

Table 2a presents associations between either only ROA at the PA radiograph, or ROA at either the PA, SKY or ML view, and the different pain trajectories. Table 2b shows the ORs when implemented in the previously defined model. The full model shows associations of ROA phenotypes assessed when using the ROA data from all three views (K&L grade ≥1 on the PA view, ≥1 osteophytes on the ML view, and ≥1 osteophytes and/or JSN ≥1 on the skyline view) these patients have less chance of a decreasing pain trajectory: OR 0.53 (95% CI 0.30-0.94). In the slightly decreasing trajectory, the AUC actually decreased from 0.83 to 0.59 when the SKY and the ML radiographs were added to the PA radiograph.

Table 1a. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) for radiologic osteoarthritis (ROA) phenotype and hip pain trajectory in 588 patients with hip pain.

ROA phenotype	Mild pain (N=231)	Moderate progression (N=132)	
		OR	**95% CI**
K&L ≥ 1 (N=166)	Ref.	1.18	(0.75-1.88)
K&L ≥ 1 and/or FP JSN ≥ 1 (N=195)	Ref.	0.93	(0.59-1.46)

Bold indicates significant at $p < 0.05$, R^2= R squared, Ref. = reference group
K&L = Kellgren and Lawrence score FP = faux profile JSN = Joint space narrowing

Table 1b. Full model* odds ratios (OR) and 95% confidence intervals (CI) for ROA phenotype and hip pain trajectory in 588 patients with hip pain.

ROA phenotype	Mild pain (N=231)	Moderate progression (N=132)	
		OR	**95% CI**
K&L ≥ 1 (N=166)	Ref.	1.16	(0.65-2.05)
K&L ≥ 1 and/or FP JSN ≥ 1 (N=195)	Ref.	1.04	(0.60-1.82)

K&L = Kellgren and Lawrence score, FP=faux profile, JSN=joint space narrowing, OR=odds ratio, Ref.= Reference, R^2= R squared.
*Full model included the variables: highest achieved education, PCI subscale pain transformation, WOMAC physical function subscale, and painful internal rotation hip.

	Decreasing pain (N=94)		Always pain (N=88)		R^2
	OR	**95% CI**	**OR**	**95% CI**	
	0.62	(0.35-1.09)	1.02	(0.59-1.77)	0.1
	0.51	**(0.30-0.88)**	0.85	(0.50-1.45)	0.14

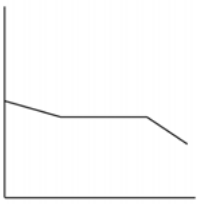
	Decreasing pain (N=94)		Always pain (N=88)		R^2
	OR	**95% CI**	**OR**	**95% CI**	
	0.65	(0.34-1.25)	0.88	(0.41-1.89)	0.41
	0.58	(0.31-1.10)	0.89	(0.42-1.88)	0.41

Table 2a. Unadjusted odds ratios (OR) and their 95% confidence intervals (CI) for radiographic osteoarthritis (ROA) phenotype and knee pain trajectory in 520 patients with knee pain.

ROA assessment	Stable low (N=137)	Severe regression (N=15)			Slight regression (N=157)		
		OR	95%CI		OR	95%CI	
PA K&L ≥ 1 (N=292)	Ref.	0.45	0.16	1.31	0.80	0.53	1.23
PA K&L ≥ 1& SKY (osteophytes) (N=423)	Ref.	0.66	0.26	1.67	0.80	0.52	1.22
PA K&L ≥ 1& SKY (JSN) (N=314)	Ref.	0.50	0.18	1.35	0.77	0.50	1.17
PA K&L ≥ 1& SKY (osteophytes & JSN) (N=428)	Ref.	0.81	0.32	2.05	0.85	0.56	1.31
PA K&L ≥ 1& SKY (osteophytes & JSN) & ML (osteophytes) (N=492)	Ref.	2.52	0.78	8 1.14	0.74	0.44	1.25

PA=posterior-anterior; Sky=skyline. ML=mediolateral, JSN=joint space narrowing, K&L= Kellgren & Lawrence score

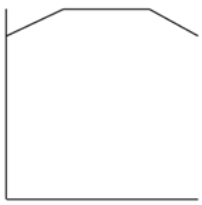
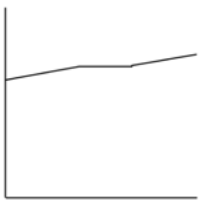
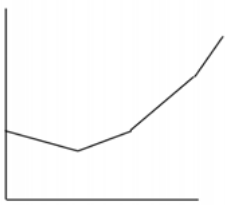
Table 2b. Full model* odds ratios (OR) and their 95% confidence intervals (CI) for radiographic osteoarthritis (ROA) phenotype and knee pain trajectory in 520 patients with knee pain.

ROA assessment	Stable low (N=137)	Severe regression (N=15)			Slight regression (N=157)		
							
		OR	lower	upper	OR	lower	upper
PA K&L ≥ 1 (N=292)	Ref.	0.41	0.12	1.48	0.64	0.38	1.06
PA K&L ≥ 1 & SKY (osteophytes) (N=423)	Ref.	1.05	0.94	2.66	0.66	0.39	1.10
PA K&L ≥ 1 & SKY (JSN) (N=314)	Ref.	0.49	0.14	1.65	0.62	0.37	1.04
PA K&L ≥ 1 & SKY (osteophytes & JSN) (N=428)	Ref.	1.09	0.32	3.74	0.71	0.42	1.18
PA K&L ≥ 1 & SKY (osteophytes & JSN) & ML (osteophytes) (N=492)	Ref.	1.89	0.36	9.89	**0.53**	**0.30**	**0.94**

PA=posterioranterior; Sky: skyline. ML=mediolateral. JSN=joint space narrowing.
Bold indicates significant at $p < 0.05$.

	Stable high (N=52)			Slight progression (N=128)			Severe progression (N=31)			Total
	OR	95%CI		OR	95%CI		OR	95%CI		R^2
	1.40	0.80	2.47	1.13	0.74	1.75	1.21	0.58	2.53	0.01
	1.94	**1.02**	**3.70**	1.20	0.77	1.89	1.21	0.56	2.61	0.01
	1.49	0.83	2.66	1.13	0.73	1.74	1.03	0.49	2.15	0.02
	1.94	**1.02**	**3.70**	1.26	0.80	1.98	1.21	0.56	2.61	0.01
	0.92	0.42	2.05	0.99	0.57	1.70	0.72	0.28	1.87	0.01

Bold indicates significant at $p < 0.05$, R^2= R squared, Ref.=Reference group

	Stable high (N=52)			Slight progression (N=128)			Severe progression (N=31)			Total
										
	OR	lower	upper	OR	lower	upper	OR	lower	upper	R^2
	1.14	0.50	2.59	1.19	0.67	2.14	1.19	0.52	2.71	0.42
	2.50	0.98	6.36	1.45	0.79	2.68	1.31	0.55	3.12	0.43
	1.12	0.49	2.77	1.15	0.64	2.06	0.98	0.43	2.24	0.42
	2.39	0.94	6.09	1.51	0.82	2.79	1.32	0.56	3.15	0.42
	1.16	0.43	3.12	0.99	0.51	1.94	0.85	0.34	1.17	0.42

*The full model included the variables: highest achieved education, WOMAC physical function subscale, having more than 1 comorbidity, joint space tenderness, and painful flexion. R2= R squared. Ref.=Reference group

DISCUSSION

Using data from the longitudinal CHECK study, the aim of this investigation was to assess whether an association exists between ROA phenotypes assessed with multiple views and different pain trajectories.

The use of a combination of different radiographic views (e.g. skyline, ML and FP radiographs) is reported to lead to earlier detection of cases of ROA of knee and hip compared with the commonly used method (i.e. in general practice and most imaging studies) of defining ROA based on a single radiographic projection.[7] Our group also reported the usefulness of LCGA and predictors of different pain trajectories. [8,9] However, in the present study, combining these data did not demonstrate a clear association between ROA found on different radiographic views and different pain trajectories. Therefore, our main conclusion is that the different ROA phenotypes distinguished at baseline do not provide additional value with regard to the prediction of pain trajectories over a 5-year period.

It is difficult to compare the present results with other investigations because this is the first study to combine longitudinal pain trajectories and multiple view radiography. McAlindon et al.[17] showed that ROA on different views was related to pain and disability, but did not test whether there was an additive effect of multiple views. Lequesne et al. more frequently revealed ROA using both hip views, but did not assess whether pain was related to ROA. In a cross-sectional study, Duncan et al. showed better associations with knee pain when multiple radiographs were combined to define ROA, but did not assess this with respect to prognosis of pain.[4]

Therefore, this is first study to examine these multiple angled radiographs to assess whether ROA features are useful in predicting pain trajectories. At this point there seems to be only a trend that patients presenting with pain, but with no ROA on multiple views, tend to recover from their pain.

Strengths and limitations

The early OA stage and these LCGA techniques applied provide a strong basis for examining the progression of early OA symptoms and the related signs of ROA. The research question is a clinical challenge and the cohort investigated should be large enough to allow to draw conclusions.

Limitations of the present study are mainly related to the cohort itself. Since imaging in early ROA is difficult, we addressed this by lowering the threshold for ROA from K&L ≥2 to K&L ≥1. Also, although LCGA seems a sensitive method to address different pain trajectories, the NRS was recorded only once a year during follow-up; more frequent assessments might allow to better assess pain trajectories. Moreover, although we used data from a large cohort, LCGA might identify small subgroups with different pain trajectories and, in very small subgroups, statistical power might represent an issue for association studies.

Conclusion

At this point we cannot recommend the use of radiography, including multiple angle radiography, to predict pain trajectories.

Acknowledgments

The authors thank all participants of the CHECK cohort and all collaborators of the different sites for their efforts. CHECK is funded by the Dutch Arthritis Association on the lead of a steering committee comprising 16 members with expertise in different fields of osteoarthritis chaired by Prof. J.W.J. Bijlsma and coordinated by J. Wesseling. Involved are: Erasmus MC University Medical Center Rotterdam; Academic HospitaMaastricht; Jan van Breemen Institute/VU Medical Center Amsterdam; Kennemer Gasthuis Haarlem; Martini Hospital Groningen/Allied Health Care Center for Rheumatology and Rehabilitation Groningen; Medical Spectrum Twente Enschede/Twenteborg Hospital Almelo; St Maartenskliniek Nijmegen; Leiden University Medical Center; University Medical Center Utrecht and Wilhelmina Hospital Assen.

REFERENCES

1 Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry:analysis of longitudinal data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken)2010;62:932–7.

2 Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.

3 Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? Osteoarthritis Cartilage 2009;17:1151–5.

4 Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. How do pain and function vary with compartmental distribution and severity of radiographic knee osteoarthritis? Rheumatology (Oxford) 2008;47:1704–7.

5 Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis: it all depends on your point of view. Rheumatology (Oxford) 2006;45:757–60.

6 Lequesne MG, Laredo JD. The faux profile (oblique view) of the hip in the standing position: contribution to the evaluation of osteoarthritis of the adult hip. Ann Rheum Dis1998;57:676–81.

7 Damen J, Runhaar J, Kloppenburg M, Meijer R, Bierma-Zeinstra SMA, Oei EHG. Additional Value of Different Radiographic Views on the Identification of Early Radiographic Hip and Knee Osteoarthritis and Its Progression: A Cohort Study.. Arthritis Care Res (Hoboken). 2017 Nov;69(11):1644-1650

8 Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, Bierma-Zeinstra SM. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis. 2012

9 Bastick AN, Verkleij SP, Damen J, Wesseling J, Hilberdink WK, Bindels PJ, Bierma-Zeinstra SM. Defining hip pain trajectories in early symptomatic hip osteoarthritis--5 year results from a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage. 2016 May;24(5):768-75

10 Bastick AN, Wesseling J, Damen J, Verkleij SP, Emans PJ, Bindels PJ, Bierma-Zeinstra SM.Defining knee pain trajectories in early symptomatic knee osteoarthritis in primary care: 5-year results from a nationwide prospective cohort study (CHECK). Br J Gen Pract. 2016 Jan;66(642):e32-9.

11 Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SMA, Boers M, Cats HA, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Annals of the Rheumatic Diseases 2009;68:1413–9.

12 Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee Buckland-Wright C. Osteoarthritis Cartilage 1995;3(Suppl A):71-80

13 Damen J, Schiphof D, Wolde ST, Cats HA, Bierma-Zeinstra SM, Oei EH. Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (cohort hip and cohort knee) study. Osteoarthritis Cartilage 2014;22:969–74

14 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases 1957;16:494–502.

15 Altman R, Gold G. Atlas of individual radiographic features in osteoarthritis, revised1. Osteoarthritis and Cartilage 2007;15:A1–A56.

16 A Radiographic Atlas of Osteoarthritis. S burnett, DJ hart, C Cooper TD Spector. London: Springer Verlag; 1994.

17 McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992;51:844–9. 21.

CHAPTER 7

Disc Degeneration of the Upper Lumbar Discs is Associated with Hip Pain

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Eur Spine J. 2013 Apr;22(4):721-6

ABSTRACT

Purpose

A possible cause of hip pain is the presence of radiating pain from the higher lumbar spine. Identification of factors associated with hip pain arising from the lumbar spine would aid the physician. The first step in identifying possible factors is to look at the association between hip pain and osteoarthritis of the lumbar spine.

Methods

In an open population based study of people 55 years and older (Rotterdam study), 2819 lumbar radiographs were scored for the presence and severity of individual radiographic features of disc degeneration. Hip osteoarthritis was scored on anteroposterior pelvic radiographs, and questionnaires including self-reported hip pain were taken. Logistic regression adjusted for possible confounders was used to determine the association between self-reported hip pain and the individual radiographic features of lumbar disc degeneration.

Results

The presence of disc space narrowing grade ≥ 1 at level L1/L2 was significantly associated with hip pain in the last month (men OR = 2.0; 95% CI: 1.1 to 3.8 and women OR = 1.7; 95% CI: 1.1 to 2.5). The presence of disc space narrowing grade ≥ 1 at level L2/L3 was only significantly associated with hip pain in women. The strength of the associations increased for self-reported chronic hip pain, especially in men (L1/L2 OR = 2.5; 95% CI: 1.3 to 5.0). The presence of disc space narrowing at the lower levels (L3/L4/L5/S1) was not significantly associated with hip pain.

Conclusion

Our data provide evidence for an association between hip pain and disc space narrowing at disc level L1/L2 and L2/L3. In case of uncertainty of the cause of hip pain, evaluation of lumbar radiographs may help to identify those hip pain patients who might have pain arising from the lumbar spine.

INTRODUCTION

Hip pain is a common symptom among older adults, with a point prevalence of 14.3% reported in the United States.[1] The differential diagnosis of hip pain is broad and includes intra-articular pathology, extra-articular pathology and other causes like radiating pain from the lumbar spine. Differentiating back pain from hip pain in patients who present with classic signs and symptoms is mostly not difficult and generally does not require further testing to establish an accurate diagnosis. However, in some cases, patients present with nonspecific complaints of pain in the lumbar spine, buttock, lateral hip, or thigh.[2] The differentiation of signs and symptoms suggestive of hip disorders versus spine disorders is important in giving patients the most beneficial treatment, especially if the treatment includes a major reconstructive surgery, such as hip replacement.

Differentiating whether hip-pain originates from the hip, the spine or both may be challenging. Brown et al.[3] attempted to determine which physical signs and symptoms best predict the primary source of pain in patients with hip-, spine- or concomitant disorders. After final diagnosis with imaging studies, they found that although limited internal rotation, groin pain and a limp are more commonly associated with a hip disorder, these symptoms are also seen in patients with spine alone or both hip- and spine-disorders.

To make a differentiation between hip and spine originated hip pain there have been a few studies about the usefulness of local anaesthetic with(out) corticosteroid hip infiltrations, to differentiate intra-articular causes of hip pain from spinal causes.[4,5,6,7] To our knowledge, there have been no studies about the usefulness of local spine infiltrations to differentiate hip and spine originated hip pain. However, infiltration of every patient with atypical hip pain for possible coexistent lumbar spine osteoarthritis would be counterproductive and costly. Preoperative identification of factors associated with hip pain arising from the lumbar spine would aid the physician by identifying the subgroup of patients who might not experience full relief of pain with a hip arthroplasty.

One of the first steps to identify possible factors is to look at the association between hip pain and osteoarthritis of the lumbar spine. The purpose of this study was to explore the association of self-reported hip pain with the different individual radiographic features (IRF) of spinal osteoarthritis by vertebral level, including osteophytes and disc space narrowing.

METHODS

Study population

The data for this study originate from data of the Rotterdam Study, an open population prospective cohort of people aged 55 years and older. The objective of the Rotterdam Study is to investigate the incidence of, and risk factors for, chronic disabling diseases. The study design has been described previously.[8] All 10,275 inhabitants of Ommoord (a district in Rotterdam, the Netherlands) were invited to participate. The baseline measurements were conducted between 1990 and 1993. In total, 7983 participants were examined. For this study, 2819 lumbar radiographs were scored. The selection was based on the availability of radiographs of the hip and spine at a follow-up measurement 6.6 years later.[9,12]

Radiographic scoring

Lumbar lateral radiographs were scored by a single observer trained by a radiologist for the presence of the individual radiographic features of disc degeneration. The observer was blinded to clinical characteristics of the participants. Each vertebral level from L1/2 to L5/S1 was reviewed for the presence and severity of osteophytes (anterior) and vertebral narrowing, using the Lane atlas.[10,11] In this atlas grade 0 = none; grade 1 = mild; grade 2 = moderate; and grade 3 = severe. The lumbosacral disc space was defined as narrowed when its height was less than that of the disc space between the third and fourth lumbar vertebrae. This is due to a normal progression of increasing disc-space height from the third and fourth to the fourth and fifth lumbar vertebrae, and then a relative narrowing of the height of the lumbosacral disc space. Sclerosis was not scored because of the earlier reported low ICC for this feature.[11]

Inter-observer reproducibility was assessed by a second independent observer who evaluated a random selection of 140 (5%) X-rays. The ICC was 0.83 for osteophytes and 0.77 for vertebral narrowing, indicating good reproducibility.

Weight bearing anteroposterior radiographs of the pelvis were obtained. One trained reader evaluated the radiographs obtained at baseline, unaware of the clinical status of the participants.[9] At baseline, radiological osteoarthritis of the hip was quantified by measurements following the Kellgren & Lawrence grading system (atlas-based) in five grades (from 0 to 4). A person was considered to have osteoarthritis of the hip, if the Kellgren & Lawrence score of one or both joints was equal to or larger than two.[9]

Hip pain

Hip pain and low back pain were determined from interviewing the participants during the home visits. Participants were asked "Did you have complaints of the (left and/or right) hip during the last month?". Hip pain was defined to be present if the answer was positive. Participants were subsequently asked "What is the duration of the present hip complaints?". For low back pain similar questions were asked. We defined chronic hip pain to be present if the duration of the hip joint pain was more than one year.

Participants also visited the research center, where X-rays were obtained. Height and weight were measured with participants wearing indoor clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by length in meters squared (kg/m^2).

Statistical Analyses

We defined disc space narrowing to be present if the grade was mild, moderate, or severe (grade ≥1). Because of the small proportion of subjects without osteophytes, we used a higher cutoff value for this feature. We defined osteophytes to be present if the grade was moderate or severe (grade ≥2).[12] Using these definitions we calculated the prevalence of the IRF by vertebral level (L1/2 to L5/S1) and gender.

In order to explore the association between the IRF by vertebral level and hip pain, hip pain was used as the dependent variable with adjustments made for age and gender. The assessments of the associations were also adjusted for radiological hip osteoarthritis, as this variable was shown to be associated with disc space narrowing and of course with hip pain. The same was true for low back pain.[12] In addition, the assessments of the association were also adjusted for BMI, as this variable has been reported to be associated with both hip pain and some of the individual radiographic features.[13,14,15]

In a separate analysis we explored the association between the IRF by vertebral level and hip pain in subjects with no sign of radiological hip osteoarthritis. The results of the analyses are expressed as odds ratios (OR) with 95% confidence intervals (CI), stratified for gender. The same methods were used to explore the association between the IRF and chronic hip pain. Statistical analysis was performed using SPSS version 15 (SPSS Inc, Chicago, USA).

RESULTS

Subject characteristics

Baseline characteristics are shown in Table 1. There were 1204 men (mean age 65.3 years, standard deviation (SD) 6.4) and 1615 women (mean age 65.9 years, SD 6.8). Hip pain during the last month was reported more often by women than men (244 (15.1%) vs. 84 (7.0%) $p < 0.05$) (Table 1). Chronic hip pain was reported in the majority (82%) of the current hip pain cases and was also more often reported by women (208 (12.9%) vs. 62 (5.1%) $p < 0.05$). Radiological hip osteoarthritis was observed in 209 (7.4%) persons (Kellgren & Lawrence ≥2 in one or both hips).

Influence of gender and vertebral level

The prevalence of the IRF in men and women is shown in Table 1. Osteophytes were the most frequent observed radiographic feature and were slightly more common in men than women (95% vs. 91%; $p<0.05$). Disc space narrowing was more frequent in women than men (65% vs. 53%; $p<0.05$). In terms of their distribution by vertebral level, narrowing was more frequent at the lower lumbar disc levels.

Disc space narrowing grade ≥ 1 at level L1/L2 was more common in persons with hip pain (19% vs. 10%; $p <0.05$). And hip pain was more common in persons with disc space narrowing grade ≥ 1 at level L1/L2 (21% vs. 11%; $p <0.05$).

Association with LDD

Table 2 shows the association between hip pain and the IRF, adjusted for age, gender, BMI, hip arthritis and low back pain. The presence of disc space narrowing grade ≥ 1 at level L1/L2 was significantly associated with hip pain in the last month, both in men and women (men OR = 2.0; 95% CI: 1.1 to 3.8 and women OR = 1.7; 95% CI: 1.1 to 2.5) (Table 2). The presence of disc space narrowing grade ≥ 1 at level L2/L3 was significantly associated with hip pain in the last month, only in women (OR = 1.6; 95% CI: 1.1 to 2.2). The strength of the associations increased for the participants with chronic hip pain, especially for men (L1/L2 OR = 2.5; 95% CI: 1.3 to 5.0). The strength of the associations also increased for the group of subjects with no radiological hip osteoarthritis (men chronic pain L1/L2 OR = 2.7; 95% CI; 1.3 to 5.5 and women chronic pain L1/L2 OR = 2.0; 95% CI; 1.3 to 3.2).

