PAIN, COURSE AND TREATMENT OF OSTEOARTHRITIS IN PRIMARY CARE

Pijn, beloop en behandeling
van artrose in de huisartsenpraktijk

Saskia Pauline Jantina Verkleij

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Pijn, beloop en behandeling van artrose in de huisartsenpraktijk

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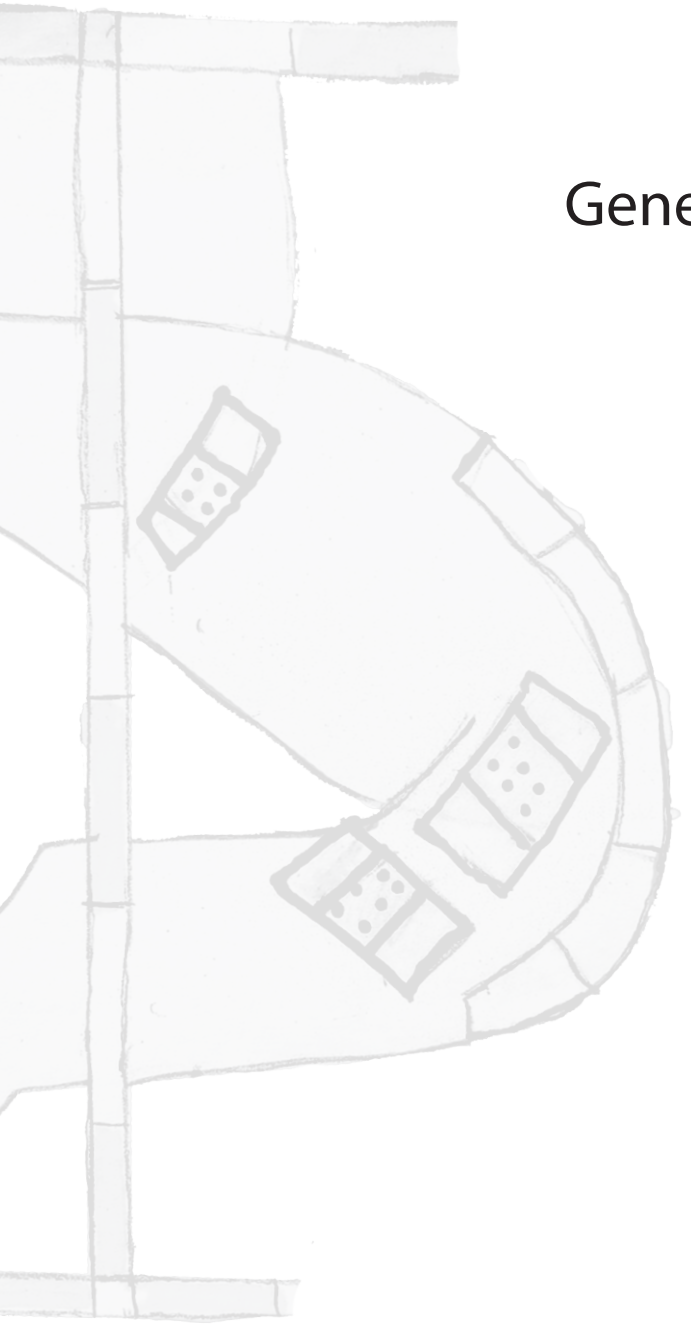
CONTENT



CHAPTER 1

General introduction

Osteoarthritis

Osteoarthritis (OA) is the most frequently occurring joint disease and causes pain and functional disability in middle-aged and elderly persons.[1-4] The knee and hip are the most likely joints to suffer disability, with knee OA being more prevalent than hip OA.[3,5] It is estimated that the worldwide prevalence of OA is 9.6% for men and 18% for women aged 60 years and over.[3] Because the prevalence of OA increases with age,[3] the incidence of OA will rise even further in the coming years due to the ageing of the population. This will have a considerable impact on society in general and healthcare costs in particular.[4,6]

Etiology and diagnosis

OA affects the whole joint and is most often characterized as loss of articular cartilage within the synovial joint, the presence of osteophytes, and subchondral sclerosis.[3] Pain due to OA is known to be of multifactorial origin, but its precise etiology is still unknown. There is evidence that bone marrow lesions and joint effusions are associated with knee pain. In addition, there is conflicting evidence for the association between pain and cartilage defects, meniscal lesions and bone attrition.[7]

The presence of OA is mostly determined by clinical findings. The American College of Rheumatology provided classification trees for both hip and knee OA.[8,9] For the knee, the classification tree consists of having knee pain and three or more of the following: age > 50 years, morning stiffness < 30 minutes, crepitus on active motion, tenderness of the bony margins of the joint, bony enlargement noted on examination and a lack of palpable warmth of the synovium8. For the hip, the classification tree consists of having hip pain and fulfilling one of the following: 1) hip internal rotation of < 15 degrees and hip flexion of ≤ 115 degrees or 2) hip internal rotation of ≥ 15 degrees, pain on internal hip rotation, morning stiffness of the hip ≤ 60 minutes and age > 50 years.[9]

Although the clinical criteria alone are sufficient to diagnose OA,[10] radiographs are often taken to confirm the presence of OA. This radiographic examination takes place even though it is not part of routine care in the Netherlands,[11] and despite that agreement between clinical symptoms and findings on radiographs are reported to be low.[12] The presence of radiographic OA is most often determined using the Kellgren and Lawrence (K&L) classification criteria.[13] These criteria classify OA into 5 grades: grade 0 (none); grade 1 (doubtful); grade 2 (minimal OA); grade 3 (moderate OA); grade 4 (severe); based on the presence of joint space narrowing, osteophytes, sclerosis and deformity of bone ends.[13] To further simplify the presence of OA it is often divided into no OA/possible OA (grade ≤ 1) and mild/definite OA (grade ≥ 2).

A relatively new method to diagnose OA or visualize abnormalities within the joint due to OA, is magnetic resonance imaging (MRI). MRI allows to visualize more structures than on radiographs. Moreover, MRI visualizes structural damage or lesion joint damage earlier than is seen on radiographs.

Pain

Pain is the most common complaint in OA and an important reason for seeking medical care. It is often used as the primary outcome in clinical trials assessing the effectiveness of treatments in OA. Different questionnaires to measure pain due to OA are available. The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), the Knee Osteoarthritis Outcome Score (KOOS) and the Hip Osteoarthritis Outcome Score (HOOS) are most often used and recommended by the OMERACT.[14] Other frequently used pain questionnaires are the Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS); both are reported to be effective and understandable for measuring pain in OA.[15] One recently developed questionnaire identifies the presence of Intermittent and Constant Osteoarthritis Pain (ICOAP).[16]

The WOMAC pain subscale measures pain during a wide range of activities in daily living (e.g. pain during walking, standing, stair climbing, pain at rest and at night).[17] A previous study proposed to classify these pain items according to homogeneity into: weight-bearing pain (pain during walking, standing and stair climbing) and non-weight-bearing pain (pain at rest and at night).[18] In this thesis, weight-bearing pain and non-weight-bearing pain were used to establish whether they were related to MRI features of the knee.

In most trials, pain severity reported by patients slowly deteriorates over time regardless of the treatment.[19,20] However, individual pain can vary greatly over time.[4,21,22] Identifying distinct pain trajectories and its predictors is important to provide patients with a more individually-tailored treatment in OA. One study reported four such trajectories in patients with hip/knee OA;[23] that study identified trajectories with cluster analysis using the maximum absolute first difference, the slope, the proportion of variance R^2 explained by the linear model, and the ratio of the maximum absolute second difference to the mean over time.[23] Cluster analysis is a relatively restrictive method to identify subgroups of patients. In this thesis, a less restrictive technique, i.e. latent class growth analysis, was used to reveal distinct trajectories of pain over multiple time points in patients with hip OA.

Treatment

Since disease-modifying OA treatments are lacking, treatment options are mainly symptom driven and consist of pharmacological and non-pharmacological therapies. They are focused on alleviating pain, maintenance of activities in daily life, enhancing quality of life and postponing the moment of total joint replacement.

Recommended non-pharmacological therapies include education, exercises coached by physiotherapists and the provision of walking aids.[24] With pharmacological therapies, current guidelines for non-traumatic knee complaints recommend acetaminophen as the medication of first choice (when medication for OA is indicated) because it has a better safety profile.[11,24,25] However, it has been shown that non-steroidal anti-inflammatory drugs (NSAIDs) were more effective (albeit a modest improvement) than acetaminophen.[26] In the Netherlands, the general practitioner

(GP) is the initial caregiver in OA. Despite the general consensus to use acetaminophen with OA, NSAIDs are still often prescribed in primary care OA patients. The GP might be more confident in prescribing acetaminophen in the knowledge of the mutual effectiveness of acetaminophen and NSAIDs in primary care OA patients. In addition, patients in clinical practice are often familiar with the prescribed medication, which is accompanied by certain expectations. In this situation, a pragmatic trial which (as far as possible) reflects daily practice will inform GPs about the differences in effectiveness that they can expect and can help them to adequately inform their patients. Therefore, this thesis presents the results of a pragmatic randomized controlled trial that was performed to provide the GP with more evidence-based information about the effectiveness of an NSAID versus acetaminophen in daily practice for patients with knee OA.

A drawback of earlier OA studies is that there are many differences in trial design and methodology, inclusion criteria and outcomes. For instance, most studies include only highly selected patients already using NSAIDs and needing a wash-out period, or even a flare of symptoms, prior to randomization. Furthermore, most studies used different medications or dosages, different pain questionnaires and/or received industry funding. Such differences can influence the magnitude of the outcome of these studies. Therefore, this thesis also focus on the heterogeneity between studies in relation to the outcomes of these particular studies.

Aims and outline of this thesis

The overall goal of the work presented in this thesis is to improve our understanding of the reported severity of pain due to OA. The first part of this thesis aims at improving the evidence-based information regarding pain medication used in OA. Chapter 2 presents the study design of a pragmatic open-label randomized-controlled trial conducted among 104 patients with knee OA. This study was performed in Dutch general practices during 2009 and 2011. The outcomes of this trial are described in Chapter 3. In Chapter 4, we present the results of a systematic review assessing the heterogeneity in studies evaluating NSAIDs versus acetaminophen in patients with knee and hip OA.

The second part of this thesis focuses on the course and etiology of patients' reported pain severity. Chapters 5 and 6 describe longitudinal pain trajectories of patients with hip OA. Chapter 7 reports on the specific features of the knee assessed with MRI and its associations with both weight-bearing and non-weight-bearing knee pain. Finally, Chapter 8 discusses the main results of our findings and the clinical implications for further research.

REFERENCES

1. **Felson DT**, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, et al. Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med* 2000;133:726-737.
2. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-97.
3. **Woolf AD**, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-656.
4. **Buckwalter JA**, Martin JA. Osteoarthritis. *Adv Drug Deliv Rev* 2006;58:150-167.
5. **Quintana JM**, Arostegui I, Escobar A, Azkarate J, Goenaga JI, Lafuente I. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. *Arch Intern Med* 2008;168:1576-1584.
6. **Reginster JY**. The prevalence and burden of arthritis. *Rheumatology (Oxford)* 2002;41 Supp 1:3-6.
7. **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;70:60-67.
8. **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.
9. **Altman R**, Alarcon 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;34:505-514.
10. **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.
11. **Belo JN**, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F. NHG-Standaard niet-traumatische knieproblemen bij volwassenen. *Huisarts en Wetenschap* 2008;51:229-240.
12. **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.
13. **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
14. **Bellamy N**, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;24:799-802.
15. **Hawker GA**, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S240-252.
16. **Hawker GA**, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:415-422.
17. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
18. **Stratford PW**, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266-272.

19. **Dieppe P**, Cushnaghan J, Tucker M, Browning S, Shepstone L. The Bristol 'OA500 study': progression and impact of the disease after 8 years. *Osteoarthritis Cartilage* 2000;8:63-68.
20. **van Dijk GM**, Dekker J, Veenhof C, van den Ende CH, Carpa Study G. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. *Arthritis Rheum* 2006;55:779-785.
21. **Hutchings A**, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *J Rheumatol* 2007;34:2291-2300.
22. **Paradowski PT**, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. *Health Qual Life Outcomes* 2005; 3:59.
23. **Leffondre K**, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *J Clin Epidemiol* 2004;57:1049-1062.
24. **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981-1000.
25. **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, 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;62:1145-1155.
26. **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006:CD004257.

CHAPTER 2

Effectiveness of diclofenac versus acetaminophen in primary care patients with knee osteoarthritis: NTR1485, DIPA-trial: design of a randomized clinical trial

S.P.J. Verkleij, P.A.J. Luijsterburg, B.W. Koes, A.M. Bohnen,S.M.A. Bierma-Zeinstra
BMC Musculoskeletal Disorders 2010, 11:7.

ABSTRACT

Background: Osteoarthritis is the most frequent chronic joint disease which causes pain and disability of especially hip and knee. According to international guidelines and the Dutch general practitioners guidelines for non-traumatic knee symptoms, acetaminophen should be the pain medication of first choice for osteoarthritis. However, of all prescribed pain medication in general practice, 90% consists of non-steroidal anti-inflammatory drugs compared to 10% of acetaminophen. Because general practitioners may lack evidence showing a similar efficacy of acetaminophen and non-steroidal anti-inflammatory drugs, we present the design of a randomized open-label trial to investigate the effectiveness of a non-steroidal anti-inflammatory drugs (diclofenac) compared with acetaminophen in new consulters with knee osteoarthritis in general practice.

Methods/design: Patients aged 45 years or older consulting their general practitioner with non-traumatic knee pain, meeting the clinical American College of Rheumatology criteria and with a pain severity score of 2 or higher (on a 0-10 scale), will be randomly allocated to either diclofenac (maximum daily dose of 150 mg) or acetaminophen (maximum daily dose of 3000 mg) for 2 weeks and, if required, an additional 1-2 weeks, with a total follow-up period of 12 weeks. The primary outcomes are knee pain measured with a daily diary and pain and function measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) at baseline and at 3, 6, 9 and 12-weeks follow-up. Secondary outcomes are patients' perceived recovery, quality of life, medical, patient and productivity costs, compliance to therapy, co-interventions and adverse reactions.

Discussion: The successful completion of this trial would lead to a better understanding of which medication should be used in the treatment of primary care patients with mild knee osteoarthritis.

Trial registration: Dutch trial registry NTR1485.

INTRODUCTION

Osteoarthritis (OA) is the most frequent chronic joint disease causing pain and disability of especially hip and knee.[1] For most patients the general practitioner (GP) is the initial caregiver and may provide advice and/or pain medication. International guidelines and the Dutch GP guidelines for treating non-traumatic knee symptoms recommend acetaminophen as medication of first choice in the management of OA pain.[2-4] However, a prospective cohort of first consulters with non-traumatic knee symptoms in 40 Dutch general practices showed that GPs prescribed pain medication in 27% of these patients, 90% received non-steroidal anti inflammatory drugs (NSAIDs) and only 10% received acetaminophen (Belo JN, Berger MY, Koes BW, Bierma-Zeinstra SMA: Medical treatment and medical consumption in adults with nontraumatic knee complaints in general practice.*Submitted*).

Despite general consensus that acetaminophen has a better safety profile, there may be insufficient evidence for the efficacy of acetaminophen in mild OA to convince GPs that NSAIDs should be avoided as first choice medication. Indeed, a systematic review of 15 randomized clinical trials (RCTs; median length 6 weeks) on the comparative effectiveness of NSAIDs versus acetaminophen in patients with hip/knee OA reported that although acetaminophen was more effective than placebo, it provided less pain relief than NSAIDs.[5] The efficacy of NSAIDs was especially found in patients with moderate to severe OA, whereas others report that the efficacy of NSAIDs and acetaminophen is probably similar in patients with mild OA.[6]

A limitation of most RCTs is that they seldom include patients consulting for OA (i.e. new patients) but mostly prevalent cases already receiving treatment for OA. Most studies included a highly selected patient group already using a daily dose of NSAIDs and needing a wash-out period prior to randomization.[7-10] One trial reported (not surprisingly) that prior use of NSAIDs predicted a better response of NSAIDs compared to acetaminophen.[8] Therefore, these latter studies do not represent patients with OA in general practice, or patients who consult their GP for the first time with a new episode of complaints.

In view of the lack of trials comparing the efficacy of NSAIDs with acetaminophen in new consulters with OA, we designed an RCT to explore whether there is a clinically relevant difference between diclofenac (an NSAID) and acetaminophen in new patients with knee OA in general practice. A pragmatic open-label design was chosen to approximate GPs' daily practice and because patients are aware of the type of prescribed medication. Secondary aims were to establish: 1) whether there are predefined predictors of treatment responders after 4-6 weeks and at 12-weeks follow-up, and 2) the cost-effectiveness of diclofenac compared to acetaminophen in patients with knee OA in primary care over a 12-week period.

Presented below is the protocol of the diclofenac versus acetaminophen trial (DIPA trial), which is registered in the Dutch trial registry (NTR1485).[11]

METHODS/DESIGN

Study design

This study is a pragmatic randomized open-label trial with a follow-up period of 12 weeks. In this design, the patients, researchers and GPs are not blinded for the assigned treatment. The study is approved by the Medical Ethics Committee of the Erasmus Medical Center (MC). Figure 1 presents the flow chart of the study.