The presence of disc space narrowing at the lower levels (L3/L4/L5/S1) was not significantly associated with hip pain. The presence of disc space narrowing grade ≥ 2 was not explored, because of the low number of persons with disc space narrowing grade ≥ 2 at the upper levels. The presence of osteophytes grade ≥ 2 was not significantly associated with hip pain at any level (data not shown).

Table 1, Baseline characteristics

	Men, N = 1204	**Women, N = 1615**	**All, N = 2819**	**Hip pain, N = 328**
Age (years) Mean ± SD	65.3 ± 6.4	65.9 ± 6.8	65.7 ± 6.6	66.2 ± 6.8
Body mass index (BMI) Mean ± SD	25.9 ± 2.9	26.6 ± 3.8	26.3 ± 3.5	27.0 ± 3.9
Hip pain (%)†	84 (7.0)	244 (15.1)	328 (11.6)	328 (100)
Chronic hip pain (%)‡	62 (5.1)	208 (12.9)	270 (9.6)	270 (82.3)
Hip osteoarthritis (%)	94 (7.8)	115 (7.1)	209 (7.4)	51 (15.5)
Osteophytes low back (%)				
Grade ≥ 1	1148 (95.3)	1467 (90.8)	2615 (92.8)	306 (93.3)
Grade ≥ 2	832 (69.1)	929 (57.5)	1761 (62.5)	217 (66.2)
Grade 3	536 (44.5)	505 (31.3)	1041 (36.9)	134 (40.9)
Narrowing low back (%)				
Grade ≥ 1	637 (52.9)	1048 (64.9)	1685 (59.8)	210 (64.0)
Grade ≥ 2	286 (23.8)	525 (32.5)	811 (28.8)	115 (35.1)
Grade 3	40 (3.3)	107 (6.6)	147 (5.2)	20 (6.1)
Osteophytes ≥2 (%)				
L1-2	282 (23.4)	297 (18.4)	579 (20.5)	84 (25.6)
L2-3	347 (28.8)	404 (25.0)	751 (26.6)	105 (32.0)
L3-4	428 (35.5)	364 (22.6)	792 (28.1)	100 (30.5)
L4-5	403 (33.5)	354 (21.9)	757 (26.9)	94 (28.7)
L5-S1	312 (25.9)	303 (18.8)	615 (21.8)	68 (20.7)
Narrowing ≥1 (%)				
L1-2	107 (8.9)	201 (12.5)	308 (10.9)	63 (19.2)
L2-3	135 (11.3)	307 (19.0)	442 (15.7)	81 (24.7)
L3-4	153 (12.7)	342 (21.1)	495 (17.6)	78 (23.8)
L4-5	268 (22.2)	526 (32.6)	794 (28.2)	111 (33.8)
L5-S1	408 (34.0)	662 (41.0)	1070 (38.0)	127 (38.7)

† Hip pain: complaints of the hip joint during last month

‡ Chronic hip pain: duration present hip joint complaints > 1 year

Table 2. Association between disc space narrowing and hip pain

Men = 1204			
Narrowing level	N (%)	Hip pain OR (95% CI)	Chronic hip pain OR (95% CI)
L1-L2	107 (8.9)	2.0 (1.1 – 3.8)*	2.5 (1.3 – 5.0)**
L2-L3	135 (11.3)	0.9 (0.4 – 1.8)	1.1 (0.5 – 2.4)
L3-L4	153 (12.7)	1.1 (0.6 – 2.1)	1.1 (0.5 – 2.2)
L4-L5	268 (22.2)	1.2 (0.7 – 2.0)	1.4 (0.8 – 2.5)
L5-S1	408 (33.9)	0.7 (0.4 – 1.1)	0.6 (0.4 – 1.1)
Women N= 1615			
Narrowing level	N (%)	Hip pain OR (95% CI)	Chronic hip pain OR (95% CI)
L1-L2	201 (12.5)	1.7 (1.1 – 2.5)*	1.8 (1.1 – 2.7)**
L2-L3	307 (19.0)	1.6 (1.1 – 2.2)*	1.6 (1.1 – 2.3)*
L3-L4	342 (21.1)	1.0 (0.7 – 1.4)	1.1 (0.7 – 1.5)
L4-L5	526 (32.6)	0.9 (0.7 – 1.3)	1.0 (0.7 – 1.4)
L5-S1	662 (41.0)	1.0 (0.7 – 1.3)	0.9 (0.7 – 1.2)
All N= 2819			
Narrowing level	N (%)	Hip pain OR (95% CI)	Chronic hip pain OR (95% CI)
L1-L2	308 (10.9)	1.8 (1.3 – 2.5)**	2.0 (1.4 – 2.8)**
L2-L3	442 (15.7)	1.4 (1.0 – 1.9)*	1.5 (1.1 – 2.1)*
L3-L4	495 (17.6)	1.1 (0.8 – 1.4)	1.1 (0.8 – 1.5)
L4-L5	794 (28.2)	1.0 (0.8 – 1.3)	1.1 (0.8 – 1.5)
L5-S1	1070 (38.0)	0.9 (0.7 – 1.1)	0.8 (0.6 – 1.1)

Adjusted for age, gender, BMI, hip arthrosis and low back pain

* p = < 0.05

** p = < 0.01

OR odds ratio

CI confidence interval

DISCUSSION

The differentiation of signs and symptoms suggestive of hip disorders versus spine disorders is important in giving patients the most beneficial treatment. The purpose of this study was to explore the association of self-reported hip pain with the different individual radiographic features (IRF) of spinal osteoarthritis. In this study, disc space narrowing at level L1/L2 appeared to be associated with pain in the hip region, especially in men. The strength of the associations increased for participants with chronic hip pain and in those without radiological signs of hip osteoarthritis. These results suggest that in case of uncertainty of the cause of hip pain, evaluation of lumbar radiographs may help to identify those hip pain patients that may benefit most from further diagnostic evaluation.

Our data provides evidence for radiating pain from the higher lumbar spine as a possible cause of hip pain in a cross-sectional open population based study. One of the explanations that can be found for the association between hip pain and disc space narrowing at level L1/L2 and L2/L3 is "referred pain". The term "referred pain" is used for pain localized not in the site of its origin but in areas that may be adjacent or at a distance from such a site. Several theories have been proposed to explain the "referred pain" phenomenon, with the convergence-projection theory the most widespread.[16,17] Input from different tissue types converge on the same dorsal horn neurons.[18] And after activation, increased nociceptive input is transmitted supraspinally and misinterpreted at the cortical level as pain from other tissues. It is possible that the reduction of space between the vertebrae as a consequence of the degenerative disc leads to increased pressure on spinal ligaments and other supporting tissues. This can be misinterpreted at the cortical level as pain from other tissues, like the hip region. Experimental studies have confirmed that noxious stimulation of interspinous ligament, facet joint, and paravertebral muscles causes referred pain that can radiate into the extremity.[19,20,21]

Another explanation for the radiating pain from the higher lumbar spine can be found in the dermatomal innervations of the hip region. It is suggested that impingement of the higher lumbar spinal nerve roots (L1-L3) can cause pain in the dermatomal distribution surrounding the hip. The dermatomal distribution of the L1 spinal nerve is located in the groin and the upper part of the buttock. The distribution of the L2 spinal nerve is located in the outside thigh. It is possible that reduction of space between the vertebrae as a consequence of the degenerative disc is more likely to lead to impingement of the L1 and L2 nerve roots, and therefore causes pain in the dermatomal distribution. Spinal nerve roots pass through the intervertebral foramen as they travel from the spinal cord toward the periphery. It has been reported that narrowing of the disc space can reduce the vertical diameter of this intervertebral foramen.[22]

The explanation for the stronger association between hip pain and disc space narrowing compared with the presence of osteophytes is unknown. This study evaluates the severity of anterior osteophytes, unfortunately we could not evaluate any bony aspects of the intervertebral foramen. The explanation for the stronger association between hip pain and disc space narrowing at L1/L2 in men compared with the association in women is also unknown. It is possible that even though women reported hip pain more often, only a small proportion of the complaints are due to disc space narrowing, whereas other factors determine the feeling of pain. Men and women could also report pain differently therefore effecting the association between hip pain, disc space narrowing and gender. Cecchi et al., showed that women presented with significantly more severe pain than men.[23] Finally, the explanation for the absence of an association between hip pain and disc space narrowing at L2/L3 in men compared to women is also unknown. It is maybe due to an evidently lower prevalence of disc space narrowing at L2/L3 in men compared to women.

Our study had several advantages. It was population based with a relatively high number of subjects. We used a semi-quantitative score, using standard radiographs, to characterize the presence and severity of hip and spine osteoarthritis. Assessment of the radiographs was carried out without knowledge of the questionnaire data, and so any errors in classification are likely to have been non-directional. We defined chronic hip pain and chronic low back pain to be present if the duration of the hip joint pain was more than one year. In literature, others have chosen three months or even six months as the dividing line between acute and chronic pain.[24] However, with our definition, chronic pain included long lasting chronic complaints with long lasting impact on ones life.

However, there are several limitations in our explorative study that need to be considered when interpreting the results. Our data did not include the precise location of the hip pain. This limitation is partly undermined by the fact that the dermatomal distribution of L1 and L2 includes the upper part of the buttock, the groin and the lateral thigh, which covers a wide area of the hip region. Further, our data did not include a clinical evaluation of the hip pain. In this way we could not account for the potential of soft-tissue pathology contributing to the reported hip pain. Moreover, hip osteoarthritis was only considered when the Kellgren & Lawrence score of one or both joints was equal to or larger than two in agreement with conventional epidemiological definitions for hip osteoarthritis.[25] In this way there is still a possibility of the presence of hip osteoarthritis which is not clearly visible yet on radiographs at that time point. To exclude the possibility of this confounding, we reanalyzed the data with adjusting for presence of radiographic hip osteoarthritis 6.6 years later. We defined a new variable that included all the participants with hip osteoarthritis at baseline and/or hip osteoarthritis 6.6 years later (n = 413). The strength of the associations was unchanged (for chronic pain the L1/L2 OR was 1.9; 95% CI; 1.3 to 2.7; again higher in men (OR = 2.7; 95% CI; 1.4 to 5.3) than in women (OR = 1.7; 95% CI; 1.1 to 2.6).

Furthermore, there could be some selection bias in favor of relatively healthy participants. The participants in the present study had to be mobile enough to visit the research center for X-ray examination, both for the baseline and follow up appointments (mean 6.6 years).[9] In other words, patients with the most severe symptoms were most likely not included, but this may be inevitable in long-term prospective cohort studies.

What are the implications of these findings for researchers and clinicians?
Accurate diagnosis of pain originating from the hip joint can be clinically challenging. There have been several studies about the usefulness of hip injections to differentiate intra-articular causes of hip pain from spinal causes.[4,5,6,7] To our knowledge, there have been no studies about the usefulness of local spine infiltrations to differentiate hip and spine originated hip pain. A possible explanation for this is the availability of a successful treatment for degenerated hip disease (hip arthroplasty), but less predictable treatment options for degenerative spine disorders.

The differentiation of signs and symptoms suggestive of a hip disorder is important in giving patients adequate information regarding their condition and for applying the most beneficial treatment. Our data provides evidence for an association between hip pain and disc space narrowing at disc level L1/L2 and L2/L3. In case of uncertainty of the cause of hip pain, evaluation of lumbar radiographs may help to identify those hip pain patients who might have pain arising from the lumbar spine. Perhaps hip infiltration in patients without higher lumbar disc degeneration is even unnecessary. However, well designed studies are needed to verify this hypothesis.

Conclusion
In conclusion, this study explores the association of self-reported hip pain with lumbar spine osteoarthritis. Our data provides evidence for an association between hip pain and disc space narrowing at disc level L1/L2 and L2/L3. In case of uncertainty of the cause of hip pain, evaluation of lumbar radiographs may help to identify those hip pain patients who might have pain arising from the lumbar spine. Well designed studies are needed to verify this hypothesis.

REFERENCES

1 Christmas C, Crespo CJ, Franckowiak SC, et al. How common is hip pain among older adults? Results from the Third National Health and Nutrition Examination Survey. J Fam Pract 2002;51(4):345-348.

2 Illgren R, Honkamp N, Weisman M, et al. The Diagnostic and Predictive Value of Hip Anesthetic Arthrograms in Selected Patients Before Total Hip Arthroplasty. The Journal of Arthroplasty. 2006;21(5):724-730

3 Brown MD, Gomez-Marin O, Brookfield KF, et al. Differential diagnosis of hip disease versus spine disease. Clin Orthop Relat Res 2004(419):280-284.

4 Ashok N, Sivan M, Tafazal S. The diagnostic value of anaesthetic hip injection in differentiating between hip and spinal pain. Eur J Orthop Surg Traumatol. 2009;19:167-171

5 Faraj A, Kumaraguru P, Kosygan K. Intra-articular bupivacaine hip injection in differentiation of coxarthrosis from referred thigh pain: A 10 year study. Acta Orthopaedica Belgica. 2003;69(6):518-521

6 Kleiner J, Thorne R, Curd J. The Value of Buvicaine Hip Injection in the Differentiation of Coxarthrosis from Lower Extrimity Neuropathy. The Journal of Rheumatology. 1991;18(3): 422-427

7 Pateder D, Hungerford M. Use of Fluoroscopically Guided Intra-articular Hip Injection in Differentiating the Pain Source in Concomitant Hip and Lumbar Spine Arthritis. Am J Orthop. 2007;36(11):591-593

8 Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: objectives and design update. Eur J Epidemiol 2007;22(11):819-829.

9 Reijman M, Hazes JM, Pols HA, et al. Role of radiography in predicting progression of osteoarthritis of the hip: prospective cohort study. Bmj 2005;330(7501):1183.

10 Kettler A, Wilke HJ. Review of existing grading systems for cervical or lumbar disc and facet joint degeneration. Eur Spine J 2006;15(6):705-718.

11 Lane NE, Nevitt MC, Genant HK, et al. Reliability of new indices of radiographic osteoarthritis of the hand and hip and lumbar disc degeneration. J Rheumatol 1993;20(11):1911-1918.

12 de Schepper E, Damen J, van Meurs JB, et al. The association between lumbar disc degeneration and low back pain: the influence of age, gender and individual radiographic features. Spine 2010;35(5):531-6.

13 Lievense AM, Bierma-Zeinstra SM, Verhagen AP, et al. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. Rheumatology (Oxford) 2002;41(10):1155-1162.

14 Pye SR, Reid DM, Adams JE, et al. Influence of weight, body mass index and lifestyle factors on radiographic features of lumbar disc degeneration. Ann Rheum Dis 2007;66(3):426-427.

15 Tukker A, Visscher T, Picavet H. Overweight and health problems of the lower extremities: osteoarthritis, pain and disability. Public Health Nutr 2008:1-10.

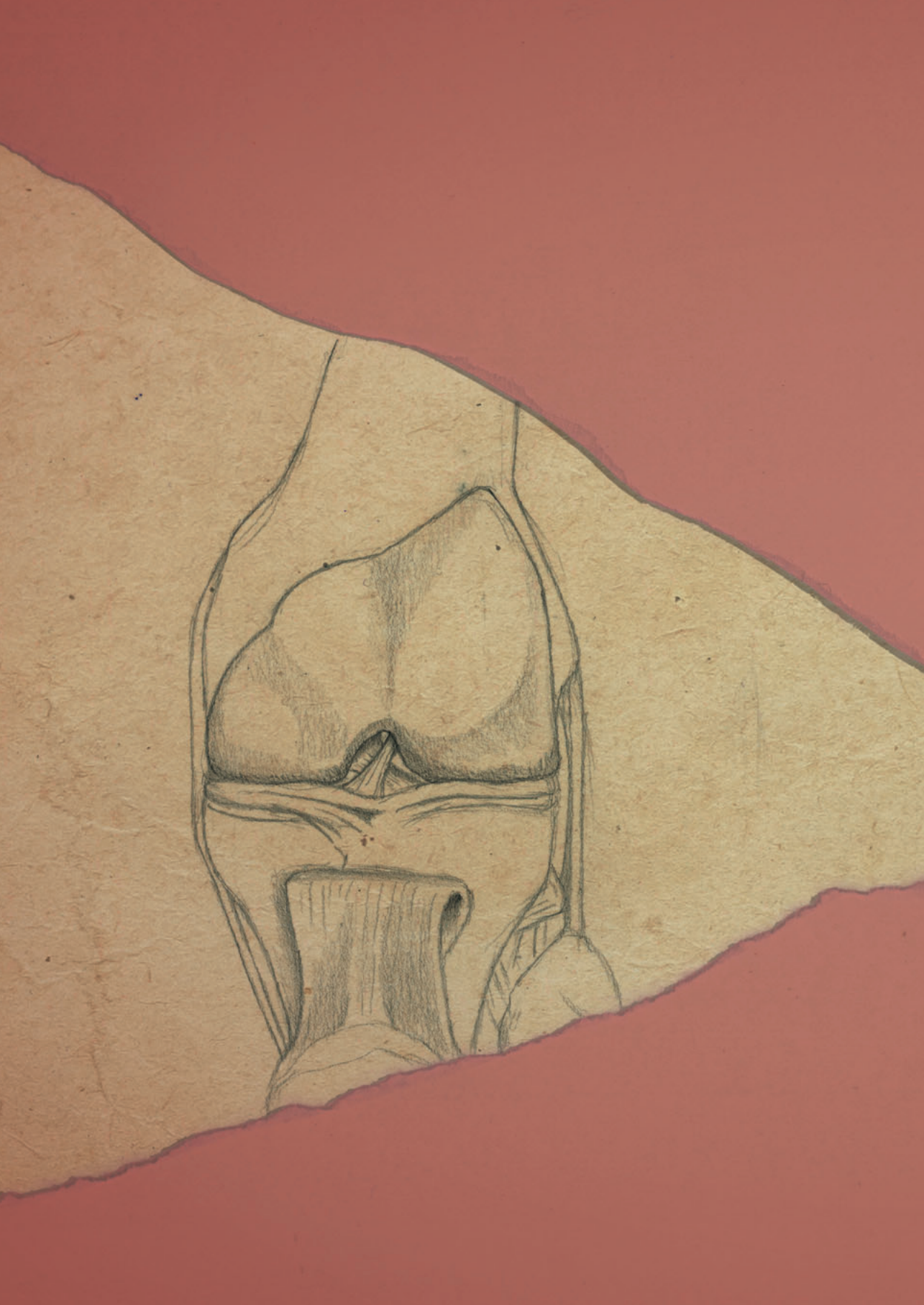
16 Frey Law LA, Sluka KA, McMullen T, et al. Acidic buffer induced muscle pain evokes referred pain and mechanical hyperalgesia in humans. Pain. 2008 Nov 30;140(2):254-64

17 Graven-Nielsen T. Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesie. Scand J Rheumatol 2006;35:1-43

18 Willis WD, Coggeshall RE. Sensory mechanisms of the spinal cord. New York: Kluwer Academic/Plenum Publishers; 2004.

19 Feinstein R, Langton J, Jameson R, et al. Experiments on pain referred from deep somatic tissues. J Bone Joint Surg Am 1954;36A:981-97

20 Kellgren J. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. Clin Sci 1939;4:35-46
21 O'Neill CW, Kurgansky ME, Derby R, et al. Disc stimulation and patterns of referred pain. Spine. 2002;27:2776-81
22 Cinotti G, De Santis P, Nofroni I, et al. Stenosis of lumbar intervertebral foramen. Spine 2002;27(3):223-229
23 Cecchi F, Debolini P, Lova RM, et al. Epidemiology of back pain in a representative cohort of Italian persons 65 years of age and older: the InCHIANTI study. Spine 2006;31(10):1149-1155.
24 Bonica J. The management of pain. Philadelphia: Lea and Febiger, 1990.
25 Reijman M, Hazes JM, Pols HA, et al. Validity and reliability of three definitions of hip osteoarthritis: cross sectional and longitudinal approach. Ann Rheum Dis. 2004 Nov;63(11):1427-33



CHAPTER 8

Variation of the GCH1 gene is associated with joint pain

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ABSTRACT

Objectives

To examine whether common genetic variation in the GTP-cyclohydrolase1 gene (GCH1) and its promoter is associated with self-reported pain in the hip, knee and hand and to chronic widespread pain.

Methods

The study population consisted of 5747 participants from the Rotterdam Study, a large prospective population-based cohort study of Caucasian subjects aged 55 and over, for whom genotype and self-reported pain data were available. We studied 15 tagging SNPs stretching +/-50Kb upstream of the GCH1 gene and encompassing all common (>5% allele frequency) genetic variation in that area. Pain in the hip, knee and hand was defined as having pain the month prior to the interview. Chronic widespread pain (existing for more then 6 months) was defined according to the ACR-criteria for widespread pain with two minor adaptations. Logistic regression models were used to model the risk of pain by polymorphism.

Results

A polymorphism (rs8007267, allele frequency 15%) situated in the promoter area of the GCH1 gene, was associated with pain in the hip, hand and knee. Homozygous T individuals had 45% (p=0.04) and 49% (p=0.01) decreased risk for hip and hand pain, respectively, in comparison to C-carriers. Knee pain showed a trend in the same direction (OR 0.74(95%CI:0.5-1.1)). For the widespread pain phenotype, arguable the most disabling phenotype of all four, the Odds were even more protective for the T allele homozygotes (OR:0.32(95%CI:0.14-0.72)).

Conclusions

In this study we showed that a promoter variant of the GCH1 gene is associated with the presence of site-specific and chronic widespread-pain.

INTRODUCTION

Joint pain in hip and knees is common in the elderly and a major cause of disability and morbidity. Osteoarthritis (OA) is an important cause of chronic joint pain, and its prevalence increases with ageing of the population.[1] OA is characterized by structural damage to articular cartilage, subchondral bone alterations, meniscal degeneration and extrusion, synovial inflammatory response, and bone overgrowth.[2] Despite efforts to study pain in OA, until now the pathophysiology of pain in OA is not completely clear. Nociceptive pain is a part of OA and clear associations exist between pain and synovial inflammation and bone marrow lesions.[3] Joint pain is a complex trait in which both genetic and environmental factors play an important role.[2] Estimated heritability for joint pain ranges between 35% and 65% depending on the site.[4,5,6]

This means that a substantial proportion of the variation in OA-related pain is attributed to genetic variation in genes involved in the etiology of OA-related pain.[7] Scientists now increasingly believe that a person's pain thresholds reflect their risk of developing chronic pain. Thus, persons that develop chronic pain might possess a combination of genetic variations that increase their sensitivity to pain.

Not many genetic studies have been conducted examining pain sensitivity and perception, and certainly not for OA-related pain. One of the genes that has recently been studied in relation to pain severity and perception is the GTP-cyclohydrolase (GCH1) gene. GCH1 is the rate-limiting enzyme in tetrahydrobiopterin (BH4) biosynthesis. BH4 is an essential cofactor for the synthesis of several pain neuromodulators including catecholamine, serotonin and nitric oxide synthesis and is also important in phenylaline metabolism. Loss of function mutations in GCH1 leads to BH4-deficiency and causes dopa-responsive motor, psychiatric and cognitive disorders or malignant hyperphenylalaninemia. [8,9,10] Tegeder et al. showed that BH4-concentrations are critical for neuropathic and inflammatory pain. [8] Therefore, changes in GCH1 activity would alter BH4 levels and could thereby modulate pain signaling.

Tegeder et al. found in a small cohort of patients (n=168) that common genetic variation in GCH1 gene is associated with reduced pain after radicular low back pain surgery.[8] This study identified a relatively common "pain protective" haplotype which encompassed the full extension of the gene. The haplotype (allele frequency of 15%) comprised 15 SNPs and was associated with changes of GCH1 upregulation after stimulation. In addition, in a small study of healthy individuals (n =32), this same haplotype exhibited reduced sensitivity to experimentally-induced pain.[9] However, two other studies (n=956 and n=632, respectively) failed to replicate such association with pain [11,12] Since those first studies GCH1 has also been linked to postoperative pain, and neuropathic pain although these results are not always replicated. [13,14,15,16] Also in degenerative spine disease a relation with pain and GCH1 has been found. [17] All the studies on

the relation between pain and GCH1 variation were conducted on small populations, leaving the possibility of false-positive or negative findings open. Therefore, large populations assessing the influence of this polymorphism on pain perception are necessary to obtain more conclusive results.

The objective of the present study was to examine whether common genetic variation in the GCH1 gene and its promoter is associated with self-reported pain in the hip, knee and hand, and also in relation to the presence of chronic widespread pain within the Rotterdam-Study, a large population-based cohort of elderly individuals. Furthermore, we examined if such associations of the GHC1 gene with pain are different in people with or without OA.

METHODS

Study population

The study population comprises men and women aged 55 years and older of the Rotterdam Study, which is a longitudinal population-based cohort study on the incidence of and risk factors for chronic disabling diseases. A detailed description of the study design has been published previously.[18] The medical ethics committee of Erasmus University Medical Center approved the study and written informed consent was obtained from each participant. In short 10,275 individuals aged 55 years and older were invited to participate; the response rate was 78%. Of a total of 7983 participants of the first interview 6494 persons visited the research centre for the baseline examination (including radiography of the knees, hips and hand). Genotype data was available for 5974 persons, data on joint pain was available for 5747 persons while radiographic evaluations were available in 3033, 3237, and 3325 for the knee, hip and hand).

Anthropometric measurements

Height and weight were measured in standing position with indoor clothing without shoes. BMI was calculated as weight in kilograms divided by length in meters squared (kg/m^2).

Pain

Joint pain was assessed with a questionnaire; all participants were asked whether they have had pain in any joint during the last month. They were asked to indicate were they had pain in a schematic drawing of the human body. Chronic widespread pain was defined according to the ACR-criteria for widespread pain with two minor adaptations. [19] The used criteria are: pain above and below the waist, and in addition, axial skeletal pain (cervical spine or low back pain) must be present. Low back pain is considered lower segment pain. These complaints should be present for at least six months. This differs from the original criteria where thoracic spine and anterior chest are also used as possible painful sites above the waist. We could not use these sites as we had no data on these sites.

Radiological OA assessment

The radiographic scoring was described in detail previously [20,21] Radiographs were scored for the presence of radiographic OA (ROA) of the hip, knee and hand according to the Kellgren/ Lawrence (K/L) score.[22] Knee and hip ROA were defined as a K/L score ≥ 2 of one or both joints. Hand ROA was defined as presence of a K/L score ≥ 2 in 2 out of 3 hand-joint groups (Distal inter phalangeal joint (DIPs), proximal interphalangeal joints (PIPs), Carpometacarpal 1/ trapezioscaphoid (CMC1/TS) of one or both hands.

Genotyping

All participants of the original Rotterdam Study cohort with proper quality DNA-samples (n=6,449) were considered for genotyping. The genetic variants were genotyped using genomic DNA extracted from peripheral venous blood samples according to standard procedures.[23]
All SNPs were genotyped using the version 3 Illumina Infinium II HumanHap550 SNP chip array in the framework of a Genome-Wide Association Study (GWAS) database. Genotyping procedures were followed according to manufacturer's protocol (Illumina, San Diego,CA,USA). Details on GWAS genotyping data in our cohort can be found elsewhere. [24] We used all SNPs from the array that were either in the coding region of GCH1 or in 50Kb upstream of the first exon. In total 15 SNPs were analysed.

Statistical analyses

For the individual SNPs, allele frequencies were estimated by allele counting and Hardy-Weinberg Equilibrium (HWE) was tested in Haploview4.1. Haplotypes, haplotype frequencies and pairwise linkage disequilibrium measures (r2 and D') were calculated also using Haploview4.1. Differences between genotype groups in means of baseline measurements were compared using analysis of (co)variance (AN(C)OVA) and linear regression. Odds ratios (OR's) with 95% confidence intervals (CI) were estimated from logistic regression models for cross-sectional analysis of all the binary pain variables. We estimated crude OR's and adjusted the OR's for age and BMI.

As the rs8007267 SNP, is the main predictor for the "protective pain haplotype" found in previous studies, and we found a consistent effect with this SNP on pain, we focused on the results of this SNP.[9,25] Therefore, we assessed with logistic regression, corrected for age, BMI and stratified for sex, whether there was a difference between participants with the homozygous minor allele and carriers (homozygous and heterozygous) of the major allele. SPSS-15 (SPSS Inc,, Chicago,USA) was used for all analyses. Corrections for multiple testing were not applied, because our detailed analysis was hypothesis-based. In addition, many of the studied variables were correlated. We considered a two-sided p-value £ 0.05 statistically significant.

RESULTS

Figure 1 and 2 show the GCH1 gene and the studied SNPs together with the pair wise linkage disequilibrium measures (D' and r^2) in the Rotterdam Study. In total, four common haplotypes were observed in our population (figure 3). Genotype distribution and allele frequencies of the studied SNPs are shown in Table 1. The HWE p-value for rs17738966 was borderline significant and the allele and genotype frequencies of rs104948472 deviated very significantly from HWE proportions. For this reason, rs10488472 was not studied further for association with pain. In addition, rs7146775 was left out of the analysis as the prevalence of the minor allele was below 5% in our population. High LD (D') was found across the GCH1 gene. In addition, the previously identified "pain protective haplotype" had an allele frequency of 15.7%. This haplotype was sufficiently well predicted by rs8007267, as previously described [6,18]. This SNP was highly correlated to rs8022453 (r2=0.94) and to a somewhat lesser extent to rs2057368 (r2=0.64), rs7146285 (r2=0.43), rs8009997 (r2=0.5) and rs8012152 (r2=0.43).

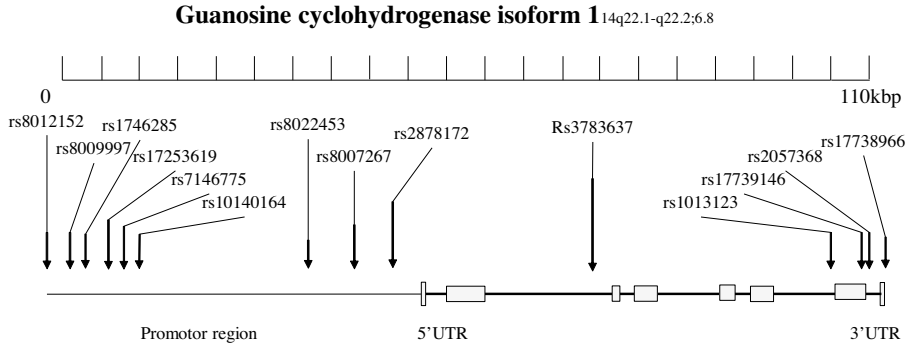

Figure 1. Schematic overview of polymorphisms in the GCH1 gene with the position of all the polymorphisms examined in this study

Genetic variation of GHC1 in relation to pain

In Table 2, the risk for pain in the knee, hip and hand by the different genotypes of the 13 individual SNPs is presented. For the rs8007267 a consistent association was found with self-reported hip and hand pain. Homozygote carriers of the T-allele, had an almost 50% reduced risk for pain at the hip and hand when compared to the C homozygotes. A similar trend towards a lower risk was seen for knee pain, however not reaching significance (OR:0.74(95%CI:0.5-1.1). The two SNPs that were highly correlated to rs8007267, rs2057368 and rs8022453, also showed an association with either hand or hip pain. These findings were consistent between both sexes and did not change when corrected for potential confounders as age and BMI. Since possible functionality of the rs8007267 was demonstrated previously and this SNP is able to fully tag the "pain protective haplotype" identified in previous studies, we focused all further analyses on this SNP.

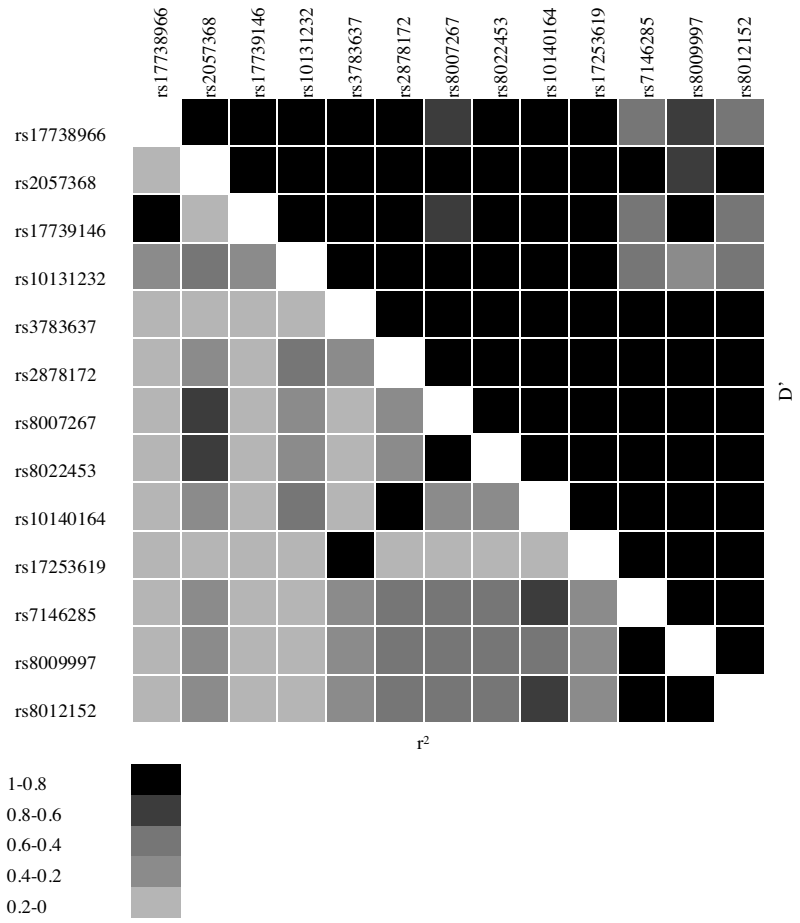

Figure 2. Graphical overview of pair wise disequilibrium coefficients (D' and r2) between the studied polymorphisms. Each box represents D' or r2 between the two SNPs indicated by color

SNP		rs17738966	rs2057368	rs17739146	rs10131232	rs3783637	rs2878172	rs8007267	rs8022453	rs10140164	rs17253619	rs7146285	rs8009997	rs8012152	Frequency
Haplotype	1	C	A	A	A	A	A	A	A	A	A	A	A	A	0.534
	2	C	C	A	C	A	C	C	C	C	A	C	C	C	0.157
	3	C	A	A	A	C	C	A	A	C	C	C	C	C	0.106
	4	A	A	C	C	A	C	A	A	C	A	A	A	A	0.082

Figure 3. The four haplotypes observed in our population with the allele frequencies observed in our population.

Table 1. Genotype distribution of the studied SNP's

		Number			HWE p-value
SNP	Major-Minor allele	0/0	0/1	1/1	
rs17738966	G-A	4779	1102	82	0,04
rs2057368	G-A	3826	1825	224	0,73
rs17739146	A-G	4737	1152	84	0,14
rs10131232	G-A	2869	2564	536	0,28
rs3783637	C-T	4669	1240	63	0,15
rs10498472	T-G	4994	792	65	<0.001
rs2878172	A-G	2005	2910	1058	0,42
rs8007267	C-T	4012	1779	182	0,37
rs8022453	G-A	3933	1834	207	0,70
rs10140164	A-G	1950	2887	1118	0,39
rs7146775	G-A	5605	363	5	0,72
rs17253619	T-C	4600	1281	77	0,25
rs7146285	T-C	2666	2655	651	0,79
rs8009997	T-G	2869	2410	548	0,20
rs8012152	T-C	2665	2656	650	0,76

0/0= homozygote major allele, 0/1 heterozygote, 1/1= homozygote minor allele, HWE= Hardy Weinberg equilibrium

Rs8007267 and pain

The genotype distribution and baseline characteristics for the rs8007267 are shown in Table 3. Since Table 2 showed consistently that T homozygous individuals had a lower risk for pain compared to the other genotypes, we tested a recessive model, which is shown in Figure 4, Homozygous T individuals had a 45% and 49% decreased risk for hip and hand pain respectively. Knee pain showed a trend in the same direction (OR:0.74(95%CI:0.5-1.1)). For the widespread pain phenotype, arguable the most disabling phenotype of all four, the odds ratio was even more protective for the homozygous T allele carriers (OR:0.32(95%CI:0.14-0.72)). The risk estimates did not change considerably after adjustment for age and BMI. The findings were consistent in men and women, but did not reach significance in all stratified analysis, probably because of lower power.

Table 2. Risk of pain in the knee, hip, hand by the 13 individual SNPs

SNP	*Kneepain OR (95% CI)*	
	0/1	1/1
rs17738966	0,95 (0,8-1,1)	1,01 (0,6-1,8)
rs2057368	1,04 (0,9-1,2)	0,69 (0,5-1)
rs17739146	0,95 (0,8-1,1)	0,99 (0,5-1,8)
rs10131232	0,96 (0,8-1,1)	0,93 (0,7-1,2)
rs3783637	1,04 (0,9-1,2)	0,62 (0,3-1,4)
rs2878172	0,97 (0,8-1,1)	1,05 (0,9-1,3)
rs8007267	1,07 (0,9-1,2)	0,74 (0,5-1,1)
rs8022453	1,05 (0,9-1,2)	0,89 (0,6-1,3)
rs10140164	1,01 (0,9-1,2)	1,06 (0,9-1,3)
rs17253619	1,09 (0,9-1,3)	0,76 (0,4-1,5)
rs7146285	1,09 (0,9-1,3)	0,88 (0,7-1,1)
rs8009997	1,13 (1,0-1,3)	0,90 (0,7-1,2)
rs8012152	1,10 (0,9-1,3)	0,88 (0,7-1,1)

Logistic regression analysis for the 13 individual SNPs that were analysesd. Homozygotes of the minor allele were taken as the reference group. OR=Odds ratio, 95%CI= 95% confidence interval, 0/1= heterozygotes, 1/1= homozygotes of the minor allele. ORs are adjusted for age, BMI, Sexe

Hippain OR (95% CI)		*Handpain OR (95% CI)*	
0/1	1/1	0/1	1/1
0,98 (0,8-1,2)	1,48 (0,8-2,7)	1,03 (0,9-1,2)	0,92 (0,5-1,7)
1,00 (0,8-1,2)	0,62 (0,4-1)	1,11 (0,9-1,3)	**0,53 (0,3-0,8)**
0,94 (0,8-1,1)	1,44 (0,8-2,7)	1,04 (0,9-1,2)	0,90 (0,5-1,7)
0,98 (0,8-1,2)	0,91 (0,7-1,2)	1,07 (0,9-1,2)	0,86 (0,7-1,1)
1,00 (0,6-2,7)	1,28 (0,8-1,2)	0,94 (0,8-1,1)	0,43 (0,2-1,1)
1,08 (0,9-1,3)	1,08 (0,7-1,1)	0,98 (0,8-1,1)	0,90 (0,7-1,1)
1,03 (0,9-1,2)	**0,56 (0,3-0.99)**	1,08 (0,9-1,3)	**0,54 (0,3-0,9)**
1,02 (0,9-1,2)	**0,49 (0,3-0,9)**	1,07 (0,9-1,3)	0,69 (0,5-1,1)
1,10 (0,9-1,3)	0,89 (0,7-1,1)	0,93 (0,8-1,1)	0,89 (0,7-1,1)
1,01 (0,8-1,2)	1,61 (0,9-3,0)	0,89 (0,7-1,1)	0,50 (0,2-1,1)
1,11 (0,9-1,3)	0,84 (0,6-1,1)	0,96 (0,8-1,1)	**0,75 (0,6-1,0)**
1,08 (0,9-1,3)	0,90 (0,7-1,2)	0,98 (0,8-1,1)	**0,75 (0,6-1,0)**
1,11 (0,9-1,3)	0,84 (0,6-1,1)	0,96 (0,8-1,1)	**0,76 (0,6-1,0)**

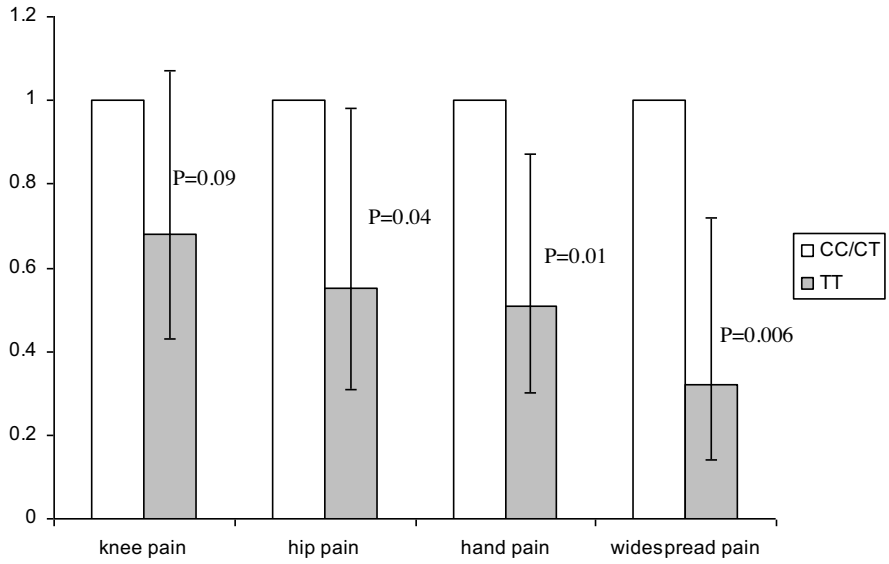

Figure 4. Risk for pain with 95% confidence limits, according to the genotype of rs8007267.

Table 3. Baseline characteristics by rs8007267

	C/C	C/T	T/T
Number (%)	4012(67)	1779(30)	182(3)
Females, %	59	59	61
Age (sd)	69.5 (9.3)	69.4 (8.8)	69.4 (8.7)
BMI (sd)	26.3 (3.7)	26.3 (3.8)	26.5 (3.6)
Kneepain, %	18	18	14
Hippain, %	12	13	8
Handpain, %	16	17	9
Widespread pain, %	10	10	4

RS 8007267 and osteoarthritis pain

We next studied whether the risk for pain was depended on the presence of radiographic OA damage to the joint. Therefore, we stratified our population into subjects that had radiological OA (KL>=2) or not (Table 4). Here we demonstrated that the rs8007267 polymorphism was associated with a decline in pain perception in hip, hand and knee in both patients with and without ROA, however these association were not statistically significant.

Table 4. crude ORs for pain in the knee, hip, hand by the rs8007267 stratified for joint specific OA

	Osteoarthritis	
	No	Yes
Knee pain OR (95%CI)		
0/0	ref	ref
0/1	1,19 (0,9-1,6)	0,84 (0,6-1,2)
1/1	0,98 (0,5-2,1)	0,76 (0,3-2,0)
Hip pain OR (95%CI)		
0/0	ref	ref
0/1	1,01 (0,8-1,3)	0,87 (0,4-1,7)
1/1	0,67 (0,3-1,6)	0,74 (0,1-6,8)
Hand pain OR (95%CI)		
0/0	ref	ref
0/1	0,79 (0,6-1,1)	1,07 (0,8-1,5)
1/1	0,77(0,3-1,7)	0,42 (0,1-1,4)

0/1= heterozygotes, 1/1= homozygotes of the minor allele

DISCUSSION

In the present study we examined the relationship between genetic variations in the GCH1 gene and self-reported joint pain in the Rotterdam Study, a large population-based cohort of elderly Caucasians. We find that homozygote carriers of the T allele of the rs8007267 SNP have 50% less hip pain, 50% less hand pain, and 70% less widespread pain.