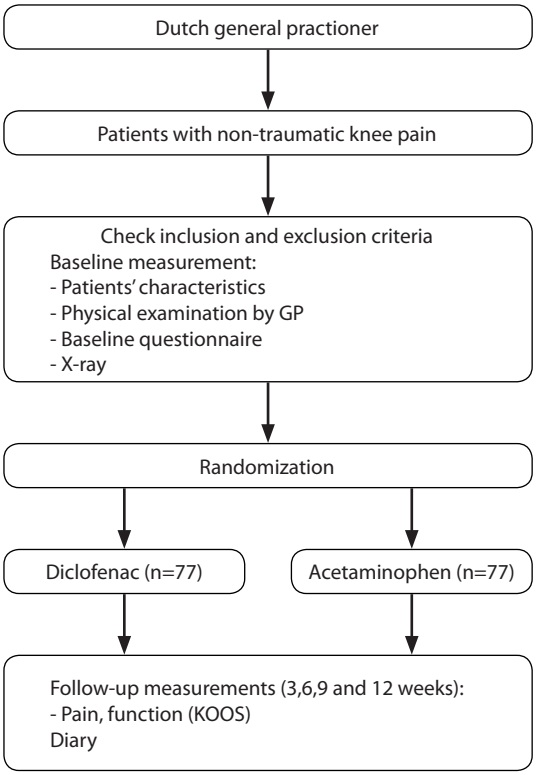


Figure 1. Flow chart of the study

Inclusion/exclusion criteria

Patients are eligible for the DIPA trial (Table 1) if they meet all four inclusion criteria: 1) consulting their GP for a new episode of non-traumatic knee pain. A new episode of knee pain is defined as pain presented to the GP for the first time, or if a patient did not consult the GP with these symptoms in the previous 3 months,[12] 2) aged 45 years or older, 3) meeting the clinical American College of Rheumatology (ACR) criteria for OA of the knee,[13] and 4) having a pain severity of 2 or more (on a 0-10 scale).

Patients are excluded if they are: 1) contra-indicated for NSAID or acetaminophen use, i.e. gastrointestinal bleedings in history or active, blood dyscrasia, bone marrow depression (myelosuppression), serious heart failure, serious liver or kidney disease

(glomerular filtration < 30 ml/min), alcoholism, colitis ulcerosa, Crohn's disease, sulphite hypersensitivity, asthma, urticaria, angioedema, nasal polyps or rhinitis after use of acetylsalicylic acid or other prostaglandin synthetase inhibitors, or use of anti-depressive medication (SSRIs), 2) having an arthroplasty or osteotomy of the knee on the contralateral or unilateral side, 3) already taking NSAIDs or acetaminophen at doses similar to or higher than the study dose, 4) surgery or major trauma of the affected joint within the previous 6 months, 5) myocardial infarction or stroke in the last 6 months, and 6) oral use of a corticosteroid.

Table 1. Inclusion and exclusion criteria of the DIPA trial.

Inclusion Criteria	Exclusion Criteria
People with a new episode of non-traumatic knee pain	Contra-indication for NSAID or acetaminophen
Age ≥ 45 years	Arthroplasty/osteotomy
Comply with clinical ACR-criteria*	Already on NSAID or acetaminophen use^
Pain severity scale ≥ 2 on a 11-point numeric rating scale	Surgery or major trauma of affected knee in previous 6 months
	Oral corticosteroid use
	Myocardial infarction or stroke in previous 6 months

* Clinical ACR criteria: Age > 50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, and no palpable warmth. Patients comply with the clinical ACR criteria if they meet at least 3 of the 6 criteria. ^ Excluded are those with a pre-study medication use comparable with the study dose of diclofenac (≥ 150 mg/day) or acetaminophen (≥3000 mg/day)

Patient selection

An academic research network of GPs in the south-west of the Netherlands agreed to participate and to refer patients who consult for a new episode of non-traumatic knee pain to the DIPA trial. The GP takes the patient's history and performs the physical examination as part of the usual daily care. The GP gives study information to the patient, and sends the patient's name and information regarding history taking/ physical examination by fax to the research department at Erasmus MC. Within two days after the GP visit, patients are contacted (by the researcher), checked for eligibility (in- and exclusion criteria), and asked for written informed consent. Baseline measurements and randomization then take place.

Randomization

Patients are allocated to the diclofenac or the acetaminophen group using a randomization list (with random blocks of 4, 6 or 8) produced by a computer-generated table. The GP is informed about the randomization results and sends a prescription of the allocated medication to the patient's pharmacy.

Interventions

Patients are randomly allocated to either diclofenac (maximum daily intake of 3 x 50 mg) or acetaminophen (maximum daily intake of 3 x 1000 mg). Both medications are prescribed in accordance with the Dutch clinical guidelines for GPs for non-traumatic knee symptoms.[2] The guideline recommends analgesics for 2 weeks and, if required, for an additional 1-2 weeks.[2] This is in accordance with the EULAR and OARSI recommendations.[3-4] Patients in the diclofenac group with an increased risk of gastro-intestinal problems will also receive a mucosal protector (e.g. omeprazol once daily, 20 mg). Patients at increased risk of gastro-intestinal problems are 60 years or older and/or have a serious co-morbidity (e.g. rheumatic disease and diabetes mellitus). Patients take their allocated medication on demand, and can change their medication intake when their pain level alters. This leads to an approach that is close to usual daily care.

Outcome measures

The primary outcomes of this study are: 1) pain and function measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS)[14] and 2) pain assessed with an 11-point numeric rating scale (NRS) in a diary.[15] Secondary outcomes are: 1) patients' perceived pain measured every 3 weeks on the 11-point NRS,[15] 2) patients' perceived recovery measured on a 7-point Likert scale (1=completely recovered; 7=worse than ever), 3) constant and intermittent pain measured with the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire,[16] 4) patients' quality of life assessed with the EuroQol instrument EQ-5D,[17] 5) all direct medical, patient and productivity costs measured with the PROductivity and DISease Questionnaire (PRODISQ), [18] 6) compliance to therapy assessed in the diary, 7) co-interventions (e.g. changes in doses of co-medication), and 8) adverse reactions.

Questionnaires

The primary and secondary outcome measurements are assessed with questionnaires and diaries. During the study, patients fill out a total of 5 questionnaires (at baseline and at 3, 6, 9 and 12-weeks follow-up). After the informed consent and before randomization, the patient fills out the baseline questionnaire. After the baseline questionnaire, patients receive a follow-up questionnaire every 3 weeks.

Five validated instruments are used in all 5 questionnaires.

1) The KOOS measures the functional status of patients with knee OA.[14] The KOOS consists of 5 subscales: pain, symptoms, activities of daily living, sport and function and knee-related quality of life. The Dutch version of the KOOS is validated and suitable for use in patients with mild and moderate OA.[14] The KOOS questionnaire is an extension of the Western Ontario and McMaster osteoarthritis index (WOMAC), and WOMAC scores of pain and function can be calculated from the KOOS.[19-21] The WOMAC is recommended for use in elderly subjects with knee OA.[19]

2) The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) identifies different types of pain due to OA. The ICOAP is a reliable and valid to measure constant

and intermittent pain.[16]

3) The 11-point NRS measures the perceived level of pain intensity (0=no pain; 10=worst pain ever).[22-25] The NRS is a valid measurement to score pain intensity level.[22]

4) The EuroQol (EQ-5D) measures quality of life. The EuroQol is a generic questionnaire and consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[17] The EuroQol allows to evaluate the cost-effectiveness of a healthcare intervention[26-27] and can be converted into utilities to calculate Quality Adjusted Life Years (QALYs).[28]

5) The PRODISQ measures all direct medical, patient and productivity costs. The PRODISQ consists of 7 modules. In the present study, only modules 1-5 are used because these questions are related to the individual patient, whereas modules 6 and 7 are utilized by management. Modules 1-5 cover: 1) demography and disease, 2) profession, working situation and income, 3) absence from work, 4) compensation mechanisms, and 5) productivity costs whilst at work (efficiency loss).[18]

Besides these validated questionnaires, the baseline questionnaire addresses patient characteristics (age, gender, weight, height and social status), knee-related characteristics (history and localisation of knee symptoms), problems at work due to knee problems and co-morbidities. The four follow-up questionnaires measure medication use, adverse reactions, medical consumption, patients' perceived recovery and knee-related characteristics. Table 2 presents an overview of the questionnaire items.

Pain diary

During the DIPA trial, patients fill out a diary to score daily pain (using an 11-point NRS), medication use and compliance. Being a pragmatic trial, patients may change their medication dosage when pain alters. These alterations may be important for interpreting the results of the trial. Therefore, information on compliance to the allocated treatment is also collected.

Sample size

The sample size is calculated to detect clinically relevant differences in pain and function between the two groups (diclofenac versus acetaminophen), measured by the KOOS during the 12-week study period. To detect a clinically relevant difference of 10 points (15%) on the KOOS pain score between the two treatment groups after 12 weeks, 73 patients per group are needed (power 95%, alpha 0.05, one-sided testing). Based on an expected 5% loss to follow, 154 patients (2 x 77) should be included.

Table 2. Overview of questionnaire items

	0 weeks B.Q.	3 weeks F.U.Q.	6 weeks F.U.Q.	9 weeks F.U.Q.	12 weeks F.Q.	Diary
Demographics						
Age, gender, weight, height and social status	X					
Outcome measures						
Pain score (KOOS)	X	X	X	X	X	
Function score (KOOS)	X	X	X	X	X	
Pain score (NRS)	X	X	X	X	X	X
Perceived recovery	X	X	X	X	X	
Constant and intermittent pain (ICOAP)	X	X	X	X	X	
Quality of life (EuroQol)	X	X	X	X	X	
Direct medical, patient and productivity costs (PRODISQ)					X	
Compliance						X
Adverse reactions		X	X	X	X	
Other outcomes						
Knee related characteristics (history, duration, and localisation)	X					
Co-morbidities	X					
Medication use		X	X	X	X	X
Medical consumption (visit to GP, medical specialist, physical therapist, etc))		X	X	X	X	

B.Q. = Baseline Questionnaire; F.U.Q. = Follow-up Questionnaire; F.Q. = Final Questionnaire; KOOS = Knee Osteoarthritis Outcome Score; NRS = Numeric Rating Scale; ICOAP = Intermittent and Constant Osteoarthritis Pain; PRODISQ = PROductivity and DISease Questionnaire

Statistical analyses

All analyses will be performed on an intention-to-treat basis, analyzing all patients in the treatment group to which they were randomly allocated. Analysis per protocol will also be conducted, analyzing only those patients that have measures on the primary outcome measurement at both baseline and 12-weeks follow-up. Descriptive data of baseline characteristics will be presented for both groups to check comparability. Generalized estimating equation (GEE) analysis will be conducted to investigate (longitudinally) the 2, 4, and 6 weeks effectiveness of diclofenac compared to acetaminophen for pain assessed with the diary. Differences between the two groups over the 12-week follow-up will also be assessed with GEE. The outcome variables

are pain (measured with the NRS), and pain and function (assessed with the KOOS). Using GEE, the correlation of multiple measurements within one patient is taken into account.[29]

To detect predictive variables for treatment responders at 12-weeks follow-up multivariate regression analyses will be used. Treatment response is defined based on the OMERACT-OARSI responder criteria[30-31] as a high improvement in pain or function of ≥ 50%, or an improvement on pain ≥ 20% and function ≥ 20%.

In addition, a cost-utility analysis will be performed that expresses health improvements in QALYs assessed with the EuroQol. If the course of OA (and its related costs) appears to fluctuate (particularly if the difference between treatment arms is not stable over time), an additional modeling study using a Markov model will be performed. Statistical methods will be used to describe uncertainty in costs and effects estimates based on patient data. A 95% confidence interval for the cost-utility ratio will be calculated and an acceptability curve presented. In case of a modeling study, a probabilistic sensitivity analysis will be performed.

DISCUSSION

Recruitment of the 154 patients has started and will end in 2010. We expect to report study results in 2011. The successful completion of this trial would lead to a better understanding of which medication should be used in the treatment of primary care patients with mild knee osteoarthritis.

REFERENCES

1. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-97.
2. **Belo JN**, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F. NHG-Standaard niet-traumatische knieproblemen bij volwassenen. *Huisarts en Wetenschap* 2008;51:229-240.
3. **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, 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;62:1145-1155.
4. **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981-1000.
5. **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006:CD004257.
6. **Pincus T**, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;44:1587-1598.
7. **Boureau F**, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004;63:1028-1034.
8. **Case JP**, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-178.
9. **Geba GP**, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, Vioxx ACTG. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;287:64-71.
10. **Yelland MJ**, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ, Brown RM. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. *Rheumatology (Oxford)* 2007;46:135-140.
11. Dutch trial register. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1485.
12. **Heintjes EM**, Berger MY, Koes BW, Bierma-Zeinstra SMA. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. *BMC Musculoskelet Disord* 2005;6:45.
13. **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.
14. **de Groot IB**, Favejee MM, Reijman M, Verhaar JAN, Terwee CB. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes* 2008; 6:16.
15. **Scott J**, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-184.
16. **Hawker GA**, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409-414.

17. **Brooks R**. EuroQol: the current state of play. Health Policy 1996;37:53-72.
18. **Koopmanschap MA**. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. *Expert Rev Pharmacoecon Outcomes Res* 2005;5:23-28.
19. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
20. **Roos EM**, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes* 2003;1:17.
21. **Roos EM**, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64.
22. **Jensen MP**, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27:117-126.
23. **Jensen MP**, Karoly P, O'Riordan EF, Bland F, Jr., Burns RS. The subjective experience of acute pain. An assessment of the utility of 10 indices. *Clin J Pain* 1989;5:153-159.
24. **Jensen MP**, Miller L, Fisher LD. Assessment of pain during medical procedures: a comparison of three scales. *Clin J Pain* 1998;14:343-349.
25. **Rodriguez CS**. Pain measurement in the elderly: a review. *Pain Manag Nurs* 2001;2:38-46.
26. **Dolan P**. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-1108.
27. **van Agt HM**, Essink-Bot ML, Krabbe PF, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. *Soc Sci Med* 1994;39:1537-1544.
28. **Drummond MF**, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd edition ed. New York: Oxford University Press, 2005.
29. **Twisk JWR**, ed. *Applied Longitudinal Data Analysis for Epidemiology: a practical guide*. Cambridge: Cambridge University Press 2003.
30. **Dougados M**, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. *Osteoarthritis Cartilage* 2000;8:395-403.
31. **Pham T**, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12:389-399.

CHAPTER 3

Effectiveness of diclofenac versus acetaminophen in primary care patients with knee osteoarthritis: a randomized controlled trial [NTR1485]

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Submitted

ABSTRACT

Background: The effectiveness of diclofenac versus acetaminophen in primary care patients with pain due to knee osteoarthritis (OA) is yet unclear. Therefore, we assessed the effectiveness of both medications in a 12-week follow-up pragmatic open-label randomized controlled trial.

Methods: 104 patients aged ≥45 years consulting their general practitioner with a new episode of knee pain and fulfilling the clinical American College of Rheumatology criteria for knee OA were randomly allocated to diclofenac (n=52) or acetaminophen (n=52) for 2 weeks. Primary outcomes were knee pain and function measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS;0-100) collected at 3,6,9 and 12-weeks follow-up and daily knee pain severity measured for 6 weeks with a numerical rating scale (NRS;0-10).

Results: During 12 weeks follow-up, no significant mean differences were found between both groups for KOOS pain (mean difference [acetaminophen minus diclofenac]:-1.6;95%CI:-9.3to6.0) and function (-1.7;95%CI:-9.4to5.9). However, daily measurements showed small to moderate difference (effect sizes:0.4 to 0.5) in knee pain between day 5 and 12 in favor of diclofenac users.

Conclusions: At 3,6,9 and 12-weeks follow-up no differences in knee pain and function were found between both groups in primary care patients with knee OA. However, a statistically significant reduction in knee pain severity was found at day 5 to 12 in favor of diclofenac users. Patients reported more often minor side-effects after using diclofenac (64%) compared to acetaminophen (46%). These findings support the currently available clinical guidelines recommending acetaminophen as the first choice pain medication with knee OA.

INTRODUCTION

Osteoarthritis (OA) is the most frequent joint disease, which causes pain and functional disability.[1] Worldwide estimates are that 9.6% of men and 18.0% of women aged ≥ 60 years have symptomatic OA.[2] As OA is not curable, treatment is mainly symptom driven.

The (inter)national guidelines regarding knee OA recommend acetaminophen as the medication of first choice when pain medication for OA is needed, because of its better safety profile[3-5] If acetaminophen does not provide sufficient pain relief, non-steroidal anti-inflammatory drugs (NSAIDs) can be considered.[6] However, a large cohort study showed that most patients preferred NSAIDs over acetaminophen.[7] In addition, Ausiello et al. reported that physicians prescribed acetaminophen in 10% of the OA visits, while NSAIDs were prescribed in 32.6%.[8] Thus, it seems that patients, and perhaps also general practitioners (GPs), do not consider acetaminophen as the first choice medication in OA, because of the believed superior effectiveness of NSAIDs above acetaminophen. Moreover, acetaminophen may not be perceived as a medication, because of its wide availability.[9]

For GPs working in primary care, only limited data on this comparative effectiveness is available. Most previous trials compared NSAIDs versus acetaminophen in highly selected patients already using NSAIDs and needing a wash-out period prior to randomization.[10-13] One study showed that prior use of NSAIDs predicted a better response in favor of NSAIDs vs. acetaminophen.[11] In addition, previous studies mostly included patients recruited in a secondary care setting.[11,14,15] Therefore, we conducted a pragmatic, open-labelled, randomized controlled trial with a 12-week follow-up to evaluate the effectiveness of diclofenac vs. acetaminophen in patients consulting their GP with pain due to knee OA.

METHODS

Study design

The design of the study is a pragmatic open-labelled randomized controlled trial. Patients and GPs were not blinded to the treatment received as we wanted to stay close to the daily care of the GP.