Our results are strikingly similar to the first reports of this polymorphism where Tegeder et al found significantly lower back pain in homozygous carriers of the (rs8007267) T allele.[8] Another study by the same group suggested that the protective effect of this polymorphism was mainly conferred to pain after sensitization and did not have an effect on the other pain types that were tested.[9] A small study observed an association of the same polymorphisms with ratings of pain induced by capsaicin (n=39). Another GCH1 variant, the (dbSNP rs841), located in the 3'UTR, was reported to be associated with decreased nitric-oxide excretion, increased blood pressure and heart rate in homozygous carriers of the minor allele.[10,26] This polymorphism was found to be highly correlated to the "pain protective haplotype".[9] And more recent with a higher risk of fibromyalgia susceptibility.[16] At the molecular level, the GCH1 "pain-protective" haplotype has been found to be associated with reduced GCH1 mRNA and protein upregulation after stimulation, which would result in less pain.[8] In addition, the 3'UTR polymorphism was found to affect reporter expression, implicating a direct functional consequence of this polymorphism on GCH1 expression.[26] Several other studies find that GCH1 polymorphisms are associated with less pain after surgery, less need of opioids in cancer pain and one even demonstrates potentially therapeutic options. [27,28,29,30] Despite the seemingly consistent results, two other studies failed to observe an association with pain. Kim *et al*. failed to replicate the protective effect of polymorphisms of GCH1 gene on pain sensitivity in a mixed population including European Americans, African Americans, Hispanic Americans and Asian Americans.[11] Their result could be caused by the ethnically mixed population which results in small subgroups. In addition, a recent report did not observe an effect of the rs8007267 on pain patterns or severity in pancreatitis.[12] Holliday et al. have studied a pain protective haplotype which includes the rs8007267 and the association with widespread pain using the ACR criteria and found no association. [31] The negative association studies, as well as the discovery and subsequent replication cohorts described before were very much underpowered to find the mild effects that would be expected for a common polymorphism involved in a complex trait like pain. It is generally accepted that susceptibility to chronic pain is very similar in its genetic architecture as compared to other complex traits, like cardiovascular disease, diabetes and osteoporosis. This means that multiple genes are involved and each single gene only contributes little to the overall variability in pain. For other complex traits, e.g., osteoporosis, large-scale association studies have been able to filter out the consistent "true" associations.[24] The typical risks that are found in these large-scale studies are around OR=1.2/1.3, which illustrates the need for large numbers when investigating genetics of complex traits.

We tried to address the question whether the relation between polymorphisms in the GHC1 gene and pain is different in people with or without OA. Unfortunately, our power to study this was limited given the low number of OA cases per site in combination with the recessive effect of the polymorphism. Therefore, we were unable to study the effect in ROA patients separately. Larger studies are necessary to address this issue properly. To our knowledge, we are the first to report a DNA variant to be related to chronic widespread pain in a large population based cohort. Some reports have examined association of several polymorphisms with fibromyalgia syndrome [32], but these studies have been carried out in small numbers of patients, and therefore so far no consistent associations have been reported. The inability to find genes in complex traits like pain is probably due to a difference in definition of pain between the studies and lack of power to study the association properly. We believe we could find this association due the power of our study.

A possible limitation of our study includes population-stratification. However, 98% of our cohort is ethnically homogenous, thus making false positive associations due to population stratification very unlikely. In addition, The Rotterdam Study data was examined for potential population stratification using GWAS data after excluding outliers detected by multi dimension scaling using clustering by IBS distances.[33] Another limitation of our study is that our definition of chronic widespread pain is not completely in concordance with the ACR criteria of chronic widespread pain. We did not have pain data on anterior chest or thoracic spine, which are included in the ACR criteria. This might lead to an underestimation of the number of participants with chronic widespread pain, which may have led to an underestimation of the effect of the polymorphism. The definition on joint pain used in our study is not conclusive in the type of pain, the pain could be originated in the joint itself, but it could also be referred pain or neuropathic pain (e.g. sciatica in the hip and knee and carpal tunnel syndrome in the hand). This way, the reported association might also be stronger in a study using a more homogeneous type of pain definition. Another possible bias introduces in our study is selection bias, due to loss to follow up which is probable inevitable in al long term cohort in elderly our result may be more applicable to more healthier elderly.

Conclusion

In this large open population cohort we found that homozygous T-carriers of the rs8007267 SNP have less self-reported joint pain in the hip and hand and chronic widespread pain. These results are in line with the previously found association between GCH1 polymorphisms and pain perception and highlight that GCH1 activity could be a useful target for development for novel analgesics in e.g. musculoskeletal pain [29,34]

Acknowledgements

This study was funded by the European Commission (HEALTH-F2-2008-201865, GEFOS; HEALTH-F2-2008-35627, TREAT-OA), Netherlands Organisation of Scientific Research NWO Investments (nr.175.010.2005.011, 911-03-012), Research Institute for Diseases in the Elderly (014-93-015; RIDE2), and the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) project nr. 050-060-810. We thank Pascal Arp, Mila Jhamai, Dr.Michael Moorhouse, Marijn Verkerk, and Sander Bervoets for their help in creating the GWAS-database. The Rotterdam-Study is funded by Erasmus MC and Erasmus University, Netherlands-Organization for the Health-Research and Development (ZonMw), the Research Institute for Diseases in the Elderly(RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commision (DG-XII), and the Municipality of Rotterdam.

REFERENCES

1 Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Ann Rheum Dis. 2014 Sep;73(9):1659-64

2 Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice.Lancet. 2011 Jun 18;377(9783):2115-26.

3 de Lange-Brokaar BJ, Ioan-Facsinay A, Yusuf E, Visser AW, Kroon HM, van Osch GJ, Zuurmond AM, Stojanovic-Susulic V, Bloem JL, Nelissen RG, Huizinga TW, Kloppenburg M. Association of pain in knee osteoarthritis with distinct patterns of synovitis. Arthritis Rheumatol. 2015 Mar;67(3):733-40.

4 Zhai G, Stankovich J, Ding C, Scott F, Cicuttini F, Jones G. The genetic contribution to muscle strength, knee pain, cartilage volume, bone size, and radiographic osteoarthritis: A sibpair study. Arthritis Rheum. 2004;50(3):805-810.

5 MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: A study of adult female twins. Arthritis Rheum. 2004;51(2):160-167.

6 Meloto, CB, Benavides, R, Lichtenwalter, RN, Wen, X, Tugarinov, N, Zorina-Lichtenwalter, K., et al. (2018). Human pain genetics database: a resource dedicated to human pain genetics research. Pain, 159(4), 749–763.

7 JBJ van Meurs, (2017). Osteoarthritis year in review 2016: genetics, genomics and epigenetics. Osteoarthritis and Cartilage, 25(2),181–189.

8 Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med. 2006 Oct. 22;12(11):1269-1277.

9 Tegeder I, Adolph J, Schmidt H, Woolf C, Geisslinger G, Lotsch J. Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. European Journal of Pain. 2008 Nov.;12(8):1069-1077.

10 Doehring A, Antoniades C, Channon K, Tegedere I, Lotsch J. Clinical genetics of functionally mild non-coding GTP cyclohydrolase 1 (GCH1) polymorphisms modulating pain and cardiovascular risk. Mutation Research/Reviews in Mutation Research. 2008 Sep.;659(3):195-201.

11 Kim H, Dionne RA. Lack of influence of GTP cyclohydrolase gene (GCH1) variations on pain sensitivity in humans. Mol Pain. 2007;3(1):6.

12 Lazarev M, Lamb J, Barmada MM, Dai F, Anderson MA, Max MB, et al. Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? Mol Pain. 2008;4(1):58.

13 Nasser A, Møller LB. GCH1 variants, tetrahydrobiopterin and their effects on pain sensitivity.Scand J Pain. 2014 Apr 1;5(2):121-128. doi: 10.1016/j.sjpain.2013.12.001. Review.

14 Nasser A, Møller AT, Hellmund V, Thorborg SS, Jespersgaard C, Bjerrum OJ, Dupont E, Nachman G, Lykkesfeldt J, Jensen TS, Møller LB. Heterozygous mutations in GTP-cyclohydrolase-1 reduce BH4 biosynthesis but not pain sensitivity.Pain. 2018 Jun;159(6):1012-1024.

15 Veluchamy A, Hébert HL, Meng W, Palmer CNA, Smith BH. Systematic review and meta-analysis of genetic risk factors for neuropathic pain. Pain. 2018 May;159(5):825-848.

16 I.Estévez-López F, Camiletti-Moirón D, Aparicio VA, Segura-Jiménez V, Álvarez-Gallardo IC, Soriano-Maldonado A, Borges-Cosic M, Acosta-Manzano P, Geenen R, Delgado-Fernández M, Martínez-González LJ, Ruiz JR, Álvarez-Cubero MJ. dentification of candidate genes associated with fibromyalgia susceptibility in southern Spanish women: the al-Ándalus projectJ Transl Med. 2018 Feb 27;16(1):43.

17 Kim DH, Dai F, Belfer I, Banco RJ, Martha JF, Tighiouart H, Tromanhauser SG, Jenis LG, Hunter DJ, Schwartz CE. Polymorphic variation of the guanosine triphosphate cyclohydrolase 1 gene predicts outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine (Phila Pa 1976) 2010;35:1909–14.
18 Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur. J. Epidemiol. 1991 Jul.;7(4):403-422.
19 Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College Of Rheumatology 1990 Criteria For The Classification Of Fibromyalgia. ArthritisandRheumatism,Vol ,No. 1990 Oct. 10;33(2):160-173.
20 Reijman M. Role of radiography in predicting progression of osteoarthritis of the hip: prospective cohort study. BMJ. 2005 May 21;330(7501):1183-0.
21 Dahaghin S. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Annals of the Rheumatic Diseases. 2005 May 1;64(5):682-687.
22 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957 Dec.;16(4):494-502.
23 Spector T. Risk factors for osteoarthritis: genetics1. Osteoarthritis and Cartilage. 2004;12:39-44.
24 Richards JB, Rivadeneira F, Inouye M, Pastinen TM, Soranzo N, Wilson SG, et al. Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. Lancet. 2008 May 3;371(9623):1505-1512.
25 Lotsch J, Belfer I, Kirchhof A, Mishra BK, Max MB, Doehring A, et al. Reliable Screening for a Pain-Protective Haplotype in the GTP Cyclohydrolase 1 Gene (GCH1) Through the Use of 3 or Fewer Single Nucleotide Polymorphisms. Clinical Chemistry. 2007 Apr. 19;53(6):1010-1015.
26 Zhang L, Rao F, Zhang K, Khandrika S, Das M, Vaingankar SM, et al. Discovery of common human genetic variants of GTP cyclohydrolase 1 (GCH1) governing nitric oxide, autonomic activity, and cardiovascular risk. J. Clin. Invest. 2007 Sep.;117(9):2658-2671.
27 Lee PJ, Delaney P, Keogh J, Sleeman D, Shorten GD. Catecholamine-o-methyltransferase polymorphisms are associated with postoperative pain intensity. Clin J Pain. 2011 Feb.;27(2):93-101.
28 Lötsch J, Klepstad P, Doehring A, Dale O. A GTP cyclohydrolase 1 genetic variant delays cancer pain. Pain. 2010 Jan. 1;148(1):103-106.
29 Kim S, Lee W, Lee Y, Kim D, Chang J, Kim S, et al. Effective relief of neuropathic pain by adeno-associated virus-mediated expression of a small hairpin RNA against GTP cyclohydrolase 1. Mol Pain. 2009;5(1):67.
30 Belfer I, Dai F, Kehlet H, et al. Association of functional variations in COMT and GCH1 genes with postherniotomy pain and related impairment. Pain. 2015 Feb;156(2):273–279
31 Holliday KL, Nicholl BI, Macfarlane GJ, Thomson W, Davies KA, McBeth J. Do genetic predictors of pain sensitivity associate with persistent widespread pain? Mol Pain. 2009;5(1):56.
32 Buskila D, Sarzi-Puttini P, Ablin JN. The genetics of fibromyalgia syndrome. Pharmacogenomics. 2007 Jan.;8(1):67-74.
33 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. The American Journal of Human Genetics. 2007 Sep.;81(3):559-575.
34 Lötsch J, Geisslinger G, Tegeder I. Genetic modulation of the pharmacological treatment of pain. Pharmacology and Therapeutics. 2009 Nov. 1;124(2):168-184.

CHAPTER 9

Characteristics associated with joint replacement in early symptomatic knee or hip osteoarthritis, six year results from a nationwide prospective cohort study (CHECK)

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British Journal of General Practice, Br J Gen Pract. 2016 Jan;66(642):e32-9

ABSTRACT

Background
Many patients with osteoarthritis (OA) of the knee and/or hip undergo total joint replacement (TJR) due to severely progressed symptoms.

Aim
To determine patient- and disease characteristics associated with undergoing TJR in subjects with recent onset knee and/or hip OA.

Design and Setting
Participants with hip or knee pain from a nationwide prospective Cohort Hip and Cohort Knee (CHECK) study were included.

Method
Outcome measure was total hip arthroplasty (THA) or total knee arthroplasty (TKA) during six years follow-up. Joint dependent characteristics were compared using generalized estimating equations (GEE). Multivariable models were built for both subgroups. Differences in symptomatic and radiographic progression were determined between baseline and two years follow-up (T2).

Results
751 participants (1,502 knees) were included in the knee subgroup; 538 participants in the hip subgroup (1,076 hips). 19 participants (22 knees) underwent TKA and 53 participants (62 hips) THA. Participants who underwent TKA had higher baseline BMI, painful knee flexion and higher K/L scores. Participants who underwent THA had painful internal hip rotation and showed more severe radiographic OA features. Participants who underwent TKA or THA showed more rapid symptomatic and radiographic OA progression at T2.

Conclusion
In subjects with recent onset knee or hip pain, radiographic OA features already exist and a substantial number of subjects fulfil existing criteria for knee and hip OA. We saw a trend in rapid progression of radiographic and symptomatic OA severity amongst TKA and THA subjects. Early detection of OA by the GP is important in the management of knee and hip OA.

INTRODUCTION

Knee and/or hip osteoarthritis (OA) belong to the most common diagnoses in general practice.[1] Consequently, every year thousands of patients are at risk for progression of OA and many of these patients will become eligible for total joint replacement (TJR) due to severely progressed and disabling symptoms.[2] Tens of thousands of TJRs are being performed on a yearly basis in The Netherlands and the UK alone.[3] However, not all patients with lower joint OA undergo surgery, suggesting that OA progression is dependent on patient characteristics and/or varies between so called phenotypes of OA,[4] or is dependent on the physician's choice to refer or operate. Predicting severe OA progression in the early stages of disease would aid the general practitioner (GP) in the initiation and implementation of early intervention strategies to prevent further structural damage to the joints.[5] Patients with recent onset OA whom have a low risk of OA progression and subsequent TJR can be better reassured and unnecessary interventions or referral can be avoided. Vice versa, patients with high risk of progression whom are eligible for TJR can sooner be referred for specialist treatment. The aim of our research was to determine patient- and disease characteristics associated with undergoing TJR within six years follow-up in a study population aged 45 to 65 years at baseline with recent onset knee and/or hip OA.

METHODS

Study design and population

Our data were obtained from participants enrolled in the Cohort Hip & Cohort Knee (CHECK) study. CHECK is a nationwide prospective, ten-year follow-up cohort of 1,002 participants with early symptomatic OA of the knee and/or hip, who were referred for study inclusion by their general practitioners if they were eligible for inclusion.[6] The inclusion period ran from October 2002 until September 2005. Inclusion criteria for the CHECK study were: pain and/or stiffness of the knee and/or hip; age between 45 and 65 years; and never, or less than six months prior to entry of the study, consulted a physician for these symptoms. Participants were excluded if they had any other known pathological condition that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plicasyndrome, Baker's cyst); co morbidity that did not allow physical evaluation and/or follow-up of at least ten years; malignancy in the past five years; and inability to understand the Dutch language.[6]

All CHECK participants filled out questionnaires, underwent physical examination, X-rays and laboratory examinations at five different time point during the 10 year follow-up. These time points were at baseline, at 2 years (T2), T5, T8 and T10. Details of these examinations are specified in the two following paragraphs and Table 2.

For the analyses of the current study we used data available from baseline, T2 and T5. We created two study subgroups: a subgroup of participants that reported knee pain at baseline and a subgroup that reported hip pain at baseline. An individual could be included in both the knee and hip subgroups.

Baseline characteristics

The CHECK study included a baseline medical history, physical examination and radiographs of the knees and hips, which formed the different variables.[6] The medical history was taken through questionnaires with which participant specific self-reported data were assessed. The following diseases were considered as co morbidities: asthma, chronic sinusitis, cardio-vascular disease, high blood pressure, gastric ulcer, gallstones, liver disease, renal disease, diabetes, thyroid gland disease, epilepsy, cancer, severe skin disease, and other chronic musculoskeletal diseases. Symptom severity was assessed by the Numeric Rating Scale (NRS, range 0-10) and the Western Ontario and McMaster osteoarthritis index (WOMAC) for pain, stiffness and physical functioning (range 0-100, with a higher score indicating worse health).[6] To assess pain-coping behaviour, a six scale Pain-Coping Inventory (PCI) was used: pain transformation; distraction; reducing demands; retreating; worrying; and resting. All six scales (33 items) were scored according to a four-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms

of frequency with which strategies are applied when dealing with pain.[7] Physical examination of the joints was based on the clinical criteria for knee and hip OA.[8, 9] Regarding the knee this encompassed range of motion (ROM) of knee flexion and extension measured in degrees with a goniometer, palpable warmth, crepitus, joint space tenderness, bony enlargements, effusion and painful ROM. The hip examination included ROM of hip internal and external rotation, measured in degrees with a goniometer and painful ROM.

Radiographs

Radiographs were read paired and in sequence, but with the observers blinded to all other patient characteristics.[10] Standardized radiographs of the tibiofemoral joints were made by a weight-bearing posteroanterior (PA) view, semi-flexed (7-10°) according to Buckland-Wright[6, 11] and standardized weight-bearing anteroposterior (AP) radiographs of the pelvis were made along with a weight-bearing single faux profile (FP) radiograph of the hip.[6, 12] Radiographs were scored for individual OA features according to criteria described by Altman.[13] Radiographic OA severity was defined by the Kellgren & Lawrence (K/L) classification.[14] With regards to the knee, baseline medial or lateral joint space narrowing (JSN), femoral medial or lateral osteophytes (OP), and tibial medial or lateral OP were initially scored on a 4 point scale (0 = normal; 1 = mild; 2 = moderate; and 3 = severe). However, in the present study we have dichotomized these variables into absent (score 0) and present (score 1-3). In addition, medial or lateral tibial bone attrition, and medial or lateral tibial or femoral sclerosis were scored as absent or present. Presence of spiking of the tibial spines was scored according to the atlas by Burnett.[15] The hip radiographs were scored in a similar manner as the knees: superior or medial hip JSN, superior or inferior acetabular OP, superior or inferior femoral OP, inferior acetabular OP and femoral subchondral sclerosis were scored as absent or present.[15] The α angles on AP pelvic view hip radiographs were measured to determine whether a cam-type deformity was present at baseline.[16] The α angle measures the deviation of the femoral head from a normal spherical-shaped femoral head. Cam-type deformity is one of two types of femoroacetabular impingement, which is associated with the development of hip OA. For this analysis, an α angle >60° was defined as a cam-type deformity.[16-18] In addition, the Wiberg angles on AP pelvic view radiographs were measured to determine the degree of dysplasia.[19] The center-edge angle of Wiberg is formed by a vertical line through the center of the femoral head, perpendicular to the transverse axis of the pelvis (radiographic 'teardrop' landmark),[20] and a line joining the head center with the lateral rim of the acetabulum.[21] Hips with Wiberg angle <25° were considered dysplastic.[22] On the FP radiographs, superior or posterior JSN was scored as absent (i.e. normal) or present.

Statistical analysis

Total knee arthroplasty (TKA) was assigned as primary outcome measure in the knee subgroup and total hip arthroplasty (THA) in the hip subgroup. Whether TKA or THA was performed was registered through questionnaires and confirmed on radiographs. Differences in participant

baseline characteristics were calculated using Student's *t*-test or Pearson's χ^2 test when appropriate. In addition, joint dependent characteristics were compared using generalized estimating equation (GEE) analysis, which adjusts for the existing correlation between the left and right knee of the same individual. To determine possible associations with our outcomes, we built multivariable models for both subgroups, taking into account the number of events (TJRs) per subgroup to avoid overfitting our models. The selection for including variables into the models would depend on: statistically large differences in baseline value; clinical relevance of the variables and no large co-linearity between variables (cut-off R>0.7). We attempted to select various types of characteristics (i.e. anamnestic-, clinical- and radiographic findings) as variables for the final models.

Lastly, to assess possible more rapid clinical OA progression in patients from the TJR groups, we calculated the mean change in WOMAC pain and physical functioning scores (using Student's *t*-test or GEE when appropriate). We compared between baseline and two years follow-up (T2) since WOMAC scores are not useful after TJR, and most TJR had not taken place yet at T2. The *p*-values indicate whether the change in mean WOMAC scores differed significantly between the TJR and non-TJR groups. We also determined whether the change in distribution of K/L scores for the knees and hips between baseline and T2 differed between the groups by calculating the difference in number of participants that progressed in or maintained the same K/L score, distinguishing participants with severe progression (i.e. increase K/L score by >1 or >2 and so on) from those with slight progression (i.e. increase K/L score by 1). Participants whom underwent TJR before T2 were excluded from this last analysis. All analyses were performed using *SPSS Statistical Package PASW version 20.0*.

RESULTS

Baseline characteristics

In total, 1,002 participants were initially included in CHECK of whom 94 (9 %) were lost to follow-up after 6 years. Of the lost to follow-up, 44 had been allocated to the knee subgroup, 16 to the hip subgroup and 34 to both subgroups. One of the lost to follow-up had undergone TJR (1 TKA at T2). There were no significant differences in baseline age, sex, BMI, symptom severity (NRS, WOMAC pain, WOMAC-PF) and K/L score between those lost to follow-up (n=94) and the rest of the cohort (n=908). We excluded all lost to follow-up from our analyses. In total, 829 participants reported knee pain (knee subgroup) and 588 reported hip pain (hip subgroup) at baseline (415 participants reported pain in both knee and hip). After six years follow-up, 72 participants underwent TJR: 19 participants underwent TKA in 22 knees; 53 participants underwent THA in 61 hips and 1 participant underwent both TKA (1 knee) and THA (1 hip). Hence, in total 23 knees underwent TKA and 62 hips THA. All participants who underwent TJR reported pain at baseline in the corresponding hip or knee joint. s provides an overview of the baseline characteristics of the total cohort (n=908), and the characteristics of the participants in the knee and hip subgroups. The majority of joint dependent clinical findings and radiographic features for both the knees and hips differed significantly for participants who underwent TJR and those who did not.