The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study design. Detailed information of the study design is published elsewhere.[16]

Setting and Participants

GPs in the south-west of the Netherlands recruited patients who consulted them with a new episode of non-traumatic knee pain. A new episode of knee pain was defined as pain presented to the GP for the first time and did not consult their GP with these symptoms in the previous 3 months.[17] Patients were eligible for inclusion if they met all of the following criteria: 1) age ≥ 45 years old; 2) consulted their GP with a new episode of non-traumatic knee pain; 3) knee pain severity of 2 or more (on a 0-10 scale); and 4) fulfilled the clinical criteria of the American College of Rheumatology (ACR) for

knee OA.[18] Patients were excluded if they had a contra-indication for NSAIDs and/or acetaminophen use, an arthroplasty or osteotomy of the knee on the contralateral or unilateral side, already took NSAIDs or acetaminophen at doses similar to or higher than the study dose, surgery or major trauma of the affected joint within 6 months prior to start of the study, myocardial infarction or stroke within 6 months before the start of the study, and oral use of corticosteroids.

Randomization and intervention

Eligible patients were randomly assigned to either receive diclofenac (maximum daily intake of 3 x 50 mg) or acetaminophen (maximum daily intake of 3 x 1000 mg) for a period of 2 weeks and, if required, an additional 1-2 weeks; this in accordance with the Dutch clinical guidelines for GPs treating non-traumatic knee complaints.3 During the treatment period, usual care was provided by the GP to all patients, which included education and life style advice regarding knee OA. Patients assigned to the diclofenac group with an increased risk of gastro-intestinal problems [patients aged ≥ 60 years and/or with a serious co-morbidity (e.g. rheumatic disease and diabetes mellitus)] also received a mucosal protector (e.g. omeprazole once daily, 20 mg). For the randomization procedure (after informed consent and baseline measurement), we used a computer-generated randomization list with random blocks of 4, 6 or 8 made by an independent researcher who was not involved in this study. The researcher who assigned the patients to diclofenac or acetaminophen was blinded for allocation sequence by using sealed envelopes.

Outcomes

During the 12 weeks follow-up, patients filled out 5 questionnaires (at baseline and at 3, 6, 9 and 12 weeks follow-up) and a diary. Primary outcomes were pain and function measured with the Knee injury and Osteoarthritis Outcome Score (KOOS) from 0-100 (0=no pain/function; 100=worst pain/function ever) assessed with 3-weekly questionnaires20,21 and daily severity of knee pain intensity during the first 6 weeks using a numeric rating scale (NRS) from 0-10 (0=no pain; 10= worst pain ever), measured with a diary.

Secondary outcomes were: 1) 3-weekly knee NRS knee pain intensity (questionnaire); 2) 3-weekly constant and intermittent pain measured with the intermittent and constant osteoarthritis pain (ICOAP) questionnaire;[21] 3) 3-weekly quality of life assessed with the EuroQol instrument EQ-5D;[22] 4) 3-weekly patients' perceived recovery on a 7-point Likert scale. We dichotomized patients into recovered (totally recovered and strongly improved) and not recovered (somewhat improved, no change, somewhat deteriorated, strongly deteriorated, and worse than ever) compared with baseline; 5) 3-weekly treatment response based on the OMERACT-OARSI criteria;[23,23] these defined a responder as a patient with a considerable improvement in pain or function of ≥ 50%, or an improvement on pain of ≥ 20% and on function of ≥ 20%; 6) medication compliance measured with the diary. Compliance was dichotomized into compliant

(patients who took the maximum daily dose of the allocated medication for ≥ 10 consecutive days during the first 2 weeks) and not compliant (patients who took less than the maximum daily dose of the allocated medication for ≥ 5 days during the first 2 weeks); and 7) co-medication use during the first 2 weeks.

Self-administered adverse events

Patients reported self-administered adverse events every 3 weeks if applicable. Adverse events were classified into: a) gastrointestinal events (e.g. complaints of stomach and/or bowel, diarrhea, abdominal pain, nausea, flatulence and cystitis); b) nervous system related events (e.g. dizziness, headache and tingling); c) musculoskeletal and connective tissues (e.g. muscle cramp); d) respiratory events (e.g. shortness of breath, constriction of respiratory tract, bloody nose, coughing and sore throat); e) skin and subcutaneous tissues (e.g. pruritis, rash, urticaria, sweating, alopecia and eczema); f) immune system (allergic reaction), g) organ of vestibular system (tinnitus); h) cardiovascular events (e.g. hypertension, hypotension, heart failure, chest pain, tachycardia and hemorrhage); i) psychiatric events (e.g. depression, insomnia, somnolence and fatigue); and j) general adverse events (e.g. fever, edema and hot flush).

Radiographs

At baseline, a weight-bearing antero-posterior radiograph of the affected knee was made. Two independent readers scored the radiographs using the Kellgren and Lawrence (K&L) classification criteria (grades 0-4) (agreement between readers for cut-off K&L≥2; kappa: 0.6).[25] Disagreement in K&L score was resolved by discussion. For patients who indicated to have bilateral complaints, the highest K&L score was used for analysis.

Sample size

To detect a clinically relevant and a statistically significant difference of 10 points (15%) on the KOOS pain score between the two treatment groups (diclofenac vs. acetaminophen) at 12 weeks, we needed to include 73 patients per group (power 80%, alpha 0.05, one-sided testing). A total of 154 patients (2 x 77) were needed to account for an expected 5% loss to follow-up.

Statistical analysis

All analyses were performed according to the intention-to-treat principle; analysing all patients in the treatment group to which they were randomly allocated. Descriptive data of baseline characteristics were presented for both groups to check comparability. To account for the correlation between measurements within the same person we used generalized estimating equations (GEE) analyses to estimate the model using the compound symmetry working correlation structure. Because of the relationship between the knee pain scores and the day of measurement we used a broken-stick model (i.e. a linear spline function) with interior knots at weeks 3, 6 and 9 for the

questionnaire data and at days 3, 7, 14, 21, 28 and 35 for the diary data. All analyses were adjusted for age, gender, BMI and baseline scores of knee pain severity.

GEE analyses were also used for the continuous secondary outcomes and logistic regression analyses were used for the dichotomous secondary outcomes (perceived recovery and defined treatment responders).

Adjusted effect sizes were calculated using the adjusted mean differences divided by the pooled standard deviation (SD) at baseline of both groups. Effect sizes of 0.2-0.5 are considered to be small, 0.5-0.8 is a medium effect, and a score of ≥ 0.8 indicates a large treatment effect.[26]

Analyses were performed using SPSS software (version 17, SPSS Inc., Chicago, IL, USA) and SAS (version 9.2, Institute Inc., Cary, NC, USA).

RESULTS

Figure 1 presents the flow chart of the present study. Between April 2009 and September 2011, 76 GPs referred 290 patients to the trial. Of these, 186 were excluded: 93 were not interested in participating, 36 did not want to use pain medication, 23 had insufficient pain, 13 already used pain medication, 12 had a contra-indication for NSAIDs, 5 found the study too demanding, 2 had a surgery or trauma of the affected knee prior to the start of the study, 2 did not fulfil the ACR-criteria of the knee. Finally, 104 patients were included and randomized (52 to acetaminophen, 52 to diclofenac). Of the 104 randomized patients, 97 (93.3%) participated at the 12-week follow-up assessment. Three patients (5.8%) in the acetaminophen group withdrew: 2 due to personal circumstances and 1 patient gave no reason. In the diclofenac group 4 patients (7.7%) withdrew: 2 because of personal circumstances, 1 because of an error of the research team and 1 due to unknown reasons. Compared with the total study population, patients who withdrew were older, had a lower BMI but had a comparable knee pain severity.

Table 1 presents the baseline characteristics. At baseline, 61.5% of the patients in the acetaminophen were women compared to 63.5% in the diclofenac group. Mean age was 64.0 (SD 9.0) years for the acetaminophen group and 63.9 (SD 9.2) years for the diclofenac group. Although there were no significant differences between the groups at baseline, some clinical relevant differences were present. Of the patients in the acetaminophen group, 65.3% had knee symptoms lasting ≥ 3 months compared to 48.1% of the patients in the diclofenac group. Patients in the diclofenac group had slightly higher levels of pain (5.4 vs. 5.1) and somewhat more often radiologic knee OA (K&L score of ≥2; 36.2% vs. 30.8%) on x-ray.

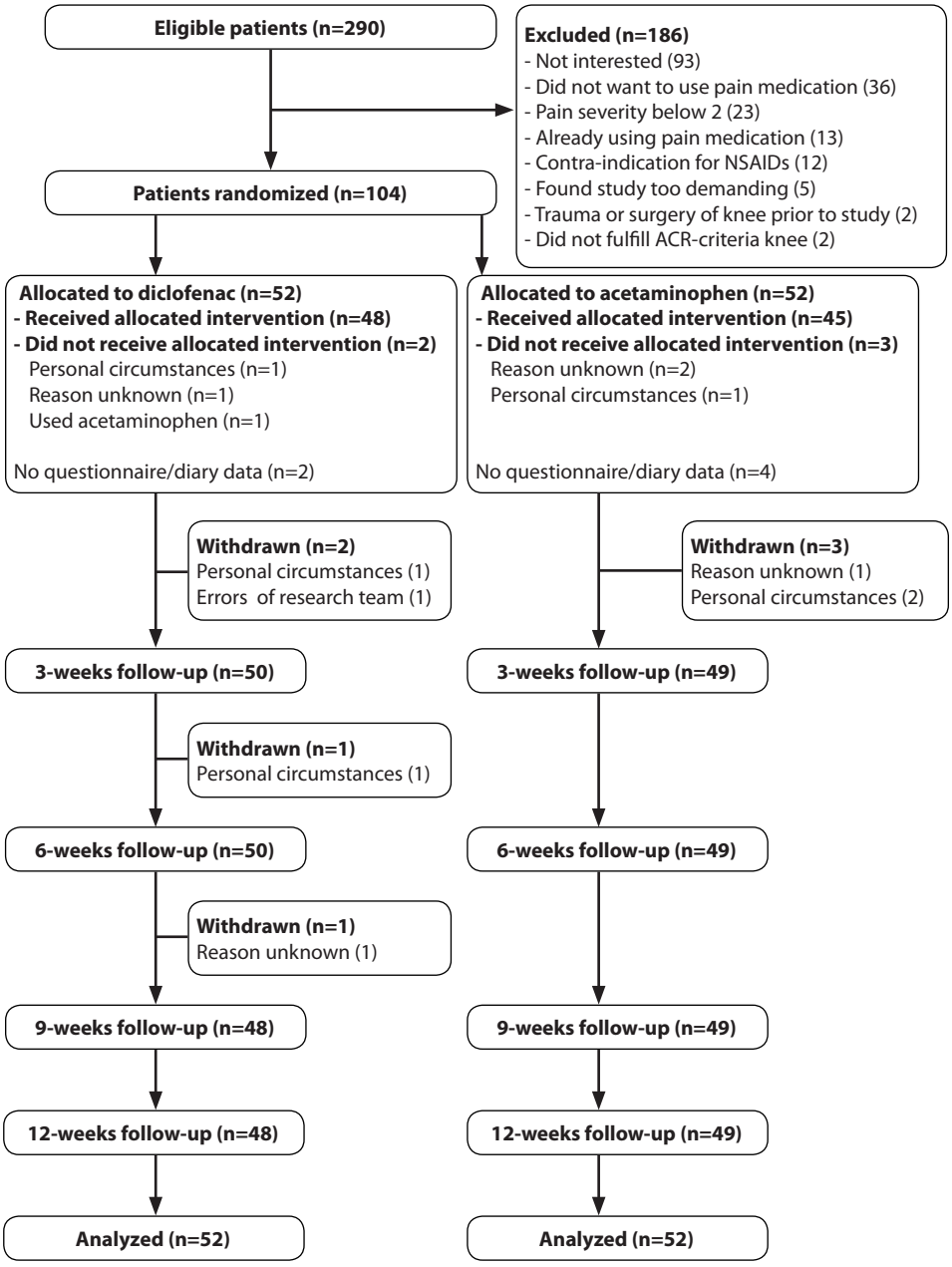

Figure 1. Flow chart of the study

Table 1. Patient characteristics at baseline (before randomization) by randomized group

	Acetaminophen (n=52)			Diclofenac (n=52)		
	n	**%**	**Mean (SD)**	**n**	**%**	**Mean (SD)**
Age, in years			64.0 (9.0)			63.9 (9.2)
Women	32	61.5		33	63.5	
Low education level	38	77.6		43	82.7	
Paid job	15	30.6		19	36.5	
Body mass index, kg/m2			27.7 (4.0)			28.6 (4.8)
Duration of symptoms						
< 3 weeks	9	18.3		10	19.2	
3 weeks-3 months	8	16.3		17	32.7	
≥ 3 months	32	65.3		25	48.1	
Side of osteoarthritis						
Left	17	34.7		16	30.8	
Right	21	42.9		18	34.6	
Bilateral	11	22.4		18	34.6	
Kellgren and Lawrence score						
Grade 0 or 1	33	63.5		33	63.5	
Grade ≥ 2	16	30.8		19	36.5	
Missing	3	5.7		0	0	
Clinical ACR criteria						
Age > 50	50	96.2		46	88.5	
Stiffness < 30 minutes	36	69.2		32	61.5	
Crepitus	34	65.4		31	59.6	
Bony tenderness	46	88.5		42	80.8	
Bony enlargement	29	55.8		22	42.3	
No palpable warmth	45	86.5		48	92.3	
Pain (NRS, 0-10)†			5.1 (1.8)			5.4 (2.1)
KOOS (0-100)‡						
Pain			47.9 (16.8)			50.7 (16.4)
ADL (function)			42.7 (18.4)			46.0 (17.7)
Symptoms			51.8 (12.8)			52.4 (13.0)
Sport & Recreation			75.3 (19.1)			69.3 (26.1)
QoL			55.6 (11.1)			56.0 (13.8)

SD= standard deviation; NRS: numerical rating scale; KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily living; QoL: Quality of life; ICOAP: Intermittent and Constant Osteoarthritis Pain; † a higher score is worse; ‡ a higher score is better

Table 1. continued

	Acetaminophen (n=52)			Diclofenac (n=52)		
	n	**%**	**Mean (SD)**	**n**	**%**	**Mean (SD)**
ICOAP scores (0-100)†						
Constant pain			32.7 (20.0)			38.2 (20.8)
Intermittent pain			41.9 (17.1)			43.8 (19.9)
Quality of life, EQ-5D (0 to 1)‡			0.74 (0.16)			0.67 (0.25)

SD= standard deviation; NRS: numerical rating scale; KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily living; QoL: Quality of life; ICOAP: Intermittent and Constant Osteoarthritis Pain; † a higher score is worse; ‡ a higher score is better

Primary outcomes

Three-weekly evaluation of pain and function

The KOOS knee pain and function scores assessed with 3-weekly questionnaires are presented in Figure 2. After 3 weeks, both groups showed within the group a significant reduction in knee pain severity. However, during 3, 6, 9 and 12 weeks no significant or clinically relevant differences were found between the groups. At 3 weeks the mean adjusted difference (acetaminophen minus diclofenac) for KOOS knee pain was -1.3 on a 0-100 scale (95% CI: -9.1 to 6.5), at 6 weeks it was -4.6 (95% CI: -12.4 to 3.1), at 9 weeks it was -2.3 (95% CI: -9.9 to 5.3) and at 12 weeks it was -1.6 (95% CI: -9.3 to 6.0). For KOOS function this was -0.4 (95% CI: -8.2 to 7.6) at 3 weeks, -0.8 (95% CI: -8.6 to 7.0) at 6 weeks, -3.3 (95% CI: -10.9 to 4.4) at 9 weeks and -1.7 (95% CI: -9.4 to 5.9) at 12-weeks follow-up (Table 2).