Knee subgroup

Due to the small number of events in the knee subgroup, we restricted to selecting 3 variables for the multivariable knee model. Multiple clinical findings differed significantly amongst the two knee groups, however the difference in prevalence of painful active knee flexion was the largest. With regards to radiographic findings, JSN and osteophytes were strongly correlated with K/L score. We therefore only included K/L score in the multivariable model. Body mass index (BMI), painful active knee flexion and K/L score all three significantly contributed to the multivariable model. The obtained odds ratios (OR) presented in the table indicate a higher risk for undergoing TKA.

Hip subgroup

JSN (AP pelvic view) and osteophytes were strongly correlated with K/L score, hence we only included K/L score. A cam-type deformity proved not to contribute to the final model and was excluded. All other radiographic hip features were not strongly correlated and were included in the multivariable hip model. As for clinical findings of the hip, painful internal rotation and reduced hip flexion ≤115° had the largest differences in distribution and were not strongly correlated. We adjusted this model for age and gender. Table 3 provides the obtained OR, with a higher OR indicating a higher risk for undergoing THA.

Table 1. Baseline characteristics of the participants with a completed follow-up of 6 years

	Total cohort
Baseline characteristics	***N=908***
Age in years ± sd	55.8 ± 0.2
Gender (% female)	79 %
Body mass index (kg/m^2) ± sd	26.2 ± 0.1
Ethnicity (% Caucasian vs other)	98 %
Education level	
% ≤ high school graduate	73 %
% college or university degree	27 %
Subjects (%) with > 1 co morbidity	45 %
NRS of the past week (iqr)	3.5 (2.0-5.0)
WOMAC pain (iqr)	25 (10-35)
WOMAC physical function (iqr)	23 (10-34)
WOMAC joint stiffness (iqr)	33 (25-50)
Pain coping strategies (iqr)	
Pain transformation	2.1 (1.8-2.5)
Distracting	2.2 (1.8-2.6)
Reducing demands	2.0 (1.7-2.3)
Resting / avoidance	1.8 (1.4-2.2)
Worrying	1.6 (1.2-1.8)
Retreating	1.5 (1.1-1.9)
Smoker or previous smoker	14 %
Alcohol consumption	78 %
Use of pain medication	38 %
Morning stiffness knees < 30 min	53 %
Morning stiffness hips < 60 min	36 %
Heberden nodes hands	48 %
Bouchard swellings hands	19 %
ESR (mm/hr) ± sd	9.8 ± 0.3

Palpable warmth of the knee joint
Joint space tenderness of the knee
Bony enlargements of the knee
Crepitus during knee flexion
Positive knee re-fill test (effusion)
Painful active knee flexion
Painful active knee extension

Knee pain subgroup			*Hip pain subgroup*		
TKA-n=732	***TKA+n=19***	***p value***	***THA-n=485***	***THA+n=53***	***p value***
55.8 ± 0.2	58.0 ± 1.1	0.07	55.4 ± 0.2	58.0 ± 0.6	<0.01
79 %	95 %	0.10	82 %	68 %	0.01
26.3 ± 0.2	29.1 ± 1.0	<0.01	26.3 ± 0.2	25.9 ± 0.5	0.60
97 %	100 %	0.47	98 %	100 %	0.32
73 % 27 %	84 % 16 %	0.29	73 % 27 %	77 % 23 %	0.55
46 %	47 %	0.91	52 %	40 %	0.13
3.5 (2.0-5.0)	4.5 (3.0-6.0)	0.04	3.6 (2.0-5.0)	4.3 (2.0-6.0)	0.03
25 (10-35)	35 (20-40)	0.02	27 (15-40)	31 (15-45)	0.07
24 (10-34)	34 (20-44)	<0.01	25 (10-35)	31 (18-40)	0.02
33 (25-50)	47 (38-63)	<0.01	34 (25-50)	38 (25-50)	0.30
2.2 (1.8-2.8)	2.2 (1.8-2.5)	0.67	2.2 (1.8-2.8)	2.2 (1.8-2.7)	0.67
2.2 (1.8-2.6)	2.3 (1.8-2.8)	0.69	2.2 (1.8-2.6)	2.2 (1.8-2.8)	0.55
2.0 (1.7-2.3)	2.0 (1.3-2.7)	0.83	2.0 (1.7-2.3)	1.9 (1.7-2.3)	0.16
1.8 (1.4-2.2)	2.0 (1.6-2.4)	0.09	1.8 (1.4-2.2)	1.8 (1.5-2.0)	0.93
1.6 (1.2-1.8)	1.6 (1.2-2.0)	0.87	1.6 (1.2-1.8)	1.6 (1.2-1.9)	0.79
1.6 (1.1-1.9)	1.5 (1.1-1.7)	0.56	1.5 (1.1-1.9)	1.5 (1.0-1.7	0.34
15 %	0 %	0.07	15 %	6 %	0.07
77 %	65 %	0.23	79 %	71 %	0.18
38 %	21 %	0.13	39 %	34 %	0.45
62 %	83 %	0.06	-	-	-
-	-	-	55 %	64 %	0.20
48 %	56 %	0.53	50 %	59 %	0.22
19 %	21 %	0.81	22 %	17 %	0.42
10.1 ± 0.3	10.7 ± 1.7	0.77	9.9 ± 0.4	12.9 ± 1.4	0.05
TKA-1,480 knees	*TKA+22 knees*	*p[1] value*	*THA-1,014 hips*	*THA+62 hips*	*p[1] value*
3 %	18 %	<0.01	-	-	-
12 %	18 %	0.59	-	-	-
2 %	0 %	0.51	-	-	-
10 %	23 %	<0.01	-	-	-
4 %	14 %	0.02	-	-	-
13 %	36 %	<0.01	-	-	-
8 %	23 %	0.04	-	-	-

Table 1. Continued.

	Total cohort
Baseline characteristics	***N=908***
ROM knee flexion ± sd	
ROM knee extension ± sd	
JSN knee score >0	
Femoral or tibial OP score >0	
Tibial attrition	
Femoral or tibial sclerosis	
Tibial spiking	
K/L score 1 (versus K/L score 0)	
ROM hip flexion ≤ 115°	
ROM hip internal rotation ≤ 15°	
Painful active hip flexion	
Painful active hip internal rotation	
JSN hip score >0 (AP)	
JSN hip score >0 (FP)	
Acetabular or femoral OP score >0	
Femoral subchondral sclerosis	
Cam-type deformity(α angle>60°)‡	
Dyspalsia (Wiberg angle<25°)‡	

Subgroups are participants who did (+) or did not (-) undergo arthroplasty during the 6 years follow-up.
TKA: total knee arthroplasty, THA: total hip arthroplasty.
Values are: mean ± standard deviation/sd, mean (interquartile range/iqr), or percentages %.
p-values obtained with Student's *t*-test or Pearson's χ^2 when appropriate.
p^1-values obtained with generalized estimating equations (GEE).

Knee pain subgroup			*Hip pain subgroup*		
TKA-n=732	***TKA+n=19***	***p value***	***THA-n=485***	***THA+n=53***	***p value***
135° ± 0.2°	127° ± 2.6°	<0.01	-	-	-
3° ± 0.1°	3° ± 0.8°	0.94	-	-	-
55 %	86 %	0.03	-	-	-
45 %	91 %	<0.01	-	-	-
0 %	10 %	<0.01	-	-	-
1 %	10 %	<0.01	-	-	-
32 %	63 %	0.03	-	-	-
39 %	86 %	<0.01	26 %	72 %	<0.01
-	-	-	41 %	68 %	<0.01
-	-	-	4 %	26 %	<0.01
-	-	-	17 %	48 %	<0.01
-	-	-	16 %	46 %	<0.01
-	-	-	31 %	79 %	<0.01
-	-	-	11 %	60 %	<0.01
-	-	-	35 %	78 %	<0.01
-	-	-	1 %	26 %	<0.01
-	-	-	11 %	38 %	<0.01
-	-	-	5 %	17 %	<0.01

NRS: Numeric Rating Scale, WOMAC: Western Ontario and McMaster osteoarthritis index, ESR: erythrocyte sedimentation rate, ROM: range of motion, JSN: joint space narrowing, OP: osteophyte, K/L: Kellgren & Lawrence, AP: anteroposterior pelvic view radiograph, FP: faux profile radiograph.
‡ Due to lower quality radiographs, these angles were determined in fewer hips (THA+: 781 hips, THA-: 45 hips). Bold indicates *p*-value < 0.05.

Table 2. Multivariable model of the knee pain subgroup for the association with TKA.

	β	***OR (95% CI)***	***p-value***
Body mass index (kg/m^2)	0.10	1.1 (1.0-1.2)	<0.01
Painful active knee flexion	1.35	3.8 (1.6-9.5)	<0.01
K/L score 1 (versus K/L score 0)	1.86	6.4 (1.7-23.4)	<0.01

β: regression coefficient (beta), CI: confidence interval, OR: odds ratio, K/L: Kellgren & Lawrence. Model obtained with generalized estimating equations (GEE). The obtained OR are unadjusted for age and gender, however all three variables do remain significant after adjustment (data not presented). An OR>1 indicates an increased risk for undergoing TKA.

Table 3. Multivariable model of the hip pain subgroup for the association with THA.

	β	***OR (95% CI) §***	***p-value***
Painful active hip internal rotation	1.65	5.2 (2.3-11.8)	<0.01
ROM hip flexion ≤115°	0.99	2.7 (1.2-6.2)	0.02
K/L score 1 (vs 0)	1.22	3.4 (1.2-9.4)	0.02
JSN on faux profile radiograph	2.53	12.6 (4.8-33.2)	<0.01
Dysplasia (Wiberg angle <25°)	2.10	8.2 (2.6-25.5)	<0.01
Femoral subchondral sclerosis	2.18	8.8 (2.9-26.7)	<0.01

β: regression coefficient (beta), CI: confidence interval, OR: odds ratio, ROM: range of motion, JSN: joint space narrowing, K/L: Kellgren & Lawrence. Model obtained with generalized estimating equations (GEE). An OR>1 indicates an increased risk for undergoing TKA.
§ OR adjusted for age and gender.

WOMAC change between baseline and T2

Table 4 provides an overview of the mean change in WOMAC pain and physical function score between baseline and T2 values for the different groups. One participant (1 knee) from the knee subgroup underwent TKA and 13 participants (14 hips) from the hip subgroup underwent THA before T2. They were excluded from this analysis. Only the mean change in WOMAC pain score differs significantly between the THA and non-THA group. There is a noticeable trend in WOMAC score increase amongst participants from the TJR groups, and a decrease amongst participants from the non-TJR group (Figure 1). The change in distribution of K/L scores between baseline and T2 for both the knees and hips differed significantly amongst the TJR and non-TJR groups: more joints in the TJR groups showed radiographic progression (Table 4).

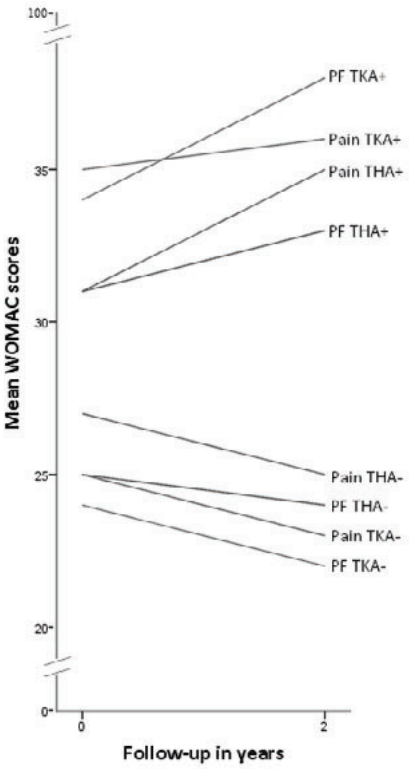


Figure 1. Depiction of the mean change in WOMAC scores from baseline to 2-year follow-up (T2). PF = physical functioning. THA= total hip arthroplasty. TKA= total knee arthroplasty. WOMAC = Western Ontario and McMaster osteoarthritis index.

Table 4. Mean change in WOMAC score and change in K/L distribution between baseline and T2.

		Knee pain at baseline			*Hip pain at baseline*		
		TKA-	TKA+		THA-	THA+	
Variable		*T0-T2*	*T0-T2*	*p-value*	*T0-T2*	*T0-T2*	*p-value*
		(n=732)	*(n=18)*	*mean Δ*	*(n=485)*	*(n=40)*	*mean Δ*
WOMAC pain		-1.7 (0.6)	4.4 (3.5)	*0.12*[§]	-1.2 (0.8)	4.7 (2.7)	*0.04*[§]
WOMAC physical function		-1.3 (0.5)	4.9 (4.8)	*0.07*[§]	-1.1 (0.7)	3.0 (2.1)	*0.10*[§]
		1,479 knees	*21 knees*		*1,002 hips*	*48 hips*	
Distribution of K/L score 0/1/2/3/4 (%)	*T0*	61/39/0/0/0	14/86/0/0/0		74/26/0/0/0	28/72/0/0/0	
	T2	50/36/13/1/0	5/15/55/20/5	*<0.01*[‡]	68/30/2/0/0	23/23/35/14/5	*<0.01*[‡]

Values are: mean change between T0 and T2 (standard error), or percentages %.

WOMAC: Western Ontario and McMaster osteoarthritis index, K/L: Kellgren & Lawrence, T0: baseline, T2: two year follow-up.

p-values obtained with * with Student's *t*-test or [‡]generalized estimating equations (GEE) and indicate whether the change in mean values (Δ) or in distribution of K/L score differ significantly. Progression of K/L score adjusted for baseline K/L score.

DISCUSSION

Summary

We found relevant patient- and disease characteristics associated with undergoing TJR in relatively young participants with recent onset knee and/or hip OA in a nationwide prospective cohort study.

In participants with recent onset knee OA, significant differences in baseline BMI, symptom severity (NRS and all three WOMAC subscales), clinical findings and radiographic OA severity were seen between participants who underwent TKA during follow-up and those who did not. In a subgroup of participants with recent onset hip OA significant differences in baseline age, gender distribution, symptom severity (NRS and WOMAC physical function), clinical findings, hip morphology and radiographic OA severity were found between participants who underwent THA during follow-up and those who did not.

The participants that underwent THA were slightly, but statistically significantly older at baseline (mean difference 2.6 years). The association between a higher age and hip OA progression has previously been established in a systematic review by Wright.[23] There remains conflicting evidence with regards to the association between gender and hip OA progression.[23-25]

Strengths and limitations

A limitation to the data under study is that, although participants were asked where the pain was located (knee and/or hip; left and/or right), the participants were not asked to which joint the NRS and WOMAC subscales assessments refer to. Consequently, an individual with both hip and knee, or bilateral symptoms could experience more pain and as a result have higher symptom scores. On the other hand, it might be difficult for an individual to score his or her pain separately for affected joints. Nevertheless, the abovementioned limitation could have led to some bias in our data.

Comparison with existing literature

In two systematic reviews on prognostic factors for knee OA progression the authors report conflicting evidence for the association between BMI and knee OA progression.[26, 27] In our knee subgroup there was a significant, and perhaps more importantly, clinically relevant difference in baseline mean BMI between the TJR and non-TJR group (mean difference 2.8 kg/m^2). Moreover, BMI remained significantly associated with undergoing TKA in the multivariable model. In accordance with existing literature we did not find an association between BMI and hip OA. This suggests that biomechanical factors such as hip dysplasia or cam-type deformity could play a greater role in the development of hip OA.

Baseline symptoms (NRS and WOMAC subscales) were significantly more severe in both TJR groups. This is in line with previous longitudinal studies showing that patients with higher pain or disability scores at baseline are more likely to undergo TJR.[28-30] The mean age of these study populations (72, 65 and 67 years respectively) however were higher than in our TJR groups (58 years). Unfortunately, symptom severity remains subjective and subsequently does not always form a clear indication for the GP to distinguish which patients are eligible for referral for TJR. The participants from both our TJR groups significantly more often had typical OA symptoms during physical examination of the knee or hip, which are consistent with the criteria for clinical knee and hip OA.[8, 9] In longitudinal studies by Birrell[31] and Lievense,[32] the authors found associations for hip ROM and painful hip movements with hip replacement surgery in similar study populations. This is in line with our findings, but again the mean age of our THA group was relatively low (58 years compared to 63 and 66 years respectively).

Participants that underwent TKA significantly more often showed radiographic knee OA features.[9] The corresponding radiographs also had worse JSN, sclerosis, tibial attrition and tibial spiking. Participants that underwent THA significantly showed more radiographic features of hip OA.[8] They also more often showed JSN on the faux profile, dysplasia and femoral subchondral sclerosis. Furthermore, the radiographs from the TJR groups more frequently showed cam-type deformity (α angle >60°) and hip dysplasia (Wiberg angle <25°), of which the associations with hip OA have previously been established.[16, 18, 24, 33, 34] Additionally, we found that participants from both the TJR groups showed earlier, more rapid radiographic progression of OA. All these abovementioned findings suggest that subjects who underwent TJR were in a more advanced stage of the disease at baseline. On the other hand, these findings could also suggest that participants from the TJR groups had a different underlying pathophysiology or phenotype of OA and therefore were prone to more rapid deterioration of the joint.[4, 5]

Lastly, at T2 a relatively large percentage of patients from the TJR groups still only had K/L score <2 (20% of the TKA group and 46% of the THA group). This is a rather remarkable observation from our data, considering that most clinical guidelines advise GPs to not request radiographic investigations at an early stage of OA[35-37] and that structural damage to the joint has proven to be a strong indicator for orthopaedic surgeons to consider TJR.[38] This causes a discrepancy between evidence based guidelines and clinical practice and should be further evaluated in future studies. Unfortunately, necessary additional information to clarify this finding was not incorporated in our data. Until this discrepancy is better understood, it seems justifiable that the existing recommendations to not request radiographs at an early stage should be enforced.

Implications for research and/or practice

We have established in a relatively young OA study population that in many subjects with recent onset knee or hip pain, radiographic OA features already exist. Moreover, subjects with more severe clinical or radiographic symptoms have an increased risk for undergoing TJR within a six-year follow-up. These findings suggest that the cascade of joint destruction may commence in a far earlier stage than the onset of symptomatic disease,[39] given that many participants showed radiographic OA features at baseline. Future research should be aimed at establishing clear criteria, both symptomatic and radiographic, for undergoing TJR which will better guide the GP in his or her decision for referral. Until these criteria are developed, GPs should refrain from unnecessary X-rays in accordance with the current OA guidelines.[35-37] However, it somehow seems justifiable for a GP to request X-rays if he or she is consulted by a relatively young patient (<55 years) with severe onset hip or knee pain due to OA (NRS >5).

REFERENCES

1 Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. Natl Health Stat Report. 2010(27):1-32.

2 Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am. 2013;39(1):1-19.

3 Delaunay C. Registries in orthopaedics. Orthop Traumatol Surg Res. 2014.

4 Kinds MB, Marijnissen AC, Viergever MA, et al. Identifying phenotypes of knee osteoarthritis by separate quantitative radiographic features may improve patient selection for more targeted treatment. J Rheumatol. 2013;40(6):891-902.

5 Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377(9783):2115-26.

6 Wesseling J, Dekker J, van den Berg WB, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis. 2009;68(9):1413-9.

7 Kraaimaat FW, Evers AW. Pain-coping strategies in chronic pain patients: psychometric characteristics of the pain-coping inventory (PCI). Int J Behav Med. 2003;10(4):343-63.

8 Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum. 1991;34(5):505-14.

9 Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.

10 Damen J, Schiphof D, Wolde ST, et al. Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (cohort hip and cohort knee) study. Osteoarthritis Cartilage. 2014;22(7):969-74.

11 Buckland-Wright C. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage. 1995;3 Suppl A:71-80.

12 Lequesne MG, Laredo JD. The faux profil (oblique view) of the hip in the standing position. Contribution to the evaluation of osteoarthritis of the adult hip. Ann Rheum Dis. 1998;57(11):676-81.

13 Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15 Suppl A:A1-56.

14 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494-502.