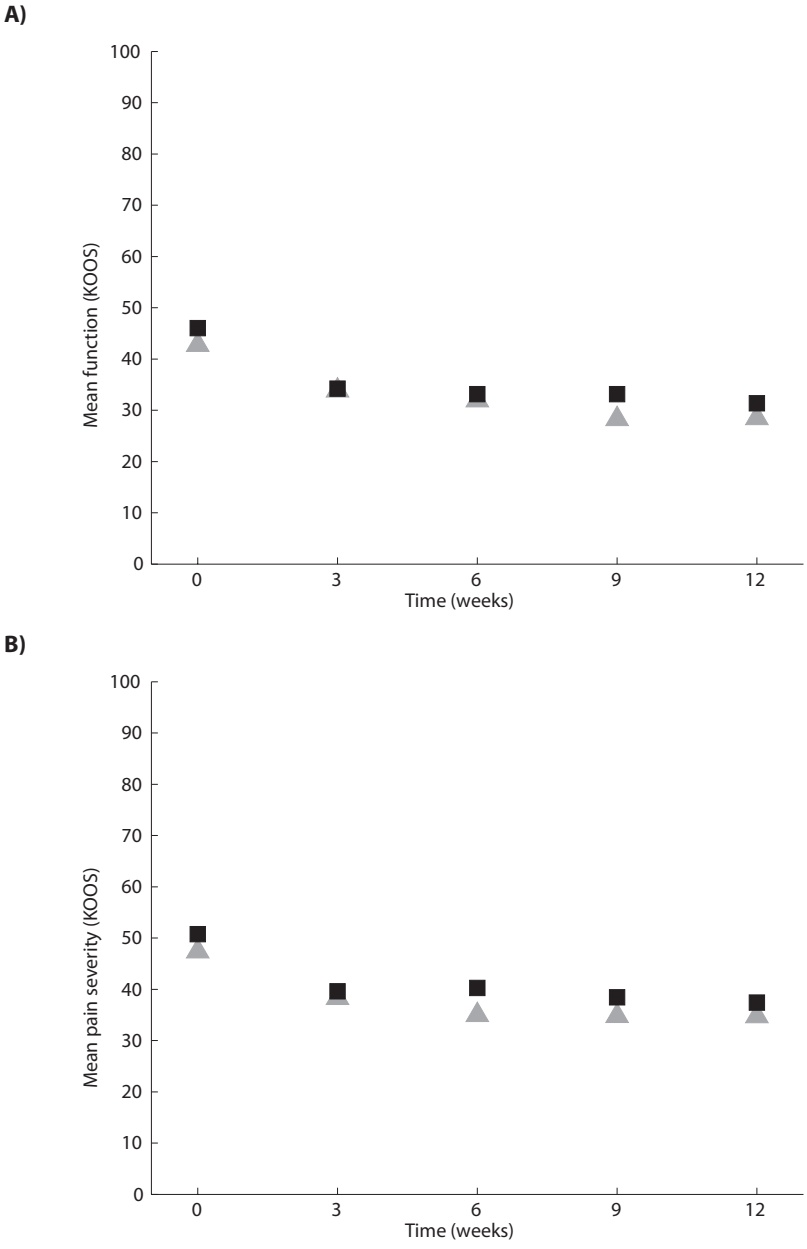

Figure 2. A) Mean pain severity between acetaminophen and diclofenac during 12-weeks follow-up. **B)** mean function between acetaminophen and diclofenac during 12-weeks follow-up; ▲ Acetaminophen, ■ Diclofenac

Table 2. Primary outcomes measured with 3-weekly questionnaires

	Acetaminophen (n=52) Mean (SD)	Diclofenac (n=52) Mean (SD)	Unadjusted differences (95% CI)	Adjusted differences* (95% CI)	Adjusted effect size*
KOOS pain†					
3-weeks	38.3 (19. 5)	39.6 (20.7)	-1.3 (-9.5 to 6.9)	-1.3 (-9.1 to 6.5)	-0.07
6-weeks	35.0 (19.4)	40.2 (22.1)	-5.3 (13.7 to 3.2)	-4.6 (-12.4 to 3.1)	-0.22
9-weeks	34.8 (18.8)	38.5 (20.7)	-3.7 (-12.0 to 4.6)	-2.3 (-9.9 to 5.3)	-0.12
12-weeks	34.8 (19.4)	37.4 (21.0)	-2.6 (-10.8 to 5.5)	-1.6 (-9.3 to 6.0)	-0.08
KOOS function†					
3-weeks	33.9 (19.3)	34.2 (21.7)	-0.4 (-8.9 to 8.2)	-0.4 (-8.2 to 7.5)	-0.02
6-weeks	31.9 (19.9)	33.1 (20.6)	-1.2 (-9.5 to 7.1)	-0.8 (-8.6 to 7.0)	-0.04
9-weeks	28.3 (19.7)	33.1 (20.3)	-4.9 (-13.4 to 3.6)	-3.3 (-10.9 to 4.4)	-0.16
12-weeks	28.4 (19.5)	31.4 (20.2)	-2.9 (-11.0 to 5.2)	-1.7 (-9.4 to 5.9)	-0.09

* adjusted for age, gender, BMI and baseline pain; † a higher score is worse; KOOS: Knee Osteoarthritis Outcome Score

Daily severity of pain

The course of pain over the first 6 weeks is given in Figure 3A. Intention-to-treat analysis on these diary data showed a significant difference between groups during the course of knee pain severity from day 5-12 in favor of the diclofenac group (Table 3). Mean adjusted differences (acetaminophen minus diclofenac) over these days ranged from 0.74-1.02 on a 0-10 scale. After day 12, no significant differences in daily knee pain severity were found between the acetaminophen and diclofenac group. In addition, during the first 2 weeks, 44 patients (85%) were compliant to diclofenac treatment compared to 45 patients (87%) in the acetaminophen group (Figure 3B).

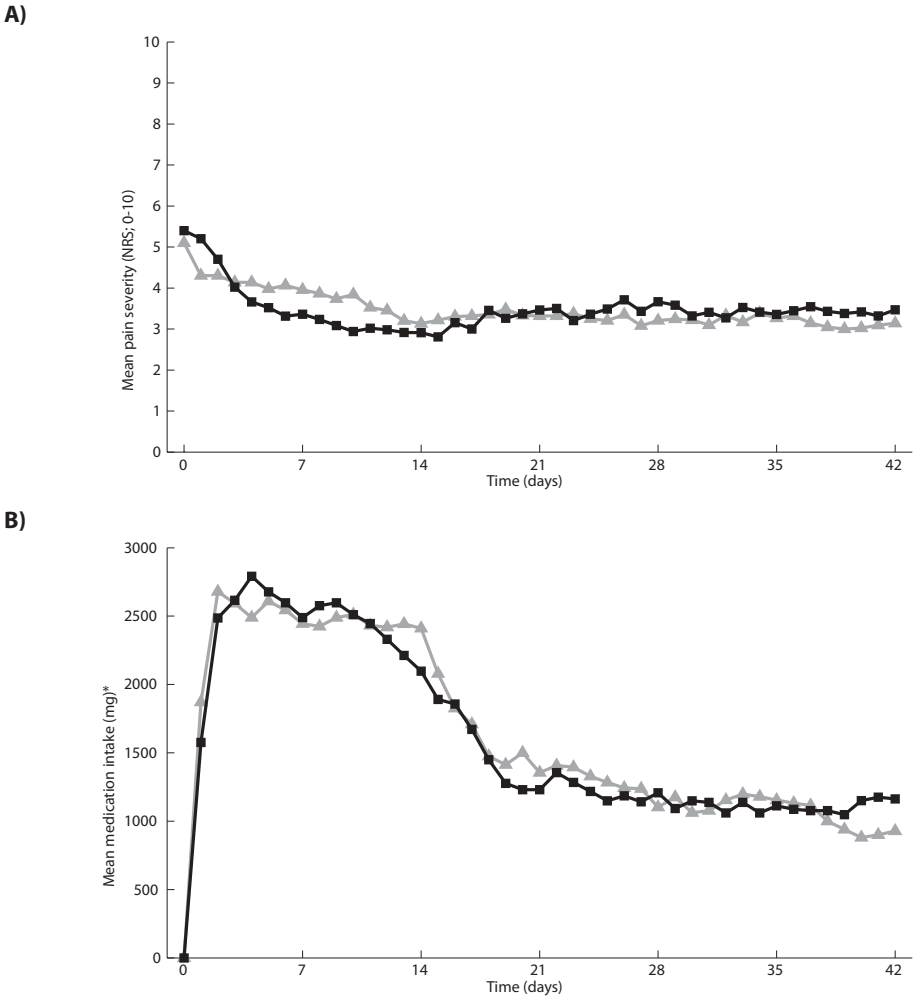

Figure 3. A) Mean pain severity between acetaminophen and diclofenac during the first 6 weeks. **B)** Mean medication intake between acetaminophen and diclofenac during the first 6 weeks. ▲ acetaminophen, ■ diclofenac. * To compare total medication intake of diclofenac versus acetaminophen users, the daily dose of diclofenac was converted (e.g. total use of 150 mg of diclofenac per day is converted to 3000 mg); NRS: Numeric Rating Scale

Table 3. Severity of daily knee pain severity measured with the 0 to 10 numeric rating scale (NRS) using a diary

	Acetaminophen (n=52) Mean (SD)	Diclofenac (n=52) Mean (SD)	Unadjusted mean differences (95% CI)	Adjusted mean differences* (95% CI)	Adjusted effect size*
NRS pain (diary)†					
Daily					
Day 1	4.3 (2.0)	5.2 (2.0)	-0.9 (-1.9 to 0.1)	-0.1 (-0.8 to 0.5)	-0.05
Day 2	4.3 (2.0)	4.7 (2.2)	-0.4 (-1.3 to 0.6)	0.2 (-0.5 to 0.8)	0.09
Day 3	4.1 (2.1)	4.0 (2.3)	0.1 (-0.8 to 1.0)	0.5 (-0.3 to 1.2)	0.22
Day 4	4.1 (2.0)	3.7 (2.2)	0.5 (-0.4 to 1.4)	0.6 (-0.1 to 1.3)	0.29
Day 5	4.0 (2.0)	3.5 (2.3)	0.5 (-0.4 to 1.3)	**0.8 (0.1 to 1.4)***	**0.35**
Day 6	4.1 (1.8)	3.3 (2.3)	0.8 (-0.1 to 1.6)	**0.9 (0.2 to 1.5)***	**0.43**
Day 7	4.0 (2.0)	3.4 (2.2)	0.6 (-0.3 to 1.5)	**1.0 (0.3 to 1.7)***	**0.49**
Day 8	3.9 (1.9)	3.2 (2.1)	0.6 (-0.2 to 1.5)	**1.0 (0.3 to 1.6)***	**0.47**
Day 9	3.7 (2.0)	3.1 (2.2)	0.7 (-0.2 to 1.5)	**0.9 (0.3 to 1.6)***	**0.44**
Day 10	3.8 (2.2)	2.9 (2.0)	0.9 (0.0 to 1.8)	**0.9 (0.2 to 1.5)***	**0.41**
Day 11	3.5 (2.2)	3.0 (2.0)	0.5 (-0.4 to 1.4)	**0.8 (0.1 to 1.5)***	**0.37**
Day 12	3.5 (2.0)	3.0 (2.2)	0.5 (-0.4 to 1.3)	**0.7 (0.0 to 1.5)***	**0.36**
Day 13	3.2 (2.0)	2.9 (2.2)	0.3 (-0.6 to 1.1)	0.7 (-0.1 to 1.4)	0.33
Day 14	3.1 (2.1)	2.9 (2.2)	0.2 (-0.7 to 1.1)	0.6 (-0.2 to 1.4)	0.30
Weekly					
Week 1	4.3 (2.0)	4.1 (2.3)	0.1 (-0.2 to 0.5)	0.6 (-0.1 to 1.2)	0.26
Week 2	3.5 (2.1)	3.0 (2.1)	**0.5 (0.2 to 0.9)***	**0.8 (0.1 to 1.5)***	0.38
Week 3	3.3 (2.2)	3.2 (2.3)	0.1 (-0.2 to 0.5)	0.4 (-0.4 to 1.1)	0.16
Week 4	3.3 (2.1)	3.5 (2.1)	-0.2 (-0.6 to 0.1)	0.1 (-0.7 to 0.9)	0.04
Week 5	3.3 (2.3)	3.4 (2.2)	-0.2 (-0.5 to 0.2)	0.2 (-0.6 to 1.1)	0.10
Week 6	3.1 (2.2)	3.4 (2.2)	-0.3 (-0.7 to 0.0)	0.1 (-0.8 to 1.0)	0.05

* Adjusted for age, gender, BMI and baseline pain; Printed bold: Statistically significant (p-value ≤0.05), † a higher score is worse; NRS: Numeric Rating Scale

Secondary outcomes

Small adjusted mean differences were found in favor of acetaminophen for NRS pain, quality of life, and constant and intermittent pain at 3, 6, 9 and 12-weeks follow-up (Table 4); however, none of these differences were significant. At 12 weeks, 26.5% of the patients in the acetaminophen group were recovered and 47.9% were defined as responder to the treatment. In the diclofenac group, 27.1% were recovered and 39.6% were responders to the treatment.

Table 4. Secondary outcomes measured with 3-weekly questionnaires

	Acetaminophen (n=52) Mean (SD)	Diclofenac (n=52) Mean (SD)	Unadjusted differences (95% CI)	Adjusted differences* (95% CI)	Adjusted effect size*
NRS pain†					
3-weeks	3.4 (2.5)	3.4 (2.4)	-0.1 (-1.1 to 0.9)	-0.0 (-0.9 to 1.0)	-0.02
6-weeks	3.0 (2.4)	3.4 (2.6)	-0.4 (-1.4 to 0.7)	-0.2 (-1.1 to 0.7)	-0.08
9-weeks	2.9 (2.2)	3.1 (2.4)	-0.2 (-1.2 to 0.8)	0.0 (-0.8 to 0.9)	0.02
12-weeks	2.8 (2.3)	2.9 (2.4)	-0.2 (-1.1 to 0.8)	-0.0 (-0.9 to 0.9)	-0.01
ICOAP constant pain†					
3-weeks	25.6 (18.9)	27.4 (23.9)	-1.8 (-10.7 to 7.1)	-2.5 (-10.7 to 5.7)	-0.12
6-weeks	22.5 (18.8)	26.6 (22.0)	-4.1 (-12.5 to 4.3)	-3.7 (-11.4 to 4.1)	-0.18
9-weeks	21.3 (17.6)	25.1 (20.2)	-3.8 (-11.8 to 4.2)	-2.4 (-9.8 to 5.1)	-0.12
12-weeks	20.6 (17.6)	22.3 (21.1)	-1.7 (-9.6 to 6.3)	-0.7 (-8.2 to 6.8)	-0.04
ICOAP intermittent pain†					
3-weeks	31.7 (17.9)	33.6 (25.1)	-1.9 (-10.8 to 7.0)	-2.3 (-10.7 to 6.1)	-0.11
6-weeks	27.0 (18.7)	31.3 (20.5)	-4.3 (-12.4 to 3.7)	-4.1 (-11.6 to 3.5)	-0.21
9-weeks	25.3 (17.3)	31.0 (20.8)	-5.8 (-13.9 to 2.4)	-5.1 (-12.6 to 2.4)	-0.27
12-weeks	24.9 (17.1)	27.3 (20.3)	-2.4 (-10.1 to 5.2)	-1.8 (-9.1 to 5.6)	-0.09
Quality of life‡					
3-weeks	0.76 (0.18)	0.75 (0.24)	0 .02 (-0.07 to 0.11)	0.01 (-0.07 to 0.10)	0.05
6-weeks	0.83 (0.11)	0.76 (0.20)	0.06 (-0.00 to 0.13)	0.07 (-0.01 to 0.14)	0.42
9-weeks	0.82 (0.12)	0.75 (0.22)	0.07 (-0.01 to 0.14)	0.07 (-0.01 to 0.14)	0.41
12-weeks	0.80 (0.14)	0.79 (0.21)	0.02 (-0.06 to 0.09)	0.02 (-0.06 to 0.09)	0.13

			Odds ratio (95% CI)	Adj. odds ratio (95% CI)*
Perceived recovery n/N (%)				
3-weeks	10/46 (21.7)	12/49 (24.5)	0.9 (0.3 to 2.2)	0.9 (0.3 to 2.4)
6-weeks	15/47 (31.9)	9/48 (18.8)	2.0 (0.8 to 5.3)	1.9 (0.7 to 5.0)
9-weeks	13/45 (28.9)	9/44 (20.5)	1.6 (0.6 to 4.2)	1.3 (0.5 to 3.7)
12-weeks	13/49 (26.5)	13/48 (27.1)	1.0 (0.4 to 2.4)	1.0 (0.4 to 2.6)
Treatment responders n/N (%)				
3-weeks	13/45 (28.9)	19/48 (39.6)	0.6 (0.3 to 1.5)	0.6 (0.2 to 1.5)
6-weeks	16/47 (34.0)	14/47 (29.8)	1.2 (0.5 to 2.9)	1.1 (0.4 to 2.9)
9-weeks	18/46 (39.1)	16/42 (38.1)	1.1 (0.4 to 2.5)	0.9 (0.4 to 2.4)
12-weeks	23/48 (47.9)	19/48 (39.6)	1.4 (0.6 to 3.2)	1.4 (0.6 to 3.4)

* adjusted for age, gender, BMI and baseline pain; † a higher score is worse; ‡ a higher score is better; NRS: Numeric Rating Scale; ICOAP: Intermittent and Constant Osteoarthritis Pain

During the first 2 weeks, 3 patients (5.6%) in the diclofenac group used acetaminophen as well as diclofenac. In addition, 5 switched from diclofenac to acetaminophen and 1 switched to an opioid (temgesic). In the acetaminophen group, no patients used co-medication and only 1 patient (1.9%) switched to diclofenac.

Adverse events

Table 5 presents the number of self-reported adverse events at 3-weeks follow-up. In total, 46.2% of the patients in the acetaminophen group and 63.5% in the diclofenac group self-reported one or more possible adverse events. All adverse events were well known and expected reactions for the allocated medications. Patients in the diclofenac group more often reported gastrointestinal (36.5% vs. 13.5%), respiratory (34.6% vs. 15.4%), skin (26.9% vs. 11.5%) and/or psychiatric (38.5% vs 28.8%) reactions.

Table 5. Possible adverse events reported by patients during the first 3 weeks

	Acetaminophen (n=52)		**Diclofenac (n=52)**	
	n	**%**	**n**	**%**
Patients reporting one or more possible adverse events	24	46.2	33	63.5
Psychiatric	15	28.8	20	38.5
Respiratory, thoracic, and connective tissue	8	15.4	18	34.6
Gastrointestinal	7	13.5	19	36.5
Nervous system	13	25	14	26.9
Skin and subcutaneous tissue	6	11.5	14	26.9
General	6	11.5	10	19.2
Cardiovascular	5	9.6	8	15.4
Immune system	0	0	2	3.8
Musculoskeletal and connective tissue	0	0	1	1.9
Organ of vestibular system	0	0	1	1.9

DISCUSSION

In this pragmatic randomized open label trial of 104 primary care patients with knee OA we found that diclofenac was slightly more effective from day 5 to 12, but at 3, 6, 9 and 12 weeks follow-up no differences in knee pain and function were present. In addition, patients in the diclofenac group reported more adverse events. The results of this trial are in line with the treatment guidelines[3-5] for knee OA that recommend acetaminophen as the first choice medication because of its safety profile while previous systematic reviews[27-31] showed that acetaminophen is less effective than NSAIDs.