15 Burnett S, Hart DJ, Cooper C, Spector TD. A Radiographic Atlas of Osteoarthritis. London: Springer Verlag; 1994.

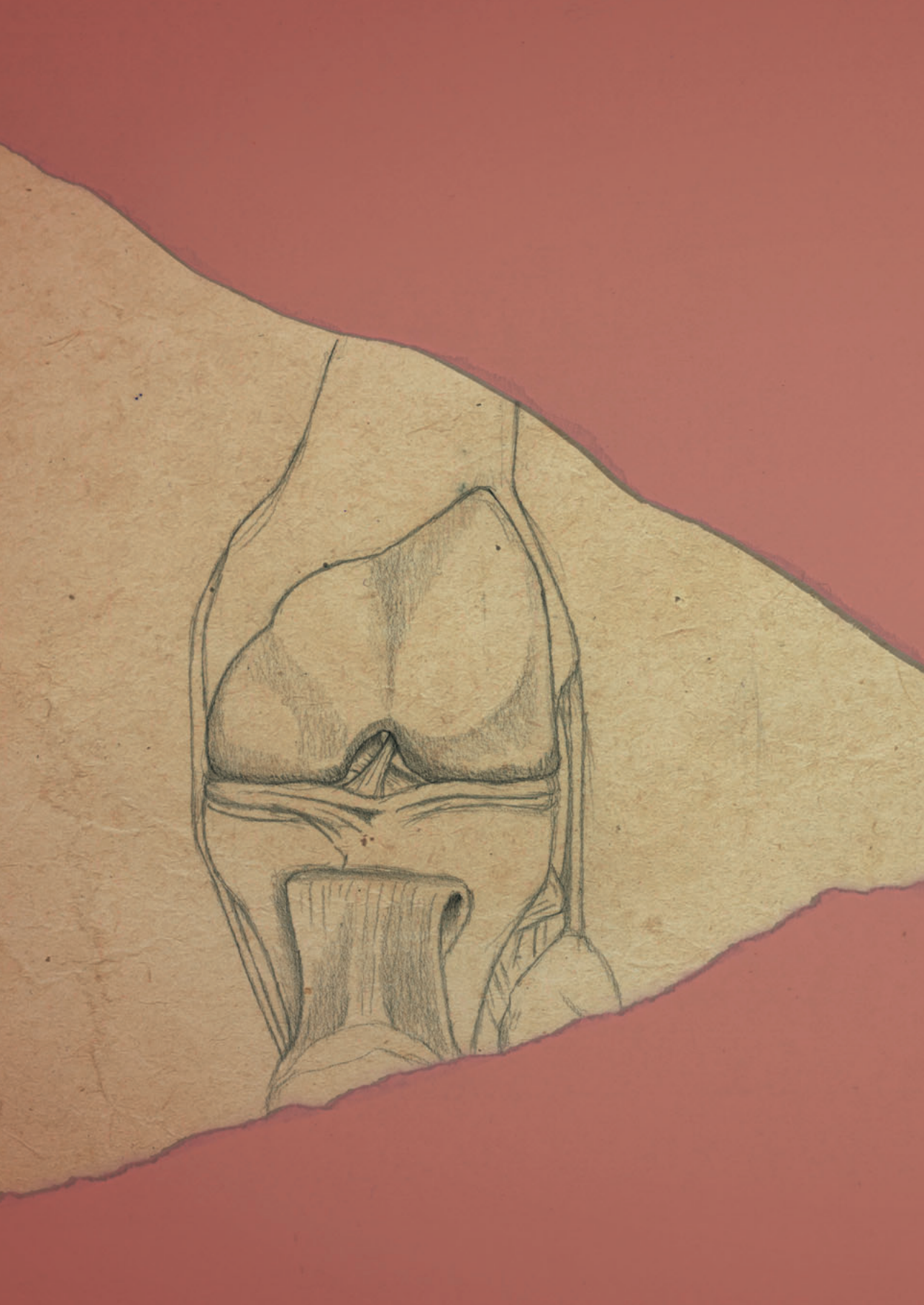
16 Agricola R, Heijboer MP, Bierma-Zeinstra SM, et al. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis. 2013;72(6):918-23.

17 Allen D, Beaule PE, Ramadan O, Doucette S. Prevalence of associated deformities and hip pain in patients with cam-type femoroacetabular impingement. J Bone Joint Surg Br. 2009;91(5):589-94.

18 Agricola R, Waarsing JH, Thomas GE, et al. Cam impingement: defining the presence of a cam deformity by the alpha angle: data from the CHECK cohort and Chingford cohort. Osteoarthritis Cartilage. 2014;22(2):218-25.

19 Wiberg G. Shelf operation in congenital dysplasia of the acetabulum and in subluxation and dislocation of the hip. J Bone Joint Surg Am. 1953;35-A(1):65-80.

20 Vare VB, Jr. The anatomy of the pelvic tear figure. J Bone Joint Surg Am. 1952;34-A(1):167-9.
21 Laborie LB, Engesaeter IO, Lehmann TG, et al. Radiographic measurements of hip dysplasia at skeletal maturity-new reference intervals based on 2,038 19-year-old Norwegians. Skeletal Radiol. 2013;42(7):925-35.
22 Tonnis D. Normal values of the hip joint for the evaluation of X-rays in children and adults. Clin Orthop Relat Res. 1976(119):39-47.
23 Wright AA, Cook C, Abbott JH. Variables associated with the progression of hip osteoarthritis: a systematic review. Arthritis Rheum. 2009;61(7):925-36.
24 Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat Clin Pract Rheumatol. 2007;3(2):78-85.
25 Lievense AM, Bierma-Zeinstra SM, Verhagen AP, et al. Prognostic factors of progress of hip osteoarthritis: a systematic review. Arthritis Rheum. 2002;47(5):556-62.
26 Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther. 2015;17:152.
27 Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care Res (Hoboken). 2011;63(8):1115-25.
28 Hawker GA, Guan J, Croxford R, et al. A prospective population-based study of the predictors of undergoing total joint arthroplasty. Arthritis Rheum. 2006;54(10):3212-20.
29 McHugh GA, Campbell M, Luker KA. GP referral of patients with osteoarthritis for consideration of total joint replacement: a longitudinal study. Br J Gen Pract. 2011;61(589):e459-68.
30 Conaghan PG, D'Agostino MA, Le Bars M, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Ann Rheum Dis. 2010;69(4):644-7.
31 Birrell F, Afzal C, Nahit E, et al. Predictors of hip joint replacement in new attenders in primary care with hip pain. Br J Gen Pract. 2003;53(486):26-30.
32 Lievense AM, Koes BW, Verhaar JA, et al. Prognosis of hip pain in general practice: a prospective followup study. Arthritis Rheum. 2007;57(8):1368-74.
33 Beck M, Kalhor M, Leunig M, Ganz R. Hip morphology influences the pattern of damage to the acetabular cartilage: femoroacetabular impingement as a cause of early osteoarthritis of the hip. J Bone Joint Surg Br. 2005;87(7):1012-8.
34 Ganz R, Leunig M, Leunig-Ganz K, Harris WH. The etiology of osteoarthritis of the hip: an integrated mechanical concept. Clin Orthop Relat Res. 2008;466(2):264-72.
35 NHG. The Dutch College of General Practitioners. NHG-Standaard Niet traumatische knieproblemen bij volwassenen [guideline in Dutch]. Huisarts en Wetenschap. 2008;5:229-40.
36 NICE. National Institute for Health and Care Excellence. Osteoarthritis: Care and management in adults. NICE clinical guideline 177 London: NICE. 2014.
37 ACR. American College of Rheumatology. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum. 2000;43(9):1905-15.
38 Maillefert JF, Roy C, Cadet C, et al. Factors influencing surgeons' decisions in the indication for total joint replacement in hip osteoarthritis in real life. Arthritis Rheum. 2008;59(2):255-62.
39 Wluka AE. Remember the Titanic: what we know of knee osteoarthritis is but the tip of the iceberg. J Rheumatol. 2006;33(11):2110-2.



CHAPTER 10

General Discussion

GENERAL DISCUSSION

Although hip and knee pain are among the most common reasons to consult a general practitioner (GP), the diagnosis of hip and knee osteoarthritis (OA), especially in the early phase of OA, remains a challenge. This is partly due to the fluctuating symptoms, particularly in the early stage of the disease. In general practice, research on the diagnosis of OA and progression remains scarce, especially in the earliest stages of the disease.[1] In addition, the role of radiography in the diagnosis of OA is still debated.[2] Although most guidelines seem reluctant to recommend radiography, this is not reflected in daily care and, in general practice, radiography is frequently used to help diagnose OA.[3, 4, 5]

The overall aim of this thesis was to investigate the diagnosis and progression of early OA in a cohort of 'first presenters' with hip and knee joint complaints. To accomplish this, we first evaluated the criteria used for OA in epidemiological research. In addition, we aimed to ascertain whether radiography would be useful in diagnosing and/or evaluating the progression of OA when using different radiographic views. OA is a disease with many phenotypes; this applies even more for OA of the knee, which consists of two different joints.[6] Therefore, we also examined whether patellofemoral OA (PFOA) is a distinct subtype, or a sign of early OA. One difficulty when investigating OA pain is that not all pain perceived in a joint has its origin in that specific joint.[7] Therefore, we investigated whether pain in the hip could be referred pain from the back. Since joint pain, and its individual perception, is very complicated and often due to multifactorial processes, we also examined the influence of genetic factors on joint pain.

Early osteoarthritic disease and the CHECK study

Generally, the conclusions and implications drawn from research are applicable only to that specific research population and the population that it represents. For example, the CHECK study aimed to evaluate first presenters (aged 45 years and older) with symptoms that could be attributable to early OA of the hip and knee. For this, eligible participants were invited through their GPs and through advertisements in newspapers. Because one inclusion criterion was that participants had to have visited their GP for these hip/knee complaints for the *first time* not longer than 6 months previously (or not yet at all), the study population was very similar to the first presenters in primary care with such complaints. The exclusion criteria were applied mainly to exclude other clear diagnoses that could explain the complaints of the hip and/or the knee. [8]

This process resulted in a population with hip and knee complaints that is prone to be diagnosed with OA later in life, in other words an 'early OA' population. The study in **Chapter 2** showed that, of the participants with knee complaints, as much as 81.3% or 73.1% were diagnosed with knee OA at baseline when applying the ACR clinical criteria or the combined clinical/radiographic criteria, respectively. Also, 27.6% or 54.7% of the participants with hip complaints were diagnosed with OA depending on which set of ACR criteria was used, i.e. clinical criteria or the combined clinical/radiographic criteria, respectively. Furthermore, depending on the set of ACR criteria used, at the 2-year follow-up 32.5% or 25.2% of the participants not fulfilling the ACR criteria at baseline were diagnosed with knee OA. Similarly, for the hip, 13.6% or 7.4% of the participants had developed hip OA at follow-up. This indicates that OA was prevalent in this cohort (aged 45 years and older) and that the prevalence of OA is even higher after only two years follow-up. Another argument for our cohort to be designated an 'early OA' group, is the mildness of the participants' symptoms. At baseline, the average WOMAC pain score was only 26.2 (range 0-100), including those participants who already fulfilled the ACR criteria for OA at baseline.

Furthermore, at baseline, radiographic OA (ROA) was uncommon, i.e. at baseline, for the knees 54% of all participants had a Kellgren and Lawrence (K&L) score of 0, whereas for the hips this percentage was even higher (65%). In this early OA cohort, due to the very low prevalence of a K&L score ≥ 2 (the usual cut-off for ROA) at baseline, we decided to define a cut-off K&L score of ≥ 1 for signs of ROA. Another indication that CHECK constitutes an early OA cohort is that, after five years follow-up, only 9 participants underwent knee replacement and, during the same period, only 37 hip replacements were performed. A final indication is presented in **Chapter 5** where we demonstrated that ROA at baseline (if present) was mostly only in one part of the joint (the patellofemoral joint) whereas after 5 years ROA was also seen in the tibiofemoral joint.

These indications that we have a cohort with 'very early stage OA' are important. They imply that conclusions drawn from these studies are applicable to early OA in first presenters with pain in the hip and/or knee visiting the general practice, in whom other clear diagnoses have been excluded. In the Netherlands, GPs are frequently consulted for these early symptoms.[9]

Pain perception

Between individual patients, the level of perceived pain is very heterogeneous. Also, the perceived level of complaints can be due to the heterogeneity between OA phenotypes; this can be caused by the complexity of both nociceptive, neuropathic and central pain mechanisms and their interaction, and even by genetic variation in pain perception.[10] Nociceptive pain mechanisms are a response of peripheral nociceptors to tissue damage or inflammation in the joint. Neuropathic pain arises from lesions or disease of the somatosensory system; this can occur in the peripheral sensory nerves, as well as in the spinal root ganglions or dorsal horn microglia.[11] Central pain mechanisms include: spinal mechanisms and enhanced activity of descending facilitation pathways, loss of descending anti-nociceptive mechanisms, over-activity of the pain matrix, and long-term potentiation of neuronal synapsis in the anterior cingulate synapsis.[12]

At the onset of OA, the genetic variation (or component) is estimated at 40-80%. Whereas very rare mutations resulting in monogenetic disorders have a large effect resulting in early-onset OA, 'normal onset' OA is multifactorial and the effect size of the genetic variation compared to the known risk factors is generally small.[13] Also, in pain perception there is genetic variation in individual predisposition to the development of pain in OA.[10] The study in **Chapter 8** shows that a precursor for a gene involved in pain sensation is related to pain perception and that persons with this genetic variation are more likely to report hip/knee pain, even though they have the same degree of ROA.

Implications for general practice

Reflections on the use of radiography in patient care

In patients with OA, conventional radiography is the least costly method for imaging joint structures. In research, the presence and radiographic severity of disease is generally determined using the K&L grading system.[14,15]

Although imaging has been unhelpful in diagnosing OA, it is suggested that imaging is helpful by refuting other diagnoses when history taking and physical examination result in an uncertain diagnosis.[16] In primary care, the use of radiographic assessment for OA is not recommended in the guideline of the Dutch College of General Practitioners.[17]

Currently, the actual use of radiography for OA in general practice is probably not in line with these guidelines; however, this so-called 'overuse' of medical resources has not yet been well investigated. For example, in the Netherlands, no published data are available on the use of radiography in suspected OA, either in primary or secondary care. The reason why many GPs continue to order radiographs remains unclear. Perhaps the diagnostic uncertainty and the perceived pressure from patients play a role in this under-investigated area. On the other hand, when the use of a relatively low-cost imaging method allows the patient to have more confidence in their primary care physician, helps them be more compliant with effective therapy (e.g. exercise), and helps to delay referral to secondary care, this might translate into some measure of cost-effectiveness. However, this idea needs further investigation.

So far, the data emerging from the present studies should tend to discourage clinicians from routinely using radiographs for OA at this early stage, for three reasons. Firstly, radiography is not a meaningful prognostic tool at this stage of disease. Not one single feature, or combination of radiographs obtained in the case of 'suspected OA', had prognostic value for pain in the subsequent five years (**Chapter 6).** The argument that radiography is useful to exclude other diagnoses is also not valid: in the entire CHECK cohort, not one case was identified with an alternative diagnosis, neither at baseline nor at the 10-year follow-up. Moreover, many patients had no signs of ROA at all (KL 0) whereas, based on other symptoms and signs, they could be classified as OA patients. Therefore, in such cases, OA radiographic examination may lead the physician to erroneously conclude that OA is not present. Finally, since no cases of advanced ROA were identified at baseline, there seems to be no advanced ROA disease in these first presenters.

One of the main reasons why radiography is not a useful prognostic tool is probably because the structures visible on radiographs only play a minor role in pain perception and progression of OA. It is debatable whether in practice the 'correct' radiograph is in fact acquired; however, in **Chapter 6** we explain that no combinations of multiple radiographs serve as a useful prognostic tool. Furthermore, joint effusion or synovitis, as well as bone marrow lesions and soft tissue structures (such as the menisci) that are known to play a crucial role in the pathogenesis and symptom perception in OA, are simply not visible on conventional radiography. Other factors which greatly affect pain and function (e.g. psychological or socio-economic status, fatigue and sleep) are often left out of the assessment. It seems that radiographs focus too much on too few tissues, which are most likely not the most relevant for pain disability and progression of OA.

However, in **Chapter 9** in a small subgroup of first presenters with rapid progressing hip and knee pain we demonstrated ROA as a risk factor for total joint replacement surgery within 6 years of follow up. One could hypothesise that a GP confronted with a severe onset HOA or KOA patient could use radiography to distinguish patients who are more likely to need a total

joint replacement. This could aid the GP to refer more specifically to an orthopaedic surgeon, although we recognise that the decision to perform a total joint replacement is not solely based on ROA features. The number of joints replaced in CHECK however, is very low
Discouraging the use of radiographic examination of the knee/hip may raise questions regarding other imaging modalities used for OA in general practice. Magnetic resonance imaging (MRI) has recently been introduced to GPs and, especially MRI of the knee, is now widely available. However, the high costs of MRI might be problematic in view of the ever-increasing OA population. Moreover, although MRI of the knee has proven more sensitive to detect structural OA, knee OA as defined by radiographs yielded similar associations with the presence of knee pain as for knee OA defined by MRI.[18] However, on MRI, the presence and severity of pain are associated with bone marrow lesions and synovitis (features not visible on X-ray) [19] and the fluctuation of pain between patients correlates with fluctuation of signs of synovitis and fluctuations in the size and numbers of bone marrow lesions.[20] Such knowledge is important, because the development of treatments that impact on these features might also affect the patient's pain; in clinical practice, fluctuations in pain can be monitored by anamneses. Ultrasound imaging is also increasingly available in general practice[21] and could be used to monitor disease and (side) effects of treatment. In diagnosing and monitoring OA, ultrasound is much more sensitive for synovitis than radiography which captures synovitis only poorly.[22] Other methods might also be used to determine increased synovitis in the knee; for example, in patients with rheumatoid arthritis, anamnestic morning stiffness correlated well with the degree of morning stiffness.[23] In traumatic knee patients, perceived swelling in the knee and physical examination also correlated with effusion on MRI.[24] These correlations in OA patients and their implication for practice require more study, especially because synovitis is reported to be one of the drivers in the development of neuropathic/sensitized pain.[7]

Diagnostic criteria in primary care

Our studies have shown that the ACR criteria are also useful in primary care, as a simplification of these criteria used at baseline could be used to predict OA at 2 and 5-year follow-up. We suggest that future studies validate whether patients with hip complaints (in whom other diagnoses have been excluded by the GP through anamnesis and physical examination) with a combination of relevant characteristics (e.g. aged over 45 years, morning stiffness, painful internal rotation, hip flexion < 115°, an erythrocyte sedimentation rate < 20 mm/h) are indeed early OA patients; this recommendation also applies to patients with knee complaints aged over 45 years. A diagnosis of OA should then be followed by appropriate treatment.

Since we found no added value for the use of radiography, we encourage physicians to perform more extensive history taking and physical examination in their patients; this may be the hallmark for the diagnosis of OA. Although this may appear to be time consuming, it might prove essential to minimalize diagnostic error and uncertainty about the diagnosis. A more extensive physical

examination may help both the physician and patient to understand that additional imaging tests (such as radiographs) may not be helpful.

When the application of these criteria leads to the identification of a larger group of patients diagnosed with OA, this might enable intervention at an earlier stage of the disease when, for example, active management, exercise and lifestyle interventions might be more successful than when applied in a more advanced stage of the disease.

Implications for future research

Defining clear diagnostic criteria for (early) OA provides a new group of patients who can be included in research. This group with an early diagnosis may provide a window of opportunity for treatment, e.g. early intervention may help to prevent or postpone the serious disability associated with OA. However, these concepts need to be validated and proven in well-designed prognostic studies.

In our studies, at 5-year follow-up the average pain scores were lower than at baseline. On further analysis, groups with different patterns of symptom emerged and there was a subgroup with pain at baseline that no longer had pain at the 2 or 5-year follow-up. It is possible that this 'decreasing pain' group experienced flare ups at baseline.[25] To further elucidate these fluctuating pain groups, future research in early OA should make use of shorter intervals of regular pain registration.

Another aim for future studies should be to understand why both patients and physicians continue to request radiographs when OA is suspected, even when the accuracy and prognostic value of radiography is known to be poor. It is too easy to blame the patient for demanding a radiograph, since there is a large factor of diagnostic uncertainty among clinicians. Further research might provide insight into why both clinicians and patients request radiographs, how radiographic findings help clinicians and patients, and their impact on management decisions. It is also worthwhile to investigate whether complaints of the hip/knee and the physical examination correlate with MRI and/or radiographic findings: this may help clinicians to better advise their patients as to whether (or not) imaging may be useful.

Furthermore it should be studied whether clear criteria can be defined for GP's referring patients for joint replacement surgery, and more specifically whether ROA features should be part of these referral criteria.

Our proposed criteria for OA in primary care need to be validated in other OA cohorts to determine whether they really do help to identify early OA. Arriving at a clear OA diagnosis may help these patients to adhere to relevant lifestyle changes that may be essential to minimalize pain and disability and (perhaps) even postpone the need for surgical intervention.

REFERENCES

1 Luyten FP, Bierma-Zeinstra S, Dell'Accio F, Kraus VB, Nakata K, Sekiya I, Arden NK, Lohmander LS. Toward classification criteria for early osteoarthritis of the knee. Semin Arthritis Rheum. 2018 Feb;47(4):457-463.

2 Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27:1513-1517

3 Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C,et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: Analysis of longitudinal data from the Osteoarthritis Initiative. Arthritis Care Res, 2010;62:932-7.

4 Zhang, M Doherty, G Peat, S M A Bierma-Zeinstra, N K Arden, B Bresnihan, G Herrero-Beaumont, S Kirschner, B F Leeb, L S Lohmander, B Mazières, K Pavelka, L Punzi, A K So, T Tuncer, I Watt, J W Bijlsma . EULAR evidence-based recommendations for the diagnosis of knee. Ann Rheum Dis 2010;69:483-489

5 Sakellariou G, Conaghan PG, Zhang W, et al EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis Ann Rheum Dis 2017;76:1484-1494.

6 Nelson AE, Golightly YM, Renner JB, et al. Differences in Multi-joint Symptomatic Osteoarthritis Phenotypes by Race and Gender: The Johnston County Osteoarthritis Project. Arthritis and Rheumatism. 2013;65(2):373-377.

7 Neogi T. Structural correlates of pain in osteoarthritis. Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 107(5):75-78.

8 Wesseling J, Dekker J, van den Berg WB, et al. CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Annals of the Rheumatic Diseases 2009;68:1413–1419.

9 www.volksgezondheidenzorg.info (2018)

10 Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. Osteoarthritis and Cartilage, 21(9), 1145–1153.

11 Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum. 2014;44(2):145-54.

12 Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. Eur J Pain. 2014;18(10):1367-75

13 van Meurs, J. B. J. (2017). Osteoarthritis year in review 2016: genetics, genomics and epigenetics. Osteoarthritis and Cartilage, 25(2), 181–189.

14 Altman R, Gold G. Atlas of individual radiographic features in osteoarthritis, revised1. Osteoarthritis and Cartilage 2007;15:A1–A56.

15 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.

16 McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM, Underwood M. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014 Mar;22(3):363-88.

17 https://www.nhg.org/standaarden/volledig/nhg-standaard-niet-traumatische-knieklachten#idp10192576

18 Schiphof, D. et al. Sensitivity and associations with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic Kellgren and Lawrence criteria: a population-based study in middle-aged females. Osteoarthritis and Cartilage, 2014; 22:440-446.

19 Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis. 2011;70(1):60-7.

20 Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. Arthritis Rheum. 2011;63(3):691-9.