Until now, only one previous study was performed solely in primary care.[10] Boureau et al. performed a multicenter, double-blinded study assessing the pain intensity over 14 days between ibuprofen and acetaminophen in 222 patients who visited their GP pain due to hip and/or knee OA. They found that ibuprofen was more effective than acetaminophen (effect size: 0.5) over 14 days.[10] Our results and those of Boureau et al.10 were in the same direction, as we also found that diclofenac was more effective within the first two weeks. Compared with Boureau et al.,[10] our patient population was slightly younger, included more men, and had less severe knee pain at baseline.

It has been proposed that patients with more severe pain will respond better to an NSAID than acetaminophen, whereas the effectiveness of these medications is reported to be more similar in mild OA pain.[32] Conversely, others did not find these differences.[33] Although we did not predefine our subgroup analysis, which may have consequences for a high risk of false results,[34] we performed an explorative post-hoc analysis. In our patients with moderate/severe pain (NRS ≥5) at baseline (acetaminophen: n=32; diclofenac: n=35), we found a greater reduction in (NRS) knee pain in favor of the diclofenac group from day 5-10. Mean adjusted differences (acetaminophen minus diclofenac) ranged from 0.8-1.3 on a 0-10 scale. Moreover, our subgroup interaction effect was highly significant (p=0.008). At 3, 6, 9 and 12-weeks follow-up no differences were found for KOOS knee pain and function between the diclofenac and acetaminophen group for moderate to severe pain patients. No differences in effectiveness between acetaminophen and diclofenac were found for mild pain (NRS <5) patients (acetaminophen: n=19; diclofenac: n=17).

Besides focusing on pain relief alone, patient preferences and patient perceived recovery are also important in the treatment of OA. Previous studies showed patient preferences for NSAIDs over acetaminophen.[7,35] In the present study, patients' preferences assessed before randomization showed that 41.4% of the patients preferred acetaminophen, 15.4% preferred diclofenac and 40.4% had no preference. However, patients with a very strong preference for one of the two study medications were probably not included in our trial. At 3, 6, 9 and 12 weeks, we found a small non-significant difference between acetaminophen and diclofenac regarding perceived recovery and treatment response.

Strength and limitations

An important strength was the pragmatic design; our results reflect daily practice better than others that used flare designs, wash-out periods and blinding of patients. Most patients included in the present study did not use pain medication for their knee symptoms during the previous 3 months. And those who did use medication prior to the study (diclofenac group: n=11; acetaminophen: n=17) did not used it in the same dosage as used in the trial. Other studies often use a wash-out period[10-12,14,15,32,36-39] or even needed a flare of symptoms[40-42] prior to randomization. Use of a flare design might result in higher treatment effects[43,44] and this might reduce generalizability of the results in daily practice. Although we stress the fact that placebo-controlled

trials are important as proof of principle, pragmatic trials are also needed to assess the effectiveness of treatments in daily practice. Another strength was the measurement of daily knee pain severity and daily medication intake with a diary. This enabled following patients' daily fluctuations in pain severity and medication use. Another study recommended daily measures in clinical trials because average pain severity over the past week, past 14 days or past month are strongly influenced by pain intensity on the day of assessment.[45]

A limitation of our study is the sample size. Our original calculation was to include 154 patients. However, even after extending the planned inclusion period (18 months) by an additional year, we could include only 104 eligible patients. This might have influenced the precision of our results. To reinforce the inclusion, the GPs' electronic medical records were searched for eligible patients. These more prevalent patients were eligible if they fulfilled the study inclusion criteria and visited their GP in the last 2 months for a new episode of knee complaints. Of the 104 patients, 33 (diclofenac: n=16; acetaminophen: n=17) were included via this medical record search. No differences between incident and prevalent patients were found for pain and function at baseline. However, not surprisingly, prevalent cases had a longer duration of symptoms than incident cases. Another limitation that can be problematic (especially in open label designs) is the use of concurrent treatment. During the first 3 weeks of our study, 14% of the patients in the diclofenac group also visited a physiotherapist compared with 7% in the acetaminophen group. In the diclofenac group 6% used co-medication, whereas none of the acetaminophen group used co-medication. Nevertheless, adjusting for concurrent treatments did not alter our results. A final limitation was the multiple testing of our diary data; significant differences could have been found by chance. However, all calculated effect sizes were in the same direction and all p-values from day 5-12 were ≤ 0.05. Therefore, we decided not to perform a Bonferroni correction.

Conclusion

At 3, 6, 9 and 12 weeks follow-up no differences in knee pain and function were found between the acetaminophen and diclofenac group in primary care patients with knee OA. A small statistically significant reduction in knee pain severity was found at day 5 to 12 in favor of the diclofenac. However, the maximum difference was 1 point on a 0-10 pain scale. Patients more often reported minor adverse reactions after using diclofenac (64%) as compared to acetaminophen (46%). These findings support the currently available clinical guidelines which recommend acetaminophen as first choice of pain medication for patients with knee OA.

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REFERENCES

1. **Buckwalter JA**, Martin JA. Osteoarthritis. *Adv Drug Deliv Rev* 2006;58:150-67.
2. **Woolf AD**, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-56.
3. **Belo JN**, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F.Dutch college of general practitioners (NHG) practice guideline - Nontraumatic knee problems in adults (in Dutch). *Huisarts en Wetenschap* 2008;51:229-40.
4. **Jordan KM**, Arden NK, Doherty M, 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.
5. **Zhang W,** Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981-1000.
6. **Smink AJ**, van den Ende CH, Vliet Vlieland TP, 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.
7. **Wolfe F**, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum* 2000;43:378-85.
8. **Ausiello JC**, Stafford RS. Trends in medication use for osteoarthritis treatment. *J Rheumatol* 2002;29:999-1005.
9. **Barozzi N**, Tett SE. Perceived barriers to paracetamol (acetaminophen) prescribing, especially following rofecoxib withdrawal from the market. *Clin Rheumatol* 2009;28:509-19.
10. **Boureau F**, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004;63:1028-34.
11. **Case JP**, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-78.
12. **Geba GP**, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, Vioxx ACTG. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;287:64-71.
13. **Yelland MJ**, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ, Brown RM. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. *Rheumatology* (Oxford) 2007;46:135-40.
14. **Batlle-Gualda E**, Roman Ivorra J, Martin-Mola E, et al. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. *Osteoarthritis Cartilage* 2007;15:900-8.
15. **Lequesne M**, Fannius J, Reginster JY, Verdickt W, du Laurier MV. Floctafenin versus acetaminophen for pain control in patients with osteoarthritis in the lower limbs. Franco-Belgian Task Force. *Rev Rhum Engl Ed* 1997;64:327-33.

16. **Verkleij SP**, Luijsterburg PA, Koes BW, Bohnen AM, Bierma-Zeinstra SM. Effectiveness of diclofenac versus acetaminophen in primary care patients with knee osteoarthritis: [NTR1485], DIPA-trial: design of a randomized clinical trial. *BMC Musculoskelet Disord* 2010;11:7.
17. **Heintjes EM**, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. *BMC Musculoskelet Disord* 2005;6:45.
18. **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;29:1039-49.
19. **Roos EM**, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64.
20. **Roos EM**, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes* 2003;1:17.
21. **Hawker GA**, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409-14.
22. **Brooks R**. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
23. **Dougados M**, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. *Osteoarthritis Cartilage* 2000;8:395-403.
24. **Pham T**, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12:389-99.
25. **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
26. **Cohen J**. Statistical power analysis for the behavioral sciences. 2nd edition ed. Hillsdale, NJ: Lawrence Erlbaum Assiocates; 1988.
27. **Lee C**, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004;51:746-54.
28. **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006:CD004257.
29. **Verkleij SP**, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis Cartilage* 2011;19:921-9.
30. **Wegman A**, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *J Rheumatol* 2004;31:344-54.
31. **Zhang W**, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004;63:901-7.
32. **Pincus T**, Koch GG, Sokka T, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;44:1587-98.

33. **Bradley JD**, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an antiinflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. *J Rheumatol* 2001;28:1073-6.
34. **Bierma-Zeinstra SM**, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. *Arthritis Res Ther* 2011;13:213.
35. **Pincus T,** Swearingen C, Cummins P, Callahan LF. Preference for nonsteroidal antiinflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. *J Rheumatol* 2000;27:1020-7.
36. **Bradley JD**, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med* 1991;325:87-91.
37. **Golden HE**, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. *Am J Ther* 2004;11:85-94.
38. **Pincus T**, Koch G, Lei H, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004;63:931-9.
39. **Shen H**, Sprott H, Aeschlimann A, et al. Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. *Rheumatology* (Oxford) 2006;45:765-70.
40. **Schnitzer TJ**, Tesser JR, Cooper KM, Altman RD. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1-7.
41. **Schnitzer TJ**, Weaver AL, Polis AB, Petruschke RA, Geba GP, Groups V-aV-S. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee. A combined analysis of the VACT studies. *J Rheumatol* 2005;32:1093-105.
42. **Temple AR**, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6-12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther* 2006;28:222-35.
43. **Scott-Lennox JA**, McLaughlin-Miley C, Lennox RD, et al. Stratification of flare intensity identifies placebo responders in a treatment efficacy trial of patients with osteoarthritis. *Arthritis Rheum* 2001;44:1599-607.
44. **Trijau S**, Avouac J, Escalas C, Gossec L, Dougados M. Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2010;18:1012-8.
45. **Perrot S**, Rozenberg S, Moyse D, Legout V, Marty M, cercle d'etude de douleur en r. Comparison of daily, weekly or monthly pain assessments in hip and knee osteoarthritis. A 29-day prospective study. *Joint Bone Spine* 2011;78:510-5.

CHAPTER 4

NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes

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ABSTRACT

Objective: To identify sources of heterogeneity (statistical, methodological, and clinical) in studies evaluating non-steroidal anti-inflammatory drugs (NSAIDs) vs. acetaminophen in patients with knee and hip osteoarthritis (OA) to elucidate variations in outcomes.

Method: A database search (1966 to January 2010) was made for (randomized) controlled trials ((R)CTs) comparing NSAIDs vs. acetaminophen in knee and hip OA. Extracted data included baseline demographic/clinical characteristics, outcomes at follow-up, and characteristics of study design. Heterogeneity was examined with subgroup-analyses by exploring changes in effect size and with I2 of Higgins. Pain measures were expressed as standardized mean differences.

Results: 15 RCTs, including 21 comparisons of NSAIDs and acetaminophen were included. Statistical heterogeneity was absent (Cochran's Q-test=14.11; I2=0; p=0.78). Moderate clinical heterogeneity was found for comparisons which included both hip and knee OA vs. knee OA only (I2=51; p=0.09). NSAIDs seemed slightly more effective than acetaminophen if more patients with hip OA were included. However, the pooled effect sizes of comparisons with knee OA vs. both knee and hip OA are equal. Low clinical heterogeneity was found for comparisons with low dosage of acetaminophen, normal dosage of NSAIDs, and moderate pain intensity at baseline. Low methodological heterogeneity was found for comparisons with a short duration.

Conclusion: Future trials should present the results of hip and knee OA separately, as moderate clinical heterogeneity was found. There might be differences in effectiveness of NSAIDs vs. acetaminophen in patients with hip vs. knee OA. No significant methodological and statistical heterogeneity was found in studies evaluating NSAIDs vs. acetaminophen.

INTRODUCTION

Guidelines for the treatment of non-traumatic knee complaints, recommend acetaminophen as the first-choice analgesic in treating pain due to osteoarthritis (OA).[1-4] This recommendation is based on a review showing a superior effectiveness of acetaminophen compared to placebo in treating pain due to OA.[5] In addition, recent reviews reported only small improvements (effect sizes from 0.2 to 0.37) in pain in favor of non-steroidal anti-inflammatory drugs (NSAIDs) compared to acetaminophen.[5-8] However, NSAIDs were consistently associated with substantially more side effects.[9-10]
Systematic reviews integrate the results of original studies. In order to pool the data of original studies in a quantitative manner (meta-analysis), the reviews investigate whether statistical heterogeneity exists (i.e. when the statistical difference between studies is larger than expected by chance). If studies are statistically heterogeneous, there is no added value of pooling while the pooled effect size might be biased. No statistical heterogeneity was reported in the four reviews comparing the efficacy of NSAIDs vs. acetaminophen.[5-8]
There are two other types of heterogeneity. Clinical heterogeneity can result from differences in the characteristics of the included patients, from the interventions applied, and from the use of different outcome measures. Methodological heterogeneity arises when different study designs are used, and with differences in the degree of control over bias.[11] However, data on clinical and methodological heterogeneity in systematic reviews are scarce.
A meta-analysis investigating the efficacy of NSAIDs vs. placebo in patients with knee OA found a higher effect size (0.32) for studies that required a flare of symptoms compared to studies without a flare design (effect size 0.23).[12] Vlad et al. examined differences in study characteristics among glucosamine trials in OA; they found consistently higher effect sizes in trials with industry funding (0.47) vs. trials without industry funding (0.05).[13] Furthermore, one randomized controlled trial (RCT) reported that NSAIDs are superior in patients with moderate to severe pain, but in patients with mild intensity pain the differences between NSAIDs and acetaminophen were negligible.[14] Bradley et al., reported that higher baseline pain intensity predicted greater pain relief at follow-up.[15]
The present review assesses the presence of statistical, methodological and clinical heterogeneity of RCTs comparing NSAIDs vs. acetaminophen in knee and hip OA, with the aim to elucidate variations in outcomes.

METHODS

Prisma recommendations

When executing the review the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[16] were followed.

Protocol

Methods of the data-analysis and selection criteria were specified in advance and documented in a protocol (not published).

Search strategy

A search (1966 to January 2010) of PubMed, Embase, Web of Science, Cinahl, Scopus and the Cochrane Library (Cochrane database of systematic reviews, database of abstracts of reviews of effects, and Cochrane central register of controlled trials) was performed to identify studies evaluating the effectiveness of NSAIDs vs. acetaminophen in OA. The databases were searched using the following terms: "Nonsteroid antiinflammatory agent", "Paracetamol", "Acetaminophen" and "Osteoarthritis". A detailed description of the full electronic search strategies is provided in Appendix A.

Selection criteria

Inclusion criteria

All RCTs, controlled clinical trials (CCTs), and quasi-RCTs (qRCTs) comparing NSAIDs and acetaminophen in OA patients aged 18 years and older were included. Trials with a cross-over design were also eligible. OA was either determined clinically and/or with radiography. Studies in the English, German, or Dutch language were included.

Exclusion criteria

Studies were excluded if they did not pertain to OA or concerned non-oral pharmacologic therapy.

Study collection

Two authors (SV and PL) independently evaluated all eligible titles, abstracts and full-text articles based on the inclusion and exclusion criteria. Disagreement was resolved by discussion. From relevant articles the references lists were searched for additional articles.

Data extraction

One author (SV) performed the data extraction using a standardized form. In case of uncertainty a second author was consulted. The following data were collected: 1) demographic and clinical characteristics at baseline (age, baseline pain intensity, previous used medication, mean duration of complaints due to OA, radiographic severity and patient preferences); 2) outcomes at follow-up (mean difference and standard deviations (SD) in pain, use of rescue medication, co-interventions and loss to follow-up); and 3) design characteristics (flare design, localisation of OA, dosage of NSAID and acetaminophen, duration of follow-up in weeks, sample size, criteria for eligible patients, setting and recruitment and industry funding).

Methodological quality of the studies

The methodological quality of the included studies was independently assessed by two authors (SV and PL, BK, AB or SB) using a predefined list by the Cochrane Collaboration,[17] which is based on the Delphi criteria.[18] Dissimilarity between researchers was resolved by discussion. Scored items were: 1) randomization procedure (randomization generation and randomization concealment), 2) blinding (participants, care provider and outcome assessors), 3) incomplete outcome data (drop-out rates and number of participants analysed in the group of allocation), 4) selective outcome reporting, and 5) other sources of bias related to comparability of study groups at baseline, co-interventions, compliance to treatment and timing of outcome assessment. Each item was rated as 'Yes' (indicating a low risk of bias), 'No' (indicating a high risk of bias) or Unclear' (indicating unclear or unknown risk of bias).

Types of outcome measures

Pain intensity was used as the main outcome measure, which was assessed by standardized and validated scales or questionnaires, such as the Western Ontario and McMaster Osteoarthritis index (WOMAC)[19] or the visual analog scale (VAS). If WOMAC or VAS data were not available, other measures of pain were used (e.g. pain at rest, pain during walking, etc.). If possible, all scales and questionnaires were converted to a standardized scale from 0-100 (0 = no pain; 100 = worst pain ever). In addition, standardized mean differences (SMD) of pain were used to measure the magnitude of the treatment effect (with negative values in favor of NSAIDs). According to Cohen, a treatment effect of 0.2-0.5 is regarded as a small effect, 0.5-0.8 is a medium effect and a score of 0.8 or higher a large treatment effect.[20] If data on the primary outcome were missing, authors of the included studies were contacted.

Data analyses

Extracted data on number of patients, mean differences in pain intensity and standard deviations (SD) were used to estimate the pooled SMD. If SDs were not reported, they were obtained from confidence intervals or standard errors. If necessary, authors of the specific study were asked for more information. Otherwise, baseline SDs were used or imputations were made using SDs from a similar study. Regarding cross-over design, only data of the first comparison before crossing-over were included for analysis. If eligible studies compared different types or multiple dosages of NSAIDs to acetaminophen, all types and dosages were included in the analyses as separate comparisons. To avoid double counting of the acetaminophen group, the number of participants in the acetaminophen group was divided by the number of comparisons of NSAIDs.

Heterogeneity was assessed using subgroup analyses. A statistical test to indicate the extent of heterogeneity is the Cochran's Q-test. However, this test has relatively low power to detect heterogeneity when meta-analysis includes a small number of studies. Therefore, the degree of heterogeneity was quantified with the method

of Higgins et al.[21-22] With the method of Higgins et al., the variation across a study caused by heterogeneity and not by chance is measured with I^2. I^2 is calculated with the Cochran's Q-test and the degrees of freedom. I^2 values range from 0% to 100%: an I^2 of 0% indicates no observed heterogeneity, and 25%, 50%, and 75% indicate low, moderate and high heterogeneity, respectively. An I^2 of 50% means that half of the total variability among effect sizes is not caused by sampling error, but by true heterogeneity between studies.[21] Besides using I^2, the extent of heterogeneity was also assessed by exploring the changes in SMD.

We hypothesized that the following trial characteristics might influence the results: baseline pain intensity, flare design, use of previous pain medication, radiographic severity, localisation of OA, methodological quality, duration of follow-up, sample size, dosage of acetaminophen, types and dosage of NSAID and industry funding.

To assess the possibility of publication bias we evaluated a funnel plot visually for symmetry.

Baseline pain intensity was categorized as 'moderate' (≤55 on a scale of 0-100) versus 'high' (>55). Dosage of NSAID was categorized, based on the Dutch information leaflet, as 'normal' for ibuprofen 1200 mg, rofecoxib 12.5 mg, naproxen 440 and 660 mg and floctafenin 800 mg. Dosage of NSAID was categorized as 'high' for ibuprofen 2400 mg, diclofenac 150 mg, rofecoxib 25 mg, aceclofenac 200 mg, celecoxib 200 mg and naproxen 750 mg. Types of NSAIDs were categorized as cyclo-oxigynase-2 inhibitors (rofecoxib and celecoxib), phenylacetic acids (diclofenac and aceclofenac) or propanoic-phenolic acids (ibuprofen and naproxen). Dosage of acetaminophen was categorized as 'low' (<3000 mg) or 'high' (≥3000 mg). Industry funding was categorized as 'absent' (no reports of industry funding were reported in the study) and 'present'. Duration of follow-up was defined as 'short follow-up' (<6 weeks) or 'long follow-up' (≥6 weeks). Sample size was divided into 'small' (<100 patients) and 'large' (≥100 patients).

We used both fixed-effect and random-effect models to analyse the results. If both models presented the results equally, only the results of the fixed-effect model are presented. Review manager 5.0 and STATA 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) were used for the analyses.

RESULTS

The literature search yielded 1659 potentially eligible studies. Finally, 14 articles were included in the present review (Figure 1).[14, 23-35] One article published data from two separate studies.[30] Four studies had more than one comparison (range 2-3).[25, 27, 31-32] In total, 15 studies and 21 comparisons were included in the present review.

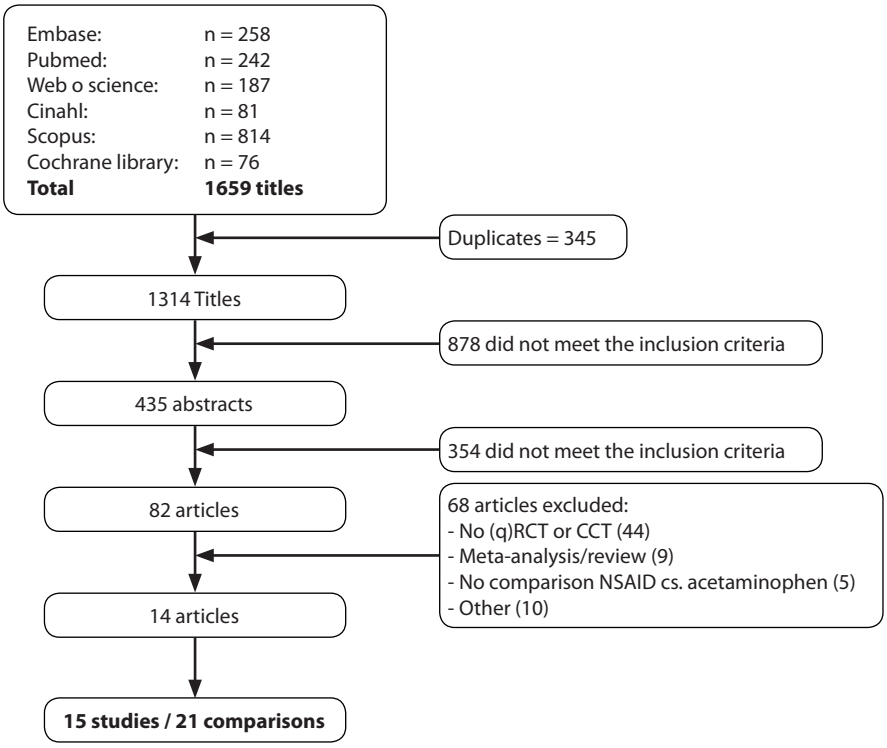

Figure 1. Flowchart of the study selection

Study characteristics

Table 1 presents the characteristics of the included studies. Both fixed-effect and random-effect models yielded the same results, so we presented the results of the fixed-effect analysis only. A total of 5133 patients were randomized, of whom 3275 received an NSAID and 1858 received acetaminophen. All studies were RCTs. Three studies had a cross-over design.[14, 29-30] All studies included patients with knee OA. Six studies also included patients with hip OA. [14, 24, 29-30, 34] Seven different NSAIDs (naproxen, celecoxib, rofecoxib, floctafenin, ibuprofen, diclofenac and aceclefenac) were compared to acetaminophen. With the exception of one study,[35] all studies used a wash-out period prior to randomization. Three studies also required a flare of symptoms after the wash-out period.[31-32, 34] Industry funding was reported in 11 of the 15 studies.[14, 23-24, 27-28, 30-34] All studies reported hip or knee pain intensity as a primary outcome for effectiveness of NSAID vs. acetaminophen. Pain intensity was measured by the WOMAC pain scale, a 0-100 mm VAS, or a 4/5-point numerical scale (pain at rest). The mean duration of follow-up was 15.4 (range 1-104) weeks.

Table 2 presents the risk of bias assessment. With the exception of one study,[33] all studies were blinded. The procedure of randomization generation, randomization concealment and blinding was satisfactorily reported in only 4 studies.[23, 29, 34-35]

Table 1. Characteristics of studies evaluating the effectiveness of NSAIDs versus acetaminophen in patients with knee and hip osteoarthritis

Study (year)	n	Joints (%)	Mean age (years)	NSAID and dose (mg/day)	Acet[$] dose (mg/day)	Baseline pain NSAID	Baseline pain acet	Duration (weeks)	Flare design	Industry involvement
Battle-Gualda (2007)[23]	168	Knee	62.4	Aceclofenac 200	3000	62.2[‡]	62.4[‡]	6	Wash out	Yes
Boureau (2004)[24]	222	Hip (29.5) Knee (70.5)	66.5	Ibuprofen 1200	3000	71.3[†]	72.2[†]	2	Wash out	Yes
Bradley (1991a)[25]	184	Knee	56.5	Ibuprofen 1200	4000	50[^]	54[^]	4	Wash out	No
Bradley (1991b)[25]				Ibuprofen 2400		49[^]				
Case (2003)[26]	54	Knee	62.5	Diclofenac 150	4000	37[†]	31.8[†]	12	Wash out	No
Geba (2002a)[27]				Celecoxib 200						
Geba (2002b)[27]	382	Knee	62.6	Rofecoxib 12.5	4000	Unknown[†]	Unknown[†]	6	Wash out	Yes
Geba (2002c)[27]				Rofecoxib 25						
Golden (2004)[28]	310	Knee	60.7	Naproxen 440/660	4000	35.3[^]	34.5[^]	1	Wash out	Yes
Lequesne (1997)[29#]	192	Hip (33.5) Knee (66.5)	64.7	Floctafenin 800	3000	64.5[‡]	60.9[‡]	1.7	Wash out	No
Pincus (2001)[14]	227	Hip (22) Knee (78)	61.5	Diclofenac 150	4000	40.2[†]	42.1[†]	9	Wash out	Yes
Pincus (2004a)[30#]	235	Hip (16.4) Knee (83.6)	63.5	Celecoxib 200	4000	48.6[†]	52.8[†]	6	Wash out	Yes
Pincus (2004b)[30#]	250	Hip (15.5) Knee (84.5)	63.7	Celecoxib 200	4000	52[†]	51.6[†]	6	Wash out	Yes
Schnitzer (2005a)[32]				Celecoxib 200						
Schnitzer (2005b)[32]	1578	Knee	62.1	Rofecoxib 12.5	4000	Unknown[†]	Unknown[†]	6	Yes	Yes
Schnitzer (2005c)[32]				Rofecoxib 25						

Table 1. Continued

Study (year)	n	Joints (%)	Mean age (years)	NSAID and dose (mg/day)	Acet[$] dose (mg/day)	Baseline pain NSAID	Baseline pain acet	Duration (weeks)	Flare design	Industry involvement
Schnitzer (2009a)[31]	403	Knee	59.8[¶]	Rofecoxib 12.5	1300	57.2[†]	58.1[†]	4	Yes	Yes
Schnitzer (2009b)[31]				Rofecoxib 25		62.1[†]				
Shen (2006)[33]	20	Knee	Unknown	Rofecoxib 25	4000	68.5[†]	90.5[†]	12	Wash out	Yes
Temple (2006)[34]	571	Hip/Knee	59.3	Naproxen 750	4000	Unknown	Unknown	52	Yes	Yes
Williams (1993)[35]	178	Knee	59.6	Naproxen 750	2600	26[^]	29[^]	104[*]	No	No

[*] Intention to treat analysis after 42 days; [#] Cross-over design; [¶] Characteristics of the intention to treat analysis; [^] Rest pain measured on a 4-point or a 5-point scale; [†] Pain measured with the WOMAC; [‡] Pain measured with a visual analogue scale (VAS); [$] acet: acetaminophen

Table 2. Risk of Bias assessment of included randomized controlled trials

Study (year)	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Drop out	Participant analysed in group of allocation	Selective outcome reporting	Similar groups at baseline	Co-inter-ventions	Compliance	Timing of outcome assessment
Battle-Gualda (2007)[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Boureau (2004)[24]	Unsure	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Yes
Bradley (1991)[25]	Unsure	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes
Case(2003)[26]	Unsure	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Geba (2002)[27]	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Yes
Golden (2004)[28]	Unsure	Unsure	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Lequesne (1997)[29]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes
Pincus (2001)[14]	Unsure	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Unsure	Unsure	Yes
Pincus (2004a)[30]	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Yes
Pincus (2004b)[30]	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Yes
Schnitzer (2005)[32]	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Unsure	Yes	Yes
Schnitzer (2009)[31]	Unsure	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes
Shen (2006)[33]	Unsure	Unsure	Unsure	Unsure	Unsure	Yes	Unsure	Yes	Unsure	Yes	Unsure	Yes
Temple (2006)[34]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unsure	Unsure	Yes	Yes
Williams (1993)[35]	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes

Effectiveness of NSAID versus acetaminophen

A total of 14 studies and 20 comparisons provided analyzable data of 2991 patients in the NSAID group vs. 1561 patients in the acetaminophen group. The pooled SMD was -0.2995% confidence interval (95% CI): -0.35 to -0.22, referring to a small treatment effect in favor of NSAIDs (Figure 2). This finding is in accordance with results from previous reviews.[5-8]

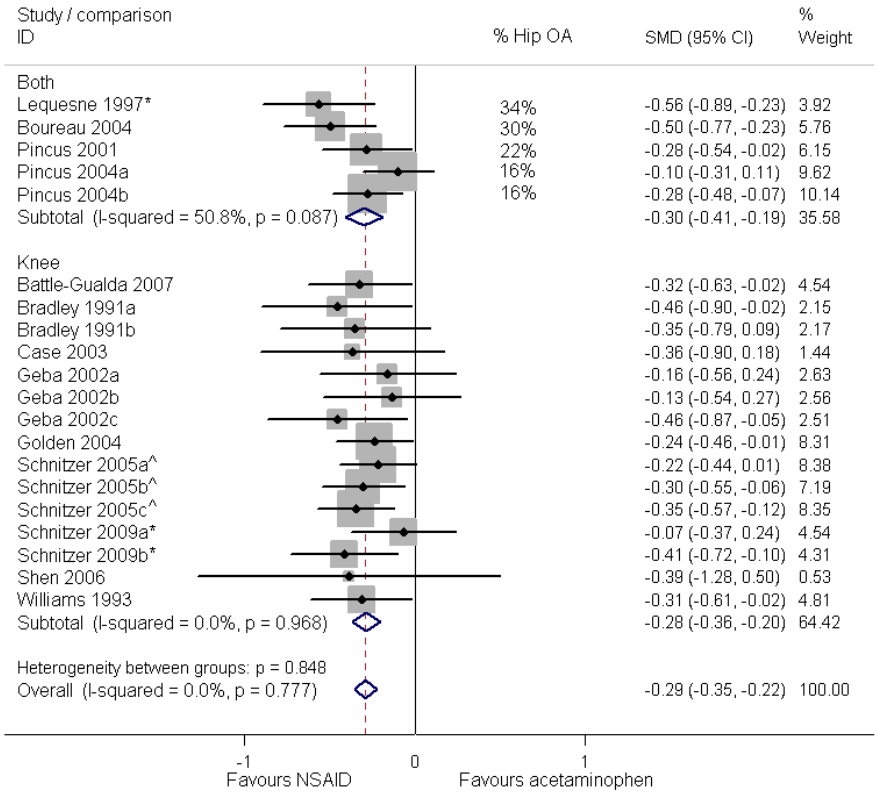

Figure 2. Forest plot of standardized mean differences for pain improvement in NSAIDs vs. acetaminophen, stratified by localisation of osteoarthritis (OA).

Heterogeneity

Statistical heterogeneity

No statistical heterogeneity was found between the included comparisons evaluating NSAIDs vs. acetaminophen in knee and hip OA (Cochran's Q-test=14.11; I^2=0; p=0.78) (Figure 2).

Methodological heterogeneity

Subgroup analysis (Table 3) showed no differences in effect between comparisons with and without a flare design (SMD: -0.27; 95% CI: -0.39 to -0.16 versus -0.30; -0.38 to -0.21), between comparison that were inadequately blinded (-032; -0.60 to -0.04) vs. adequately blinded comparisons (-0.29; -0.35 to -0.22), comparisons that adequately addressed with incomplete outcome data (-0.28; -0.35 to -0.21) vs. comparisons that inadequately addressed incomplete outcome data (-0.32; -0.47 to -0.17) and comparisons that adequately addressed other sources of bias (-0.28; -0.45 to -0.11) vs. comparisons that did not address other sources of bias adequately (-0.29; -0.36 to -0.22).

Comparisons without industry funding have a somewhat higher treatment effect in favor of NSAIDs vs. comparisons with industry funding (-0.40; -0.59 to -0.22 versus -0.30; -0.38 to -0.21). The same was found for comparisons with an adequate randomization procedure (-0.39; -0.57 to -0.21) vs. uncertainty in the randomization procedure (-0.27;-0.34 to -0.20), comparisons with a sample size of <100 patients (-0.35;-0.46 to -0.23) vs. comparisons with a sample size of ≥ 100 patients (-0.27;-0.34 to -0.19) and for comparisons with a short follow-up (-0.35;-0.46 to -0.23) vs. long follow-up (-0.26; -0.34 to -0.18). Comparisons with a short follow-up showed minor methodological heterogeneity (I^2=19%). None of these differences were of clinical or statistical significance (Table 3).

Table 3. Pooled effect estimates of clinical and methodological heterogeneity

	Number of studies / comparisons	**SMD (95% CI)**	**I^2**
All studies	14/20	-0.29 (-0.35 to -0.22)	0
Methodological characteristics			
Flare design			
Present	2/5	-0.27 (-0.39 to -0.16)	0
Absent	12/15	-0.30 (-0.38 to -0.22)	0
Industry funding			
Present	10 studies	-0.30 (-0.38 to -0.21)	0
Absent	4 studies	-0.40 (-0.59 to -0.22)	0
Randomization procedure			
Adequate	3/3	-0.39 (-0.57 to -0.21)	0
No/Unsure	11/17	-0.27 (-0.34 to -0.20)	0
Blinding			
Adequate	12/18	-0.29 (-0.35 to -0.22)	0
No/Unsure	2/2	-0.32 (-0.60 to -0.04)	0
Incomplete outcome data			
Adequate	10/16	-0.28 (-0.35 to -0.21)	0
No/Unsure	4/4	-0.32 (-0.47 to -0.17)	0

Table 3. Continued

	Number of studies / comparisons	SMD (95% CI)	I2
Bias			
Adequate	3/3	-0.28 (-0.45 to -0.11)	0
No/unsure	11/17	-0.29 (-0.36 to -0.22)	0
Sample size			
< 100 in NSAID group	7/10	-0.35 (-0.47 to -0.23)	0
≥ 100 in NSAID group	7/10	-0.27 (-0.34 to -0.19)	0
Duration of follow-up			
< 6 weeks	5/7	-0.35 (-0.46 to -0.23)	19%
≥ 6 weeks	9/13	-0.26 (-0.34 to -0.18)	0
Clinical characteristics			
Localisation of osteoarthritis			
Knee	9/15	-028 (-0.36 to -0.20)	0
Knee and hip	5/5	**-0.29 (-0.35 to -0.22)**	**51%**
Baseline pain intensity*			
Moderate	7/8	-0.37 (-0.51 to -0.24)	19%
High	5/6	-0.25 (-0.35 to -0.16)	0
Missing	2/6		
Dosage of acetaminophen†			
Low	2/3	-0.36 (-0.49 to -0.24)	21%
High	12/17	-0.26 (-0.34 to -0.18)	0
Dosage of NSAID‡			
Normal	7 comparisons	-0.32 (-0.43 to -0.20)	26%
High	13 comparisons	-0.27 (-0.35 to -0.19)	0
Type of NSAID¶			
Coxib	6/11	-0.24 (-0.33 to -0.16)	0
Phenylacetic acids	3/3	-0.31 (-0.49 to -0.12)	0
Propanoic-phenolic acids	4/5	-0.35 (-0.48 to -0.21)	0
Other	1/1		

Bold = p<0.10. I^2 = Measure of heterogeneity; SMD = standardized mean difference (negative values are in favor of NSAIDs); 95% CI: = 95% confidence interval; ^ With multi-group studies, only the highest dosage was included for analysis; † Medication acetaminophen: low ≤ 2600 mg; ‡ Medication NSAID: normal: ibuprofen 1200 mg, rofecoxib 12.5 mg, naproxen 440/660 mg, and floctafenin 800 mg; Medication NSAID high: ibuprofen 2400 mg, diclofenac 150 mg, rofecoxib 25 mg, naproxen 750 mg, aceclofenac 200 mg, and celecoxib 200 mg; ¶ cyclo-oxigynase-2 inhibitors (coxibs) are rofecoxib and celecoxib; phenylacetic acids are diclofenac and aceclofenac; propanoic-phenolic acids are ibuprofen and naproxen; Other: Floctafenin. * High baseline pain was defined as a pain score of 55 or higher on a scale of 0-100; moderate pain intensity was a pain score of 55 or lower.