21 Troels Mengel-Jørgensen & Martin Bach Jensen (2016) Variation in the use of point-of-care ultrasound in general practice in various European countries. Results of a survey among experts, Eur J Gen Prac, 22:4, 274-277

22 Abraham AM, Pearce MS1, Mann KD, Francis RM, Birrell F. Population prevalence of ultrasound features of osteoarthritis in the hand, knee and hip at age 63 years: the Newcastle thousand families birth cohort. BMC Musculoskelet Disord. 2014 May 19;15:162.

23 Dejaco, C., Duftner, C., Wipfler-Freißmuth, E., Weiss, H., Graninger, W. B., & Schirmer, M. (2012). Ultrasound-Defined Remission and Active Disease in Rheumatoid Arthritis: Association with Clinical and Serologic Parameters. Seminars in Arthritis and Rheumatism, 41(6), 761–767.

24 Kastelein, Marlous et al. Diagnostic Value of History Taking and Physical Examination to Assess Effusion of the Knee in Traumatic Knee Patients in General Practice Archives of Physical Medicine and Rehabilitation, 2009 Volume 90, Issue 1 , 82 – 86

25 Verkleij SPJ, Hoekstra T, Rozendaal RM, et al Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71:1517-1523.

CHAPTER 11

Summary
Samenvatting
Biografie
PhD Portfolio
List of publications
Dankwoord

SUMMARY

Although osteoarthritis (OA) is the most frequently diagnosed joint disorder in primary care, no clear diagnostic set of criteria are available for primary care. Radiography is often used to help diagnose this disorder, but in most guidelines this is deemed unnecessary.

This thesis focuses on early diagnosis of OA in patients who consult their primary care physician for the first time with hip and/or knee problems. This category of patients is referred to as 'first presenters'.

Diagnosing osteoarthritis

The study in **Chapter 2** evaluated the prevalence of hip and knee OA according to the criteria of the American College of Rheumatology (ACR) in participants with early symptomatic OA in the CHECK cohort. Furthermore, we assessed whether participants not fulfilling the ACR criteria at baseline, progress towards the ACR defined OA at the 2 and/or 5-year follow-up, and which factors are associated with this progression.

Of those participants presenting with hip complaints, two thirds were classified as having hip OA (HOA) at baseline according to the ACR criteria. Of those not classified with HOA at baseline, 2 out of 5 developed HOA according to the clinical or the combined clinical/radiographic ACR criteria at 2 and/or 5-year follow-up. The following factors were associated with progression to HOA: morning stiffness, painful internal rotation, hip flexion <115°, and an *erythrocyte sedimentation rate* <20 mm/h.

The vast majority of participants with knee complaints could be classified as having knee OA (KOA) at baseline. Of those who could not be classified at baseline, 55% developed KOA according to the clinical ACR criteria or the clinical/radiographic ACR criteria at 2 and/or 5- year follow-up. However, no variables seemed to be associated with the progression to KOA at the 2 and/or 5-year follow-up.

We concluded that, in persons with hip complaints, a large proportion not fulfilling the ACR criteria at baseline progress to OA after 2 and/or 5 years. Almost all persons with knee complaints already fulfilled the clinical and/or radiographic ACR criteria for OA. Therefore, it might be suggested that first presenters, aged 45-65 years, in whom other diagnoses have been excluded, with hip complaints and morning stiffness, painful internal rotation, hip flexion < 115° and an *erythrocyte sedimentation rate* <20 mm/h could be diagnosed with HOA. First presenters aged 45-65 years with knee complaints in whom other diagnoses have been excluded are prone to have KOA. However, these conclusions and recommendations need to be further validated in other cohorts before they can be implemented in routine clinical practice.

Chapter 3 investigated the prevalence and progression of early radiographic OA (ROA) of the hip and knee on different radiographic views, to determine whether different radiographic views have additional value in detecting patients with early hip and knee ROA. Furthermore, we explored whether progression was more easily detected when using different radiographic views. This study was also conducted using data from the CHECK cohort.

Five different radiographs were obtained: an anteroposterior (AP) and faux profile view of the hips, and a posteroanterior (PA), mediolateral (ML) and skyline view of the knees. Prevalence of ROA was estimated based on each view separately and in combinations. We determined whether different radiographic views had additional value in detecting and determining the progression of patients with ROA compared to standard projections. In the hip, when both views were combined, we identified almost 25% more cases of ROA. In the knee, compared with using the PA view only, over 75% more cases of ROA were detected when combining information from all three radiographic views. Progression was demonstrated in 33% more cases when using two hip radiographs and in 65% more cases when using three knee radiographs. Therefore, it was concluded that the use of different radiographic views increases the identification of participants with ROA in an early OA cohort, both at baseline and at follow-up. Also, progression of early ROA is more frequently demonstrated when multiple different radiographic views are used.
In large studies (e.g. the CHECK study) the scoring of radiographs is performed by multiple readers. Therefore, in **Chapter 4** we calculated the inter-observer reliability between four trained student readers and one experienced general practitioner reader, for early ROA features in our early OA CHECK study (cohort hip and cohort knee). The four student readers were trained to score ROA features by a musculoskeletal radiologist and an experienced reader. After this training, the student readers scored the CHECK cohort. Of the 1002 participants, 38 were scored by all readers. Five different radiographic views (three for the knee, two for the hip) at three different time points were scored and compared. Inter-observer reliability was evaluated between each of the four trained readers and the experienced reader. We evaluated both the separate ROA features and the overall Kellgren and Lawrence (K&L) scores. In addition, the reliability of the progression of ROA was determined using the K&L scores and joint space narrowing (JSN).

For the hip and knee, the inter-observer reliability was substantial for the overall K&L scores. For the knee, JSN was scored with fair to moderate reliability, osteophytes with moderate to nearly perfect reliability, and the other features were scored with fair to substantial reliability. For the hip, reliability ranged from substantial to nearly perfect. Moderate inter-observer reliability was found for progression of OA in both knee and hip, with slightly better reliability for progression based on the K&L scores than on the separate features. It was concluded that good inter-observer reliability can be achieved between trained readers and an experienced reader.

Prognosis of osteoarthritis

The natural course of different types of ROA is described in **Chapter 5**. For this, 845 middle-aged participants with early OA symptoms of the knee from the CHECK study were followed for 5 years. Participants with isolated patellofemoral osteoarthritis (PFOA) were compared with participants with tibiofemoral osteoarthritis (TFOA). At baseline, 116 had PFOA and none had TFOA or combined patellofemoral or tibiofemoral OA (COA). Of these 116 participants, 66.3% had developed COA at the 5-year follow-up. At the 2-year follow-up, PFOA, TFOA and COA were present in almost 11%, 6% and 12% of the participants, respectively. When comparing participants with radiographic PFOA or TFOA, multivariate regression analyses showed no significant differences with respect to signs and symptoms. These results suggest that OA is more likely to start in the patellofemoral joint and then progress to COA in individuals with symptoms of early knee OA. Similarly, when comparing participants with PFOA or TFOA phenotypes, no significant differences were found with respect to signs and symptoms.

The study in **Chapter 6** assessed whether the multiple view radiographs (which helped to diagnose ROA) had predictive value with respect to the longitudinal pain trajectories. Therefore, we used combinations of the anteroposterior (AP) and faux profile view of the hips, and a posteroanterior (PA), mediolateral (ML) and skyline view of the knees. For these combination views, we determined whether they were predictive for pain trajectories retrieved by latent class growth analysis also in the CHECK study. In the hip, combinations of views did not distinguish between pain patterns. In the knee, when combining the ROA data from all views (K/L grade ≥1 on the PA view, ≥1 osteophytes on the mediolateral view, and ≥1 osteophytes and/or JSN ≥1 on the skyline view) these patients had chance of a decreasing pain trajectory combined with a steady pain trajectory, OR 0.53 (95% CI 0.30-0.94. However, because the effect was small, we cannot yet recommend the use of combinations of ROA to predict future pain. **Chapter 9** addresses the subgroup of participants with rapid progressing symptoms of OA in the CHECK cohort. This rapid progression was defined as a TJR (total joint replacement) in the first 6 years after presenting with their symptoms. A TJR is often considered as the end stage of OA. In these first 6 years 62 (THR) total hip replacements and 22 TKA (total knee replacements) were performed. Participants who underwent a THR had pain with internal rotation of the hip and had more radiographic OA features, indicating more severe ROA. Participants who underwent a TKR had a higher BMI, and pain with knee flexion, they also had more radiographic OA features, indicating more severe ROA. Both in the hip and knee group we showed more progression of ROA when we compared radiographic findings after two years of follow up with baseline ROA.

Other causes of pain in osteoarthritis

Not all pain experienced in the hip originates in the hip joint itself. For example, lower back pain can result in referred pain in the hip. **Chapter 7** explored factors known to be associated with hip pain arising from the lumbar spine. Therefore, we examined the association between hip pain

and OA of the lumbar spine. In the Rotterdam Study (an open population-based study including persons aged 55 years and older), 2,819 lumbar radiographs were scored for the presence and severity of individual radiographic features of disk degeneration. Hip OA was scored on AP radiographs and questionnaires (including self-reported hip pain) were filled in. It was shown that the presence of disc space narrowing grade ≥1 at level L1/L2 was significantly associated with hip pain (in men OR = 2.0 and in women OR = 1.7). The presence of disk space narrowing grade ≥1 at level L2/L3 was significantly associated with hip pain only in women with short-term pain. The strength of the associations increased for self-reported chronic hip pain, especially in men (L1/L2 OR = 2.5). The presence of disk space narrowing at the lower levels (L3/L4/L5/S1) was not significantly associated with hip pain. Therefore, we concluded that there is evidence for an association between hip pain and disk space narrowing at disk level L1/L2 and L2/L3. In case of uncertainty of the cause of hip pain, lumbar OA should be considered.

The study in **Chapter 8** aimed to establish whether common genetic variation in the GTP-cyclohydrolase1 gene (GCH1) and its promoter is associated with self-reported pain in the hip, knee and hand, and with chronic widespread pain, since pain perception differs greatly between individuals. This was also explored in the Rotterdam Study in those participants for whom genotype and self-reported pain data were available. We studied 15 tagging SNPs stretching +/-50Kb upstream of the GCH1 gene and encompassing all common (>5% allele frequency) genetic variation in that area. Pain in the hip, knee and hand was defined as having pain during the month prior to the interview. Chronic (i.e. persisting for more than 6 months) widespread pain was defined according to the ACR criteria for widespread pain with two minor adaptations. Logistic regression models were used to model the risk of pain by polymorphism. A polymorphism (rs8007267, allele frequency 15%) situated in the promoter area of the GCH1 gene was associated with pain in the hip, hand and knee. Compared with C-carriers, homozygous T individuals had a 45% and 49% decreased risk for hip pain and hand pain, respectively. Knee pain showed a trend in the same direction (OR = 0.74). For the widespread pain phenotype (arguable the most disabling phenotype of all four), the odds were even more protective for the T allele homozygotes. This study showed that a promoter variant of the GCH1 gene is associated with the presence of site-specific and chronic widespread pain.

Chapter 10 discusses the main findings and considers their possible implications for both clinical practice and future research.

SAMENVATTING

Hoewel artrose de meest gediagnosticeerde gewrichtsaandoening in de eerste lijn is, zijn daarvoor in de eerstelijnszorg geen duidelijke diagnostische criteria beschikbaar. Vaak wordt gebruikgemaakt van röntgenopnames om de aandoening vast te stellen, maar volgens de meeste richtlijnen is dat niet noodzakelijk.

Dit proefschrift richt zich op de vroege diagnose van artrose bij patiënten die voor het eerst hun huisarts raadplegen met heup- en/of knieklachten. Deze categorie patiënten wordt '*first presenters*' genoemd.

Diagnose van artrose

Het onderzoek in **hoofdstuk 2** evalueert de prevalentie van heup- en knieartrose volgens de criteria van het *American College of Rheumatology* (ACR) bij deelnemers met vroege symptomatische artrose in het CHECK-cohort. Verder hebben we onderzocht of deelnemers die bij aanvang niet voldeden aan de ACR-criteria wel aan deze criteria voldoen na 2 en/of 5 jaar follow-up, en welke factoren verband houden met deze progressie.

Van de deelnemers die zich presenteren met heupklachten, werd twee derde op baseline geclassificeerd als heupartrose volgens de ACR-criteria. Van diegenen die aan het begin van het onderzoek niet waren geclassificeerd met heupartrose, ontwikkelden 2 op de 5 personen deze aandoening volgens de klinische of gecombineerd klinische en radiografische ACR-criteria na 2 en/of 5 jaar follow-up. De volgende factoren waren geassocieerd met de progressie van heupartrose: ochtendstijfheid, pijnlijke endorotatie, heupflexie <115 ° en een bezinking van <20 mm per uur.

De overgrote meerderheid van de deelnemers met knieklachten kon al bij aanvang van het onderzoek worden geclassificeerd als lijdend aan knieartrose. Van degenen die op baseline niet geclassificeerd konden worden, ontwikkelde 55% knieartrose volgens de klinische ACR-criteria of de klinische/radiografische ACR-criteria bij 2 en/of 5 jaar follow-up. Er bleken echter geen variabelen geassocieerd te zijn met de progressie van knieartrose tijdens de 2 en/of 5 jaar durende follow-up.

We concludeerden dat van de personen met heupklachten bij aanvang van het onderzoek een groot deel niet voldeed aan de ACR-criteria, maar na 2 of 5 jaar wel heupartrose ontwikkelde. Bijna alle personen met knieklachten voldeden al aan de klinische en/of radiografische ACR-criteria voor artrose. Daarom kan worden gesuggereerd dat *first presenters* van 45-65 jaar met heupklachten en ochtendstijfheid, pijnlijke interne rotatie, heupflexie <115 ° en een bezinking van <20, bij wie andere diagnoses zijn uitgesloten, kunnen worden gediagnosticeerd

met heupartrose. *First presenters* in de leeftijd van 45-65 jaar met knieklachten bij wie andere diagnoses zijn uitgesloten, hebben hoogstwaarschijnlijk knieartrose. Deze conclusies en aanbevelingen moeten echter verder worden gevalideerd in andere cohorten, voordat ze kunnen worden geïmplementeerd in de reguliere klinische praktijk.

Hoofdstuk 3 gaat over het onderzoek naar prevalentie en progressie van vroege artrosekenmerken van de heup en de knie op radiologische opnamen (hierna 'radiologische artrose' te noemen), om te bepalen of deze extra waarde hebben bij het detecteren van patiënten met vroege heup- en knieartrose. Ook hebben we onderzocht of progressie vaker werd gedetecteerd bij het gebruik van verschillende radiologische opnamen. Dit onderzoek werd eveneens uitgevoerd met behulp van gegevens uit het CHECK-cohort.

Vijf verschillende röntgenopnamen werden verkregen: een anteroposterior (AP) en faux-profiel van de heupen, en een postero-anterior (PA), mediolateraal (ML) en 'skyline'-aanzicht van de knieën. De prevalentie van radiologische artrose werd geschat op basis van elke opname afzonderlijk en in de verschillende combinaties. We hebben vastgesteld of verschillende röntgenopnamen extra waarde hadden bij het detecteren en bepalen van de radiologische progressie van artrose in vergelijking met de standaardprojecties. Bij een combinatie van beide opnamen constateerden we in de heup bijna 25% meer gevallen van radiologische artrose. Het combineren van de drie verschillende röntgenopnamen van de knie resulteerde, vergeleken met uitsluitend gebruik van de PA-weergave, in 75% meer knieën met radiologische artrose. Radiologische progressie van artrose werd 33% vaker aangetoond bij gebruik van twee heupröntgenopnamen en 65% vaker bij gebruik van de drie knie-röntgenopnamen. Daarom werd geconcludeerd dat het gebruik van verschillende röntgenopnamen de identificatie van deelnemers met radiologische artrose in een cohort van '*first presenters*' met heup- en/of knieklachten in de leeftijd van 45-65 jaar verhoogt, zowel bij aanvang als bij de follow-up. Ook wordt de radiologische progressie van artrose vaker aangetoond wanneer verschillende röntgenopnamen worden gebruikt.

In grote onderzoeken (zoals het CHECK-onderzoek) wordt het scoren van röntgenopnamen uitgevoerd door verschillende lezers.

Daarom berekenden we in **hoofdstuk 4** de interbeoordelaarsbetrouwbaarheid tussen vier getrainde student-beoordelaars en een ervaren huisarts-beoordelaar voor vroege kenmerken van radiologische artrose in ons CHECK-onderzoek naar vroege artrose (cohort heup en cohort knie). Voor het scoren van deze kenmerken werden de vier student-lezers getraind door een musculoskeletaal radioloog en een ervaren huisarts-beoordelaar. Na deze training scoorden de student-lezers het CHECK-cohort. Van de 1.002 deelnemers werden 38 patiënten door alle lezers beoordeeld. Vijf verschillende radiologische opnamen (drie voor de knie, twee voor

de heup) werden op drie verschillende tijdstippen gescoord en vergeleken. De onderlinge betrouwbaarheid van de beoordelaars werd door ieder van de vier getrainde lezers met de ervaren lezer geëvalueerd. We beoordeelden zowel de afzonderlijke kenmerken van radiologische artrose als de samengestelde scores voor de mate van artrose volgens Kellgren en Lawrence (K&L). Daarnaast werd de betrouwbaarheid van de radiologische progressie van artrose bepaald met behulp van de K&L-scores en de vernauwing van de gewrichtsspleetruimte of *joint space narrowing* (JSN).

Voor zowel de heup als de knie was de onderlinge betrouwbaarheid van de waarnemers aanzienlijk voor de algemene K&L-scores. Voor de knie werd JSN gescoord met redelijke tot matige betrouwbaarheid, osteofyten met matige tot bijna perfecte betrouwbaarheid en de overige kenmerken met redelijke tot aanzienlijke betrouwbaarheid. Voor de heup varieerde de betrouwbaarheid van substantieel tot bijna perfect. Matige interbeoordelaarsbetrouwbaarheid werd gevonden voor de radiologische progressie van artrose in zowel de heup als de knie, met iets betere betrouwbaarheid voor progressie op basis van de K&L-scores dan op de afzonderlijke kenmerken. Er werd geconcludeerd dat een goede interbeoordelaarsbetrouwbaarheid kan worden bereikt tussen getrainde student-beoordelaars en een ervaren huisarts-beoordelaar.

Prognose van artrose

Het natuurlijk beloop van verschillende soorten radiologische artrose in de knie is beschreven in **hoofdstuk 5**. Hiervoor werden 845 deelnemers van middelbare leeftijd met knieklachten uit het CHECK-onderzoek 5 jaar lang gevolgd. Deelnemers met geïsoleerde patellofemorale artrose (PFA) werden vergeleken met deelnemers met tibiofemorale artrose (TFA). Op baseline hadden 116 deelnemers PFA en niemand had geïsoleerde TFA of gecombineerde patellofemorale/tibiofemorale artrose (CA). Van deze 116 deelnemers met PFA had 66,3% na 5 jaar follow-up CA ontwikkeld. Tijdens de 2 jaar durende follow-up waren PFA, TFA en CA aanwezig in respectievelijk bijna 11%, in 6% en 12% van de deelnemers. Bij het vergelijken van deelnemers met PFA of TFA vertoonden multivariate regressieanalyses geen significante verschillen met betrekking tot symptomen. Deze resultaten suggereren dat radiologische artrose meer kans heeft om te ontstaan in het patellofemorale gewricht en zich vervolgens uit te breiden naar het tibiofemorale gewricht bij personen met symptomen van beginnende knieartrose. Evenzo werden bij het vergelijken van deelnemers met de PFA- en TFA-fenotypen geen significante verschillen gevonden met betrekking tot symptomen.

In het onderzoek in **hoofdstuk 6** werd beoordeeld of de aanvullende radiologische röntgenopnamen in verschillende richtingen (die aanvullende gevallen van radiologische artrose identificeerden) een voorspellende waarde hadden voor het beloop van de pijnklachten. Daarom hebben we verschillende combinaties van röntgenopnamen van de heupen (anteroposterior (AP) en faux-profiel) en de knieën (postero-anterior (PA), mediolateraal (ML) en skyline-

aanzicht) gebruikt. Voor deze combinaties van röntgenopnamen hebben we vastgesteld of ze ook voorspellend waren voor de verschillende pijntrajecten die werden gevonden met behulp van *latent class growth analysis* gedurende 5 jaar follow-up in het CHECK-onderzoek. Voor de heup maakten combinaties van opnamen geen onderscheid tussen pijnpatronen. Patiënten met knieklachten hadden bij het combineren van de radiologische artrose op basis van alle röntgenopnamen (K&L graad ≥1 op de PA-weergave, ≥1 osteofyt op de mediolaterale weergave en ≥1 osteofyt en/of JSN ≥1 op de skylineweergave) minder kans op een afnemend pijntraject, afgezet tegen een stabiel pijntraject (OR 0,53; 95% CI 0,30-0,94). Omdat het effect echter klein was, kunnen we het gebruik van gecombineerde röntgenopnamen op grond van dit onderzoek niet aanbevelen om toekomstige pijn te voorspellen.

Hoofdstuk 9 gaat in op de subgroep van deelnemers met snel voortschrijdende symptomen van artrose in het CHECK-cohort. Deze snelle progressie werd gedefinieerd als een gewrichtsvervanging in de eerste 6 jaar na presentatie van de symptomen. Een gewrichtsvervanging wordt vaak beschouwd als de eindfase van artrose. In deze eerste 6 jaar werden 62 heupvervangingen en 22 knievervangingen uitgevoerd. Deelnemers die een gewrichtsvervanging van de heup ondergingen hadden op baseline vaker pijn bij endorotatie van de heup en hadden meer radiologische artrosekenmerken. Deelnemers die een gewrichtsvervanging van de knie ondergingen hadden op baseline een hogere BMI en vaker pijn bij knieflexie. Zij hadden ook meer radiologische artrosekenmerken op baseline. Zowel in de heup- als de kniegroep zagen we meer radiologische progressie van de artrose tijdens de eerste twee jaar van de follow-up.