Clinical heterogeneity

Comparisons which included patients with hip and knee OA showed moderate clinical heterogeneity (I^2=51%; p=0.09) (Table 3). There was a small trend for a better effectiveness of NSAIDs compared with acetaminophen in studies which included a higher percentage of patients with hip OA. However, the pooled effect sizes of the comparisons with knee OA only vs. knee and hip OA are the same (Figure 2). Comparisons with moderate baseline pain intensity, low doses of acetaminophen, and normal doses of NSAIDs showed only low clinical heterogeneity (I^2 of 19%, 21% and 26%, respectively). Subgroup analysis (Table 3) showed that comparisons with moderate pain intensity at baseline have a slightly higher treatment effect in favor of NSAIDs than comparisons with high pain at baseline (SMD: -0.37; 95% CI: -0.51 to -0.24 vs. -0.25;-0.35 to -0.16). The same was found for comparisons with a low dosage of acetaminophen (-0.36;-0.49 to -0.24) vs. a high dosage of acetaminophen (-0.26;-0.34 to -0.18), comparisons with a normal dosage of NSAIDs (-0.32;-0.43 to -0.20) vs. high dosage of NSAIDs (-0.27;-0.35 to -0.19) and for comparisons of propanoic-phenolic acids (-0.35;-0.48 to -0.21) vs. phenylacetic acids and coxibs (-0.31; -0.49 to -0.12 and -0.24; -0.33 to -0.16, respectively).

Publication bias

Based on the funnel plot, there appears to be no indication for publication bias (Figure 3).

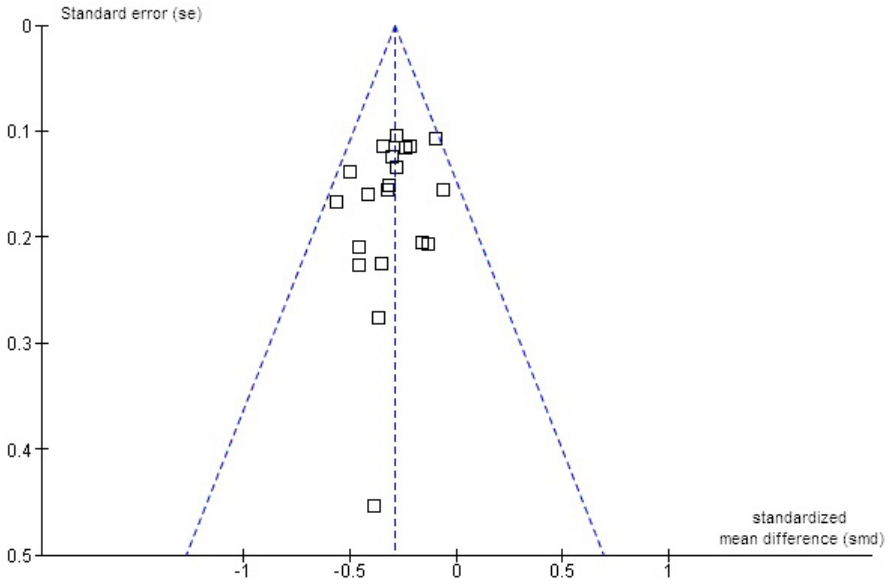

Figure 3. Funnel plot for publication bias.

DISCUSSION

This systematic review investigated various sources of heterogeneity (statistical, clinical and methodological) of RCTs evaluating the effectiveness of acetaminophen vs. NSAIDs in patients with knee and hip OA in relation to pain outcomes. We found moderate clinical heterogeneity for the five studies that included both hip and knee OA.[14,24,29-30,34] Unfortunately, data on knee and hip OA were not presented separately in the available studies. Our forest plot showed a higher effect size in favor of NSAIDs in studies that included a higher percentage of patients with hip OA. Svensson et al. also found differences in effectiveness in patients with hip and knee OA treated with naproxen. Yet, they found a greater improvement in patients with knee OA compared with hip OA.[36] Future research should stratify the results of hip and knee OA. Furthermore, our review showed low but non-significant clinical and methodological heterogeneity for comparisons evaluating low dosage of acetaminophen, normal dosage of NSAIDs, moderate pain intensity at baseline, and follow-up of ≤6 weeks.
Pincus et al. reported that efficacy of NSAIDs and acetaminophen is probably the same in patients with mild OA.[14] Our subgroup analyses showed a higher effect size in trials with moderate pain intensity at baseline compared to trials with high pain at baseline; however, the differences were small and therefore not important.

In contrast to Vlad et al.[13] our heterogeneity analyses showed that studies without industry funding have a slightly higher but non-significant effect size compared with studies with industry funding (SMD: -0.40; 95% CI: -0.59 to -0.22 vs. -0.30; -0.38 to -0.21). This finding is in accordance with Lee et al.6 In a post hoc stratification we looked more deeply for influences of industry funding. We stratified funded studies according to their SMD. Studies that were significantly in favor of NSAIDs showed no heterogeneity but, not surprisingly, showed a higher overall SMD (-0.33; -0.42 to -0.24) in favor of NSAIDs compared to those studies that were not significantly in favor of NSAIDs (-0.14; -0.26 to -0.02).

Except for one study,[35] all included studies used a pre-treatment wash-out period before randomization. Additionally, three studies also required a flare of symptoms after medication discontinuation, before the start of the study.[31-32,34] The study of Scott-Lennox et al. examined the impact of flare designs on trial results and reported a more profound pain reduction in patients with an intense flare prior to treatment.[37]
Four of the included studies compared rofecoxib (Vioxx) with acetaminophen,[27,31-33] whereas rofecoxib was withdrawn from the market in 2004. We have included these studies in the present review because we were interested in the heterogeneity of studies evaluating the effect of NSAIDs vs. acetaminophen on pain control. However, additional analysis showed that the exclusion of the rofecoxib trials did not alter the results (data not shown).

Similar to Bjordal et al.,[12] we found that mean age of the participants was relatively low (61.6 years; SD 2.46) for patients with OA. Three studies excluded participants above 75 years of age[23,26,34] and one study excluded patients aged 85 years and older.[24] Although, prescribing NSAIDs in older adults is not without risks,[38] the exclusion of

these patients could cause selection bias. Therefore, future studies should not exclude older patients but carefully screen them before inclusion and monitor them after inclusion.

In line with previous reviews,[5-8] we found a significant improvement in pain in favor of NSAIDs in patients with knee and/or hip OA. We included three additional studies[23,31,34] that were published since the last review appeared in 2006.[5]
The effectiveness of acetaminophen versus NSAIDs is an important question in all guidelines for OA. It is striking, that there is a relative lack of good quality randomized studies that evaluate the effectiveness of acetaminophen versus NSAIDs. Therefore, high quality research is needed to substantiate the effectiveness of NSAIDs over acetaminophen.

Limitations

The present review has some limitations. First, although no publication bias was revealed (Figure 3), we cannot be certain that all published/unpublished studies were retrieved. Secondly, four studies included more than one comparison of NSAIDs.[25,27,31-32] We analyzed each comparison separately and divided the number of participants of the acetaminophen group by the number of comparisons of NSAIDs which could have biased the results, possibly leading to an underestimation. Thirdly, one of our aims was to examine relevant trial characteristics that may cause heterogeneity. However, not all clinical features were always reported satisfactorily. For example, data on the use of previous pain medication was only reported satisfactorily in 4 trials (which included 9 comparisons),[26-27,30,32] the mean duration of complaints was reported in 4 trials (which included 5 comparisons)[23-24,30,35] and radiographic severity was only reported in 5 trials (which included 6 comparisons).[14,23,26,30,35] These characteristics may have influenced the reported results. Moreover, Case et al. reported that prior use of NSAIDs predicted a better response of NSAIDs compared to acetaminophen.[26]

Another limitation is that, due to the small numbers we performed subgroup analysis with only one study characteristic (univariable analysis). Based on univariable analyses it is impossible to draw broad conclusion. Furthermore, it was not possible to study interaction effects of the treatment in subgroups of patients. Therefore, future meta-analyses should focus on individual patient data (IPD). The use of IPD in meta-analyses has been described as the gold standard,[39] allowing to assess the existence of heterogeneity more reliably. Furthermore, IPD can be used to investigate specific treatment effects in various subgroups.[40]

Conclusion

In conclusion, future trials should present the results of patients with hip and knee OA separately, as we found moderate heterogeneity in trials that included patients with both knee and hip OA. Furthermore, no clinically relevant statistical, methodological, or clinical heterogeneity was found for studies evaluating the effectiveness of NSAIDs vs. acetaminophen in knee and hip OA.

REFERENCES

1. **Belo JN**, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F. NHG-Standaard niet-traumatische knieproblemen bij volwassenen. *Huisarts en Wetenschap* 2008;51:229-240.
2. **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, 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;62:1145-1155.
3. **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981-1000.
4. 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;43:1905-1915.
5. **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006:CD004257.
6. **Lee C**, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004;51:746-754.
7. **Zhang W**, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004;63:901-907.
8. **Wegman A**, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *J Rheumatol* 2004;31:344-354.
9. **Laine L**, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2006;24:751-767.
10. **Ong CK**, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007;5:19-34.
11. **Higgins J**, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002;7:51-61.
12. **Bjordal JM**, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004;329:1317.
13. **Vlad SC**, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 2007;56:2267-2277.
14. **Pincus T**, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;44:1587-1598.
15. **Bradley JD**, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an antiinflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. *J Rheumatol* 2001;28:1073-1076.
16. **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions:

explanation and elaboration. J *Clin Epidemiol* 2009;62:e1-e34.

17. **Higgins J**, Altman D. Assessing risk of bias in included studies. *Handbook for systematic reviews of interventions (version 501)*: The cochrane Collaboration; 2008.
18. **Verhagen AP**, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235-1241.
19. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
20. **Cohen J**. *Statistical power analysis for the behavioral sciences*. 2nd edition ed. Hillsdale, NJ: Lawrence Erlbaum Assiocates, 1988.
21. **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
22. **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.
23. **Batlle-Gualda E**, Roman Ivorra J, Martin-Mola E, Carbonell Abello J, Linares Ferrando LF, Tornero Molina J, et al. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. *Osteoarthritis Cartilage* 2007;15:900-908.
24. **Boureau F**, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004;63:1028-1034.
25. **Bradley JD**, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med* 1991;325:87-91.
26. **Case JP**, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-178.
27. **Geba GP**, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, Vioxx ACTG. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;287:64-71.
28. **Golden HE**, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. *Am J Ther* 2004;11:85-94.
29. **Lequesne M**, Fannius J, Reginster JY, Verdickt W, du Laurier MV. Floctafenin versus acetaminophen for pain control in patients with osteoarthritis in the lower limbs. Franco-Belgian Task Force. *Rev Rhum Engl Ed* 1997;64:327-333.
30. **Pincus T**, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004; 63:931-939.
31. **Schnitzer TJ**, Tesser JR, Cooper KM, Altman RD. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1-7.
32. **Schnitzer TJ**, Weaver AL, Polis AB, Petruschke RA, Geba GP, Groups V-aV-S. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee. A combined analysis of the VACT studies. *J Rheumatol* 2005;32:1093-1105.

33. **Shen H**, Sprott H, Aeschlimann A, Gay RE, Michel BA, Gay S, et al. Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2006;45:765-770.
34. **Temple AR**, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6-12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther* 2006;28:222-235.
35. **Williams HJ**, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis and Rheumatism* 1993;36:1196-1206.
36. **Svensson O**, Malmenas M, Fajutrao L, Roos EM, Lohmander LS. Greater reduction of knee than hip pain in osteoarthritis treated with naproxen, as evaluated by WOMAC and SF-36. *Ann Rheum Dis* 2006;65:781-784.
37. **Scott-Lennox JA**, McLaughlin-Miley C, Lennox RD, Bohlig AM, Cutler BL, Yan C, et al. Stratification of flare intensity identifies placebo responders in a treatment efficacy trial of patients with osteoarthritis. *Arthritis Rheum* 2001;44:1599-1607.
38. **Barkin RL**, Beckerman M, Blum SL, Clark FM, Koh EK, Wu DS. Should nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed to the older adult? *Drugs Aging* 2010;27:775-789.
39. **Stewart LA**, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof* 2002;25:76-97.
40. **Bierma-Zeinstra SMA**, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. *Arthritis Res Ther* 2011;13:213.

APPENDIX A.

Medical Subject Headings (mesh) and textword (tw) search strategies performed in Embase, Cinahl, Cochrane library, Scopus, PubMed, and Web of Science (1966 to January 2010)

Embase/Cinahl/ Cochrane library/Scopus	Pubmed / Web of Science
1. Nonsteroid antiinflammatory agent/syn*	1. Anti-Inflammatory Agents, Non-Steroidal[mesh
2. Paracetamol/syn*#	2. NSAIDs[tw]
3. Acetaminophen	3. Nonsteroidal Antiinflammatory Agents[tw]
4. Osteoarthritis/syn*	4. Non-Steroidal Anti-inflammatory Agents[tw]
5. Controlled clinical trial/lim^#	5. Non Steroidal Anti Inflammatory Agents[tw]
6. Randomized controlled trial/lim^#	6. Nonsteroidal Anti-Inflammatory Agents[tw]
7. Adult/lim^#	7. Nonsteroidal Anti Inflammatory Agents[tw]
8. aged/lim^#	8. Non-Steroidal Antirheumatic Agents[tw]
9. Title-abstract-keyword†	9. Aspirin-Like Agents[tw]
	10. Aspirin Like Agents[tw]
	11. Analgesics, Anti-Inflammatory[tw]
	12. Analgesics, Anti Inflammatory[tw]
	13. Anti-Inflammatory Analgesics[tw]
	14. OR 1-13
	15. acetaminophen[mesh]
	16. Acetaminophen[tw]
	17. Hydroxyacetanilide[tw]
	18. APAP[tw]
	19. N-Acetyl-p-aminophenol[tw]
	20. p-Acetamidophenol[tw]
	21. p-Hydroxyacetanilide[tw]
	22. Paracetamol[tw]
	23. Acetamidophenol[tw]
	24. Acephen[tw]
	25. Tylenol[tw]
	26. Panadol[tw]
	27. Acamol[tw]
	28. OR 15-27
	29. osteoarthritis[mesh]
	30. osteoarthritis[tw]
	31. osteoarthrosis[tw]
	32. OR 29-31

* Syn = Synonym. The term synonym is only used in Embase; ^ Lim = Limitation; # Search strategy only used in Embase.; mesh = medical subject heading; tw= text word; † Search strategy only used in Scopus.

CHAPTER 5

Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period

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ABSTRACT

Background: Although pain due to osteoarthritis (OA) generally deteriorates over time, there is a large individual variation in the course of pain. This study examines the different longitudinal trajectories of patients with hip pain due to OA.

Methods: Data from a previously performed randomized controlled trial were used to investigate the course of pain over 2-years in 222 patients with clinically and radiographically determined hip OA. Pain was measured with a visual analogue scale (VAS; 0-100). Latent class growth analysis was used to determine the number of trajectories of patients with hip pain due to OA.

Results: Analyses yielded five trajectories of pain due to hip OA. Trajectory 1 ('mild pain'; n=69) consists of patients with stable, mild pain. Patients in trajectory 2 ('moderate pain'; n=31) fluctuated slightly between moderate to severe pain levels over 2-years. Trajectory 3 ('always pain'; n=32) consists of patients with severe pain. Patients in trajectory 4 ('regularly progressing'; n=48) started with mild pain and progressed slowly to moderate pain. Trajectory 5 ('highly progressing'; n=42) also started with mild pain but quickly progressed to severe pain over 2 years. Compared with the 'mild pain' group, patients in the 'always pain' group had more severe radiographic hip OA, morning stiffness, decreased range of motion. The 'highly progressing' group had more severe radiographic hip OA and morning stiffness.

Conclusions: Latent class growth analysis applied to longitudinal data of patients with hip OA identified five distinct trajectories of pain. More studies are needed to externally validate these findings.

INTRODUCTION

Osteoarthritis (OA) is the most frequent chronic joint disease of the elderly population.[1-2] Complaints of OA include pain and disability. Although functional status and pain seem to deteriorate over time[3-4] limited data on the course of pain in OA are available.