Andere oorzaken van pijn bij artrose

Niet alle pijn in de heup ontstaat in het heupgewricht zelf. Lage rugpijn kan bijvoorbeeld leiden tot pijn in de heup. In **hoofdstuk 7** onderzochten we factoren waarvan bekend is dat ze geassocieerd zijn met pijn in de heup, voortkomend uit de lumbale wervelkolom. Daarom onderzochten we het verband tussen heuppijn en artrose van de lumbale wervelkolom. In de *Rotterdam Study* (een openpopulatieonderzoek onder personen van 55 jaar en ouder) werden 2.819 lumbale röntgenopnamen gescoord op aanwezigheid en ernst van individuele radiologische kenmerken van artrose. Radiologische artrose werd gescoord op AP-röntgenopnamen en vragenlijsten (met onder meer aandacht voor zelf gerapporteerde heuppijn) werden ingevuld. Aangetoond werd dat de aanwezigheid van een versmalling van de tussenwervelruimte ≥1 op niveau L1/L2 significant geassocieerd was met heuppijn (bij mannen OR = 2,0; bij vrouwen OR = 1,7). De aanwezigheid van tussenwervelruimteversmalling ≥1 op niveau L2/L3 was significant geassocieerd met kortdurende pijn bij vrouwen. De sterkte van de associaties nam toe bij zelf gerapporteerde chronische heuppijn, vooral bij mannen (L1/L2 OR = 2,5). De aanwezigheid van tussenwervelruimteversmalling op de lagere niveaus (L3/L4 /L5/S1) was niet significant geassocieerd met heuppijn. Daarom concludeerden we dat er

aanwijzingen zijn voor een verband tussen heuppijn en tussenwervelruimteversmalling op schijfniveau L1/L2 en L2/L3. In geval van onzekerheid over de oorzaak van heuppijn, moet lumbale artrose worden overwogen.

Het onderzoek in **hoofdstuk 8** was gericht op de vraag of genetische variatie in het GTP-cyclohydrolase 1-gen (GCH1) en de bijbehorende promotor gepaard gaat met zelfgerapporteerde pijn in heup, knie en hand en met chronische diffuse pijn, aangezien pijnrapportage sterk verschilt tussen individuen. In de *Rotterdam Study* werd dit ook onderzocht bij de deelnemers van wie genotype en zelf gerapporteerde pijngegevens beschikbaar waren. We bestudeerden 15 puntmutaties van het DNA in de buurt van het GCH1-gen en alle gangbare (> 5% allelfrequentie) genetische variatie in dat gebied. Pijn in de heup, knie en hand werd gedefinieerd als pijn in de maand voorafgaand aan het interview. Chronische (d.w.z. langer dan 6 maanden aanhoudende) diffuse pijn werd gedefinieerd volgens de ACR-criteria voor diffuse pijn, met twee kleine aanpassingen. Logistische regressiemodellen werden gebruikt om het risico op pijn door polymorfisme te modelleren. Een polymorfisme (rs8007267, allelfrequentie 15%), in de buurt van het GCH1-gen, was geassocieerd met pijn in heup, hand en knie. In vergelijking met C-dragers hadden homozygote T-individuen een 45% en 49% verlaagd risico op respectievelijk heuppijn en handpijn. Kniepijn vertoonde een trend in dezelfde richting (OR = 0,74). Voor het diffuse pijnfenotype (betwistbaar het meest invaliderende fenotype van alle vier), was de kans nog groter voor de T-allelhomozygoten. Dit onderzoek toonde aan dat een variant van het GCH1-gen geassocieerd is met de aanwezigheid van pijn in verschillende gewrichten en diffuse pijn.

Hoofdstuk 10, tot slot, bespreekt de belangrijkste bevindingen en bestudeert mogelijke implicaties voor zowel de klinische praktijk als toekomstig onderzoek.

BIOGRAFIE

Jurgen Damen is geboren op 17 augustus 1980 te Sliedrecht. In 1999 behaalde hij zijn vwo-diploma aan het Titus Brandsma College in Dordrecht. Aansluitend begon hij aan de geneeskunde-opleiding aan het Erasmus MC te Rotterdam, die hij zes jaar later succesvol afrondde. Daarna werkte hij als anios ouderenpsychiatrie bij Rivierduinen Gouda. In 2006 startte hij met de huisartsopleiding aan het Erasmus MC, waar hij in het eerste jaar werd opgeleid door Mieke Derksen en Filian Looman, in Ommoord. In 2007 begon hij aan een aiotho-traject (arts in opleiding tot huisarts en onderzoeker), waarvoor hij in 2008 een Master of Science in Clinical Epidemiology aan het Netherlands Institute for Health Sciences (NIHES) Rotterdam behaalde. Als promovendus op de afdeling Huisartsgeneeskunde werkte hij aan het in dit proefschrift beschreven Cohort Hip and Cohort Knee-onderzoek (CHECK). Het laatste jaar van de opleiding genoot hij bij Hans Ponten in Nieuw- en Sint Joosland en Middelburg. Tussen 2012 en 2015 had hij zitting in het wetenschappelijk comité van de European League against Rheumatism (EULAR), alwaar hij medeverantwoordelijk was voor de *Primary care tract*.

Sinds 2013 is Jurgen in dienst bij het Erasmus MC, waar hij praktische vaardigheden onderwijst aan bachelor- en masterstudenten geneeskunde. Voor *Huisarts en Wetenschap* schrijft hij regelmatig nieuwsberichten. Na in diverse praktijken te hebben waargenomen, werkt hij sinds 2018 als huisarts in Gezondheidscentrum Katendrecht. Jurgen woont samen met Christine en zijn dochter Madelief in Rotterdam

PHD PORTFOLIO

Year	Activity and or title	ECTS
PhD training		
2007-2008, NIHES institute, Rotterdam	Master of Science in Clinical Epidemiology	70
2006-2010, Department of General Practice Erasmus MC, Rotterdam	Vocational training for general practitioner	
2016-2018	University Teaching Qualification	10
Conferences		
EULAR 2008, Paris	Poster presentation: 'Prognostic Factors in joint complaints in the elderly'	1
Wonca 2009, Basel	Poster presentation: 'Prognostic Factors in joint complaints in the elderly'	1
CHECK symposium 2009	Oral presentation: 'Assessment of radiographic features in CHECK'	2
NHG Wetenschapsdag 2010	Poster presentation: Hip pain and radiological features in the lower back	1
EULAR 2011, Londen	Poster presentation: The Diagnostic accuracy of range of motion measurements in early hip and/or knee osteoarthritis results from the check study. Oral presentation: Clinical Challenge, hip pain in the elderly patient	3
EULAR 2012 Berlin	Key note lecture. What can rheumatologists learn from the GP?	3
EULAR 2015, Rome	Key note lecture Who Cares? Primary care perspective	3
OARSI 2016, Amsterdam	Poster presentation: Early radiographic osteoarthritis prevalence and progression determined with different view radiographs of the hip and knee: the CHECK study.	1
NVMO 2016, Egmond aan Zee	Poster presentation, Effect of structured feedback on examination result.	1
NVMO 2018, Egmond aan Zee	Poster presentation Professionalism during a high stake exam	1

Year	Activity and or title	ECTS
Teaching		
2012-2013	Teaching clinical reasoning to bachelor Medicine students	3
2015	Supervising research project medical student 'Shape characteristics of the tibial tubercles, promising for the early detection of knee osteoarthritis'	10
2013-2017	Teaching / supervising, Radiographic scoring of the CHECK cohort	10
2015-2017, Bachelor Medicine Erasmus MC, Rotterdam	Teaching workshop 'Treatment of osteoarthritis.' To bachelor Medicine students	3
2014-2018	Teaching history taking and physical examination in bachelor and master	
Scientific Committee		
Eular 2010-2014	Scientific committee of EULAR, subcommittee: 'Primary care and rheumatology'	50

LIST OF PUBLICATIONS
THIS THESIS:

1. **Damen J**, Runhaar J, Kloppenburg M, Meijer R, Bierma-Zeinstra SMA, Oei EHG Additional Value of Different Radiographic Views on the Identification of Early Radiographic Hip and Knee Osteoarthritis and Its Progression: A Cohort Study.Arthritis Care Res (Hoboken). 2017 Nov;69(11):1644-1650.

2. **Damen J**, Schiphof D, Wolde ST, Cats HA, Bierma-Zeinstra SM, Oei EH. Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (cohort hip and cohort knee) study.Osteoarthritis Cartilage. 2014 Jul;22(7):969-74.

3. Lankhorst NE, **Damen J**, Oei EH, Verhaar JAN, Kloppenburg M, Bierma-Zeinstra SMA, van Middelkoop M. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study. Osteoarthritis Cartilage. 2017 May;25(5):647-653.

4. de Schepper EI, **Damen J**, van Meurs JB, Ginai AZ, Popham M, Hofman A, Koes BW, Bierma-Zeinstra SM. The association between lumbar disc degeneration and low back pain: the influence of age, gender, and individual radiographic features. Spine (Phila Pa 1976). 2010 Mar 1;35(5):531-6.

5. **Damen J**, van Rijn RM, Emans PJ, Hilberdink WKHA, Wesseling J, Bierma-Zeinstra SMA. Predictive factors for hip and/or knee osteoarthritis according to ACR criteria.Definition of osteoarthritis in CHECK. Arthritis Research & Therapy.(2019) Jan;21(1).

6. Bastick AN, **Damen J,** Agricola R, Brouwer RW, Bindels PJ, Bierma-Zeinstra SM. Characteristics associated with joint replacement in early symptomatic knee or hip osteoarthritis: 6-year results from a nationwide prospective cohort study (CHECK). Br J Gen Pract. 2017 Oct;67(663):e724-e731.

OTHER PEER REVIEWED PUBLICATIONS:

1. Bastick AN, Verkleij SP, **Damen J**, Wesseling J, Hilberdink WK, Bindels PJ, Bierma-Zeinstra SM. Defining hip pain trajectories in early symptomatic hip osteoarthritis--5 year results from a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage. 2016 May;24(5):768-75

2. Bastick AN, Wesseling J, **Damen J**, Verkleij SP, Emans PJ, Bindels PJ, Bierma-Zeinstra Defining knee pain trajectories in early symptomatic knee osteoarthritis in primary care: 5-year results from a nationwide prospective cohort study (CHECK). SM.Br J Gen Pract. 2016 Jan;66(642):e32-9.

3. de Schepper EI, **Damen J**, van Meurs JB, Ginai AZ, Popham M, Hofman A, Koes BW, Bierma-Zeinstra SM. The association between lumbar disc degeneration and low back pain: the influence of age, gender, and individual radiographic features. Spine (Phila Pa 1976). 2010 Mar 1;35(5):531-6.

4. Holla JF, van der Leeden M, Roorda LD, Bierma-Zeinstra SM, **Damen J**, Dekker J, Steultjens MP. Diagnostic accuracy of range of motion measurements in early symptomatic hip and/or knee osteoarthritis. Arthritis Care Res (Hoboken). 2012 Jan;64(1):59-65.

5. Schiphof D, Kerkhof HJ, **Damen J**, de Klerk BM, Hofman A, Koes BW, van Meurs JB,Bierma-Zeinstra SM. Factors for pain in patients with different grades of knee osteoarthritis. Arthritis Care Res (Hoboken). 2013 May;65(5):695-702.

6. Vos PA, Welsing PM, deGroot J, Huisman AM, Oostveen JC, Reijman M, **Damen J**, Mastbergen SC, Lafeber FP. Skin pentosidine in very early hip/knee osteoarthritis (CHECK) is not a strong independent predictor of radiographic progression over 5 years follow-up. Osteoarthritis Cartilage. 2013 Jun;21(6):823-30.

7. Otters H, Schellevis FG, **Damen J**, van der Wouden FG, van Suijlekom-Smit LW, Koes BW. Epidemiology of unintentional childhood injury: a population based survey in general practice. Br J Gen Pr 2005 Aug;55(517):630-3

MISCELLANEOUS PUBLICATIONS:

1. Krul M, **Damen J**, van der Wouden JC. Vitamin E Concentration and Physical Decline in Older Persons, letter to the editor, JAMA 2008 May;17(299):2021

2. Bastick AN, Wesseling J, **Damen J**, Verkleij SP, Emans PJ, Bindels PJ, Bierma-Zeinstra SM Pain trajectories in early symptomatic knee osteoarthritis.Ned Tijdschr Geneeskd. 2016;160:D449.

3. **J Damen**, Zien roken doet roken (2). Tijdschrift voor praktijkondersteuning. Tijdschrift praktijkondersteuning 2009 Juni p61

4. **J Damen**. Krachttraining verbetert het fysiek functioneren van ouderen een beetje Huisarts en Wetenschap, jaargang 2009, nummer 13:688-688

5. van Es P, **Damen J**, Runhaar J. author reply 93. Comments on "Efficacy of neck stabilization exercises for neck pain" and Response to Letter to the Editor by van Es et al.J Rehabil Med. 2010 Jan;42(1):93;

6. **J Damen**. Kansen in de behandeling van knie- en heupartrose. Huisarts en Wetenschap, 2011; (5):233-233

7. **J Damen**, M Krul. Moeten we pre-diabetes behandelen? Huisarts en Wetenschap,2011;(2): 54-55

8. Alderliefste GJ, **Damen J**. Partydrugsgerelateerde klachten. Huisarts Wet 2018;61.

DANKWOORD

Het is klaar. Dit proefschrift is het resultaat van lang werken. Tijdens deze periode hebben velen mij geholpen, waarvoor ik erg dankbaar ben. Een aantal van hen wil ik hier in het bijzonder bedanken. Diegenen met wie ik het in de eerste uren van mijn promotie over mijn dankwoord heb gehad, wil ik vertellen dat dit onderdeel van het proefschrift valt onder de noemer 'voortschrijdend inzicht'.

Sita, bedankt voor al je tomeloze inspiratie bij het onderzoek, in het bijzonder op het gebied van artrose. De afgelopen jaren heb ik langs de zijlijn een aantal van je hoogtepunten mogen meemaken. Dat ik niet alleen sta in mijn bewondering valt te onderbouwen: je bent niet voor niets uitgeroepen tot promotor van het jaar 2013. Ook je leerstoel artrose geeft blijk van je kunde. Altijd opnieuw weet je weer kritisch te kijken naar eerder werk zonder daarmee in cirkels te lopen.

Edwin, je bent iets later aangesloten in het traject. Op het moment dat ik een duwtje in de rug nodig had, was jouw kritische blik bijzonder behulpzaam. Dank ook voor je hulp bij de analyse van alle foto's in CHECK. Afgezien van je wetenschappelijke inbreng heb ik je leren kennen als een taalpurist. Voor een matig schrijver als ik was dat soms frustrerend, maar ik heb er heel wat van geleerd.

Dan de overige commissieleden, professor Krestin, professor Ribbers en professor Burgers: van harte bedankt voor het snelle doornemen van mijn proefschrift en het goedkeuren daarvan.

Mijn dank gaat daarnaast natuurlijk uit naar alle deelnemers en de betrokken centra van de CHECK-studie, voor de flinke bijdrage die gezamenlijk is geleverd aan de wetenschap. De CHECK-bijeenkomsten heb ik als waardevol ervaren, niet in de laatste plaats door de actieve bijdrage van de deelnemers.

Beste Bellal, Kerime, Femke, Burçu, Lisanne, Murat, Elselien, Heleen en Niels, jullie inzet was onmisbaar bij het scoren van alle röntgenfoto's in CHECK. Dank daarvoor.

Hans van der Wouden, waar een Mars allemaal niet toe kan leiden! Bedankt dat je me naar de afdeling hebt gelokt. Met Hanneke mocht ik onderzoek leren doen naar ongelukken bij kinderen en kreeg ik een kijkje in de aiotho-keuken.

Een aiotho-constructie maakt deel uit van de opleiding. Voor de adviezen rond het traject wil ik René bedanken: je bent een van de drijvende krachten voor de aiotho's, ook in de manier waarop je ze betrekt bij een vervolg in onderwijs en onderzoek. Mieke, Filian en Hans, bedankt voor de wijsheid,

ondersteuning en voor de heerlijke jaren in jullie praktijken. Ik heb veel van jullie geleerd. Daarnaast wil ik al mijn mede-huisartsen in opleiding, groepsbegeleiders, ROVAH-bestuursgenoten en het landelijk aiotho-netwerk bedanken voor alle inspiratie tijdens de opleiding.

Een promotie gaat om meer dan alleen publiceren, de wetenschappelijke ontwikkeling in bredere zin heb ik wellicht (te) letterlijk opgevat. Maar toch wil ik mijn dank uitdrukken voor een aantal intermezzo's.

Nogmaals dank aan Sita en Jan omdat jullie aan mij dachten toen de vraag kwam of er een huisarts kon meedenken in een werkgroep voor EULAR.

Many thanks for my colleagues in the EALAR primary care committee, Elaine, Stefan, Fernando and Anne Marie. It was inspiring to think about how we could involve primary care in such a secondary care scientific group. Many thanks for all our meetings across Europe and three wonderful primary care side tracks. Thank you Elaine for reminding Sita I had to speed up. Stefan, *tack* for showing me your wonderful country and primary care research center. Muchas gracias a Fernando por la invitación a dar una conferencia en la Universidad Francisco de Vitoria, y para hacer varios excursiones turísticas cerca de Madrid, me encanté!

En toen was er de Roparun. Geïnspireerd door eerdere deelname van de afdeling hebben Jos en ik de uitdaging aangenomen en met veel enthousiasme en plezier zijn we met team 319 (Hanneke, René, Jantine, Ellen, Toke, Diana, Marienke, Alex, Judith, Marieke, Jos, Evelien, Marjolein, Michiel, Bart, Frits, Yvonne, David, Manuel, Desiree, Thérèse, Monique) van Parijs naar Rotterdam gerend, gereden en gefietst. Het was een mooi feest. Heel veel dank voor dit intermezzo!

Bijna nergens komen de praktijk en wetenschap meer bij elkaar dan in onze Journal club. De bijeenkomsten zijn steeds weer een feest. Elena en Tineke, bedankt dat jullie dit mee hebben opgezet. Daniel: no-nonsens, gevoelsmens, al mindful voor we wisten wat het was en voordat er wetenschappelijk bewijs voor was, ik ben blij dat ik je ken. Marjolein: gepassioneerd huisarts, theaterdier, 'doe maar even gewoon' en haarfijn zwakheden in literatuur weten te vinden. Behalve lid van de Journal club was je mijn aiotho-maatje van het eerst uur, ik ben blij dat we elkaar zijn tegengekomen. Evelien, je bent onze laatste aanwinst voor de Journal club, en wat voor een: je kennis van het vak is indrukwekkend, je hebt altijd de laatste ontwikkelingen voor ogen en deelt mijn liefde voor onderwijs. Leuk dat we elkaar ook in het Erasmus MC mogen treffen. Stefan, achter je lach en vrolijkheid misschien wel het meest serieus in de Journal club, hongerig naar saaie standaarden en degene die met de meeste succesverhalen over veranderingen in de praktijk terugkomt. Achter jouw rug fiets ik de hoogste toppen over, fijn dat je vandaag naast me staat.

Na een jarenlang intermitterend verblijf op de afdeling is het onmogelijk om iedereen persoonlijk te noemen. Graag wil ik een aantal mensen toch met naam en toenaam bedanken: Rianne, kamergenoot van het eerste uur, leuk dat ik je weer tegenkom bij PRIMEUR. Dieuwke, ook jij stamt nog uit de 'geheime kamer'. Bedankt dat je me door de NIHES hebt geholpen: je was in die tijd een grote steun en toeverlaat. Jos, rasonderzoeker en organisator, het was mooi om samen met jou de Roparun te doen. Samen met Jasper was het erg ontspannend om af toe een tafeltennistoernooi te spelen en over sport te praten.

Ontspanning houdt de geest scherp. Voor alle kilometers die we gedraaid hebben, wil ik graag de vaste groep van de gestolen overwinning bedanken: Eric, Rob, Dirk, bedankt voor alle ontsnappingen aan een drukke periode. Vanzelfsprekend kan ik ook de reus van de Marslaan niet vergeten: René, trouwe fietsvriend, nu ben ik, voorlopig, 'klaar' met studeren (maak je borst maar nat).

Fabian, van onschatbare waarde zijn onze maandagavonden: het doet me goed dat je er elke keer weer bent. Dat er nog maar veel slechte films en dus goede gesprekken mogen volgen.

Marianne, lieve Mar, jij bent er altijd. Het zou onderzocht moeten worden hoe vriendschappen kunnen intensiveren bij een toenemende afstand. Je heb ruimschoots gewonnen: jij was eerder psychiater dan ik gepromoveerd. Met jou is het altijd goed. Samen met jouw Bebek hoop ik nog vaak van ons geliefde Berlijn te genieten.

Al mijn huidige collega's op Katendrecht en van de afdeling PKV helpen mij om de combinatie praktiserend onderwijs en wetenschap vol te houden: dank voor jullie flexibiliteit. Willemijn, dank voor je actieve rol in deze combinatie.

Het thuisfront, ten slotte, is de onmisbare steun van iedere promovendus. Pa, ma, zus(ter), hier sta ik dan, bedankt dat jullie hebben geholpen met de opvang van Madelief.

Lieve schoonfamilie, dank voor alle ontspanning en liefde op de berg, in Friesland en Amsterdam.

Lieve Madelief het is eindelijk zover, we trekken onze mooiste kleren uit de kast, nemen een dag vrij, hangen de slingers op en vieren een feestje. Het is een wonder om te zien hoe je ouder en wijzer wordt: ik geniet van je. Ik ben trots om je vader te zijn.

Christine, het is klaar. Misschien was het met jouw onuitputtelijke positieve energie eerder af geweest. Waarschijnlijker hadden we die energie dan toch geïnvesteerd in vakanties andere dingen die het leven mooi maken. Dank voor je geduld. Met jou is de wereld mooier, ik hou van je.

Different Perspectives on Diagnosis and Prognosis of Hip and Knee Osteoarthritis in Primary Care.

With the aging of the population, osteoarthritis is an increasing challenge for health care worldwide. Although osteoarthritis is the most frequently diagnosed joint disorder in primary care, no clear diagnostic set of criteria are available for primary care. The overall aim of the work in this thesis was to identify early OA criteria for epidemiological research in primary care, and to establish the usefulness of radiographic signs widely used in epidemiological research and clinical practice.