Studies on patients with OA have shown a marked heterogeneity of pain scores. One study found that, after 2-years, pain and function had not changed at group level but varied greatly between individuals.[5] Another study, with a 3-month follow-up, found weekly fluctuations in levels of pain and other health outcomes among adults with OA.[6]

Describing a heterogeneous population using a single growth trajectory estimate is probably not optimal to investigate the course of pain due to OA.[7] In a study aiming to identify longitudinal patterns of change in knee and hip OA, the authors, using cluster analysis, classified patients into four subgroups based on their individual response pattern over a 4-year period.[8] With this approach, individuals within a group are more similar than individuals between groups.[7]

More data on subgroups of patients with similar response patterns are needed for all clinical health professionals to be able to optimize treatment for patients with OA. Therefore, the present study aimed to identify distinct groups of patients with different trajectories of pain due to hip OA, and to describe patient characteristics for each trajectory of pain.

METHODS

Study design

The present study used data of a published randomized controlled trial (RCT).[9-10] That trial assessed whether glucosamine sulfate compared to placebo had an effect on the symptoms and structural progression of hip OA during a 2-year follow-up. The study showed that glucosamine sulfate was *not* more effective than placebo in reducing symptoms and progression of hip OA.[9] Therefore, we used the data of that original study for the present cohort study.

Study population

During the original RCT, general practitioners (GPs) in the Rotterdam area recruited patients with hip OA who met the American College of Rheumatology (ACR) criteria. Patients were randomly allocated to either 1500 mg of glucosamine sulphate or placebo administered orally for 2 years. Patients were excluded if they 1) had undergone or were awaiting hip replacement surgery; 2) had a Kellgren and Lawrence score of 4; 3) had a renal disease; 4) had a liver disease; 5) had diabetes mellitus; 6) had a disabling comorbid condition that would make visits to the research center impossible; 7) had already received glucosamine; and 8) were unable to fill out questionnaires in the Dutch language.

Between June 2003 and February 2004, 417 patients were recruited by their GPs, of which 250 provided informed consent after receiving detailed information. Of these,

16 did not meet the inclusion criteria and another 12 withdrew their consent before random assignment. Finally, 222 patients were randomized to the study. Of these 222 randomly assigned patients, 189 (85%) completed the visual analogue scale (VAS) assessment at 2-year follow-up; 20 (9%) patients received a total hip arthroplasty during the study period.

Data collection

During the original RCT, participants filled out nine questionnaires every 3 months over a 2-year period. Pain severity was measured on a VAS (0-100). A score of ≤30 represents mild pain, >30 represents moderate pain and ≥54 indicates severe pain.[11] Pain was also measured with the Western Ontario McMaster osteoarthritis index (WOMAC).[12]
Data on patient characteristics (age, gender and body mass index (BMI)), co-morbidity, medication adherence and activity level were also collected. Details of the protocol and results of the RCT have been published elsewhere.[9-10]

Statistical analyses

Individual patient data of the RCT revealed a heterogeneous population (Figure 1). To identify possible trajectories of hip pain due to OA over time, latent class growth analysis (LCGA) was used. This technique allows us to uncover heterogeneity in a population and to find substantively clinically meaningful groups of people who are similar in their responses to measured variables or growth trajectories.[13] The fit of the pain trajectories was tested for two to seven trajectory classes. We also tested whether the course of pain was best described by linear, quadratic, or cubic trajectories. The most optimal model was determined on a combination of indices of fit and the interpretability of the model. The following indices of fit were used: 1) Bayesian information criteria (BIC). The BIC marks the balance between the impact of adding a new class on the log likelihood value and the penalty for increasing the number of model parameters that results from the addition of that class extracted from BIC by the second part of the equation. The smaller is the BIC value, the better is the model fit. 2) Vuong- Lo-Mendell-Rubin Likelihood Ratio Test (LRT) and the bootstrap LRT (BLRT). Significant LRT and BLRT for *k* groups ($p < 0.05$) indicate that the fit of the specific model is an improvement over a model with k -1 groups. 4) Entropy indices (EI) (range 0-1) were checked to ensure quality and reliability of the classification. An index close to one indicates good classification.[7,14-15]

After determining the number of trajectories by the indices of fit, we also determined the best possible model by the usefulness of the latent classes in practice. This was examined by the trajectory shapes for similarity, the number of individuals in each class, the number of estimated parameters and the differences in predictions of consequences based on different numbers of classes.[7,14-16] Subsequently, characteristics of class membership were tabulated.

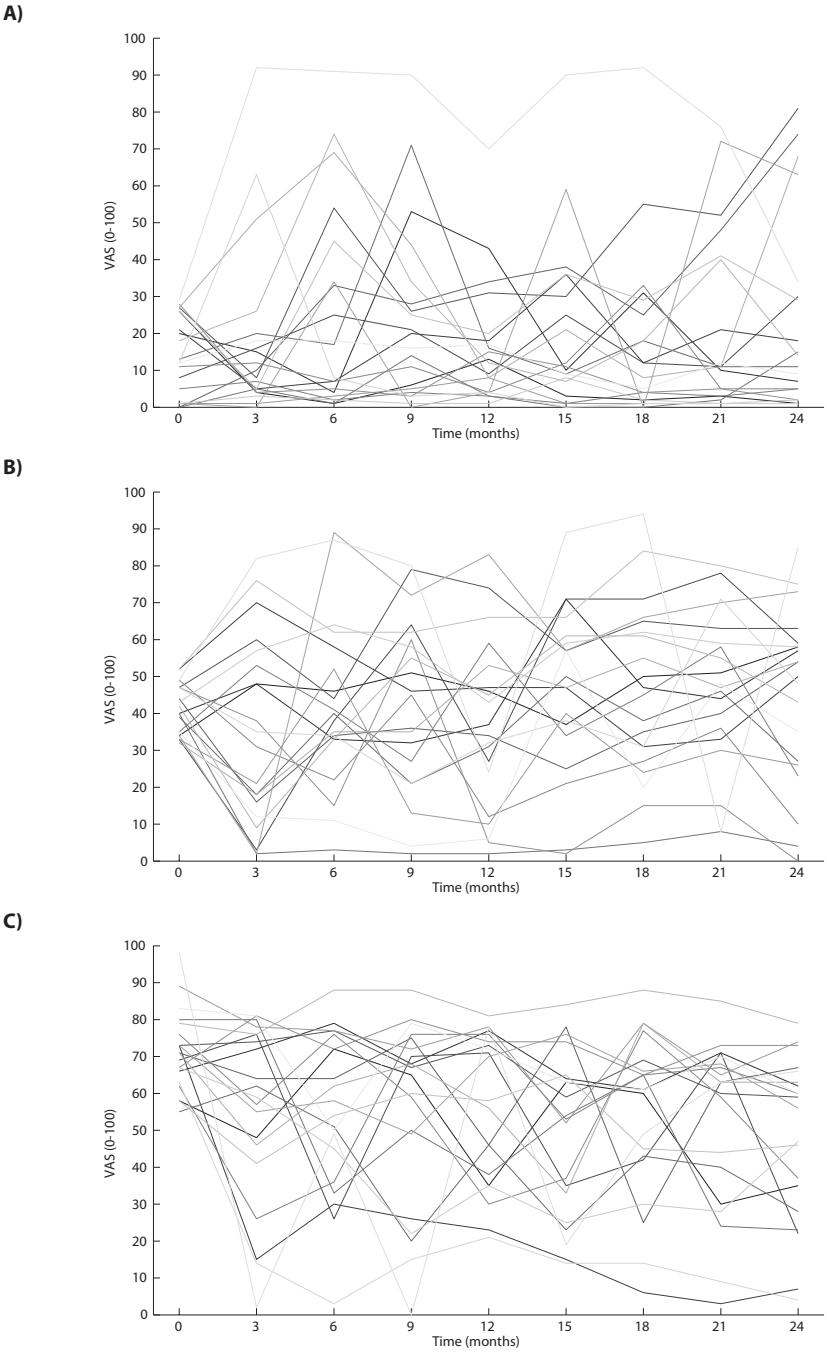

Figure 1. Course of pain in 20 patients with hip osteoarthritis. **A)** mild hip pain (VAS ≤ 30) at baseline; **B)** moderate hip pain (VAS >30 ≤ 54) at baseline; **C)** severe pain (VAS > 54) at baseline. VAS, visual analogue scale**.**

Finally, multinomial regression analyses were used to predict the effect of patient characteristics and the probability of membership in one of the trajectories. As our study population is relatively small, we did not adjust our analyses for other variables. M-plus, version 6.117 was used for LCGA. Description of the characteristics of class membership and multinomial regression analyses were performed using SPSS software (version 17, SPSS inc., Chicago, IL).

RESULTS

Patient characteristics of five trajectories for the VAS scores

Based on the BIC, LRT, BLRT, entropy and the usefulness of the classes in practice, we choose the quadratic five-group model as the most optimal solution. Most patients (n=69, 31.1%) were classified into trajectory 1 and characterized as having 'mild pain' as they had stable low levels of pain (VAS 7.3-16.3) (Table 1). Patients in trajectory 2 (n=31, 14%) oscillated between moderate and severe pain levels (VAS 42.3-58.4) during follow-up and were classified as having 'moderate pain'. Trajectory 3 consisted of 32 patients (14.4%) with permanent and severe levels of pain ('always pain') (VAS 65.9-76.3). The fourth trajectory consisted of 48 patients (21.6%) who were classified as having 'regularly progressing' pain. These patients had mild pain at baseline (mean VAS 22.2) and progressed slowly to moderate levels of pain (mean VAS 37.4). The final trajectory of the 'highly progressing' group (n=42, 18.9%) comprised patients with mild pain at baseline (mean VAS: 25.7) who quickly progressed to severe levels of pain during follow-up (mean VAS 59.4). Figure 2 shows the five pain pathways as measured by VAS during the 2-year follow-up.

Multinominal regression analysis showed that compared with patients in the 'mild pain' group, patients in the 'always pain' group were more likely to be less educated, have a higher BMI, have a higher Kellgren and Lawrence score of the hip, have a longer duration of complaints, have morning stiffness of the hip, have generalized complaints, have decreased internal rotation and flexion of the hip and have concurrent back and trochanteric pain. The 'highly progressing' group was more likely to have a higher BMI, a higher Kellgren and Lawrence score of the hip, a longer duration of complaints, morning stiffness of the hip, decreased flexion of the hip and concurrent back complaints. Patients within the 'moderate pain' group were more likely to be less educated, to have morning stiffness of the hip, to have a decreased flexion and to have concurrent back and trochanteric pain. Patients within the 'regularly progressing' group more often have morning stiffness of the hip, generalized complaints and concurrent knee pain (Table 2).

Table 1. Characteristics for each trajectory of pain measured by visual analogue scale (VAS)

	All patients (n=222)	**Class 1 Mild pain (n=69)**	**Class 2 Moderate pain (n=31)**	**Class 3 Always pain (n=32)**	**Class 4 Regularly progressing (n=48)**	**Class 5 Highly progressing (n=42)**
Age in years, mean (SD)	63.4 (9.0)	62.3 (9.5)	61.8 (8.7)	63.1 (9.3)	64.6 (8.8)	65.3 (8.1)
Women, n (%)	154 (69.4)	43 (62.3)	24 (77.4)	25 (78.1)	32 (66.7)	30 (71.4)
Low education level[a], n (%)	116 (52.3)	26 (37.7)	25 (80.6)	21 (65.6)	20 (41.7)	24 (57.1)
BMI, mean (SD)	28 (4.7)	26.3 (3.2)	28.4 (4.3)	30.1 (4.6)	28 (4.3)	28.9 (6.4)
Womac, mean (SD)						
Pain	34.2 (23.1)	17.5 (15.4)	57.9 (18.7)	58.6 (18.3)	30.9 (15.6)	29.2 (17.5)
Function	35.1(22.9)	16.9 (14.8)	53.8 (17.6)	59 (17.0)	30.6 (16.3)	37.9 (20.3)
Stifness	42.7 (25.2)	25 (20.1)	64.5 (20.4)	59.8 (22.6)	39.3 (19.5)	45.8 (22.2)
VAS, mean (SD)	32.4 (25.9)	16.3 (18.9)	58.4 (17.9)	66.1 (19.0)	22.2 (15.0)	25.7 (15.8)
Duration of complaints, ≥ 3-years, n (%)	119 (53.6)	28 (40.6)	17 (54.8)	22 (68.8)	25 (52.1)	27 (64.3)
Kellgren & Lawrence, grade ≥ 2, n (%)	105 (47.3)	23 (33.3)	14 (45.2)	20 (62.5)	23 (47.9)	25 (59.5)
Presence of morning stiffness, n (%)	128 (57.7)	19 (27.9)	28 (90.3)	25 (80.6)	26 (54.2)	30 (71.4)
Osteoarthritis, n (%)						
Generalized	137 (61.7)	33 (47.8)	16 (51.6)	24 (75)	37 (77.1)	27 (64.3)
Bilateral	107 (48.2)	29 (42)	17 (54.8)	13 (40.6)	23 (47.9)	25 (59.5)
Internal hip rotation in degrees, mean (SD)	24.4 (9.3)	26.3 (8.1)	21.8 (10)	21.8 (10.8)	24.3 (9.3)	22.8 (9.3)
Hip flexion in degrees, mean (SD)	111.6 (13.2)	116.9 (10.9)	109.5 (12.9)	101.9 (12.5)	111.4 (11.4)	112 (15.3)
Presence of conncurrent, n (%)						
Knee pain	58 (28)	11 (16.9)	9 (30)	7 (25.9)	18 (40)	13 (32.5)
Back pain	133 (64.3)	29 (44.6)	25 (83.3)	25 (92.6)	27 (60)	27 (67.5)
Trochanteric pain	121 (55)	29 (42)	21 (67.7)	23 (76.7)	30 (62.5)	18 (42.9)
Allocated to glucosamine	111 (50)	34 (49.3)	20 (64.5)	19 (59.4)	23 (47.9)	15 (35.7)
Total hip replacements after 2-years follow-up	20 (9)	1 (1.4)	3 (9.7)	6 (18.8)	2 (4.2)	8 (19)

[a] Low education level defined as elementary school and vocational training; SD = Standard deviation

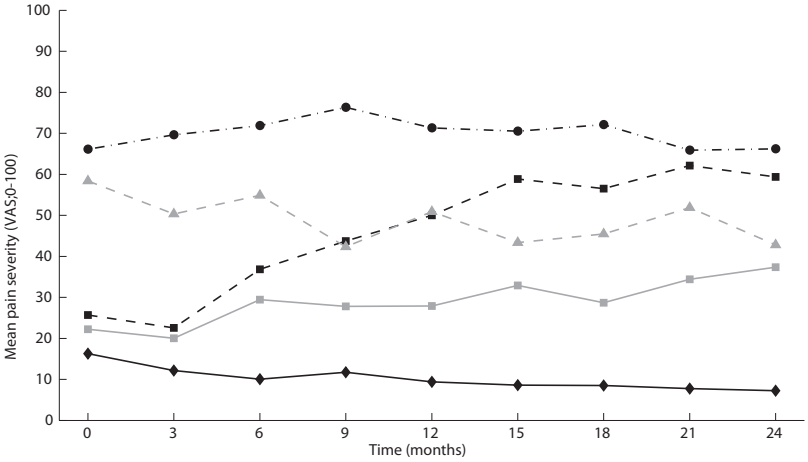

Figure 2. Trajectories of pain measured by the visual analogue scale (VAS). ◆ Mild pain (n=69) ■ Regularly progressing (n=48), ■ Higly progressing (n=42), ▲ Moderate pain (n=31), ● Always pain (n=32)

Table 2. Multinomial regression analysis for univariate predictors at baseline for each trajectory of pain (mild pain group used as reference group)

	Moderate pain (n=31)		**Always pain (n=32)**		**Regularly progressing (n=48)**		**Highly progressing (n=42)**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age	1.0	0.9 to 1.0	1.0	1.0 to 1.1	1.0	1.0 to 1.1	1.0	1.0 to 1.1
Gender								
Women	2.1	0.8 to 5.5	2.2	0.8 to 5.7	1.2	0.6 to 2.6	1.5	0.7 to 3.5
Men	Referent		Referent		Referent		Referent	
Education level								
Low	**6.9**	**2.5 to 19.0**	**3.2**	**1.3 to 7.6**	1.2	0.6 to 2.5	**2.2**	**1.0 to 4.8**
High	Referent		Referent		Referent		Referent	
Body mass index	**1.1**	**1.0 to 1.3**	**1.2**	**1.1 to 1.4**	**1.1**	**1.0 to 1.2**	**1.2**	**1.1 to 1.3**
Kellgren and Lawrence								
grade ≥ 2	1.6	0.7 to 3.9	**3.3**	**1.4 to 8.0**	1.8	0.9 to 3.9	2.9	1.3 to 6.5
grade 0 or 1	Referent		Referent		Referent		Referent	
Duration of hip complaints								
≥ 3 years	1.8	0.8 to 4.2	**3.2**	**1.3 to 7.8**	1.6	0.8 to 3.3	**2.6**	**1.2 to 5.8**
< 3 years	Referent		Referent		Referent		Referent	

Table 2. Continued

	Moderate pain (n=31)		**Always pain (n=32)**		**Regularly progressing (n=48)**		**Highly progressing (n=42)**	
Morning stiffness of the hip								
Present	**24.0**	**6.5 to 88.6**	**10.7**	**3.8 to 30.3**	**3.0**	**1.4 to 6.6**	**6.4**	**2.7 to 15.1**
Absent	Referent		Referent		Referent		Referent	
Type of osteoarthritis								
Generalized	1.2	0.5 to 2.7	**3.3**	**1.3 to 8.3**	**3.7**	**1.6 to 8.4**	2.0	0.9 to 4.3
Localized	Referent		Referent		Referent		Referent	
Side of hip osteoarthritis								
Bilateral	1.7	0.7 to 3.9	0.9	0.4 to 2.2	1.3	0.6 to 2.7	2.0	0.9 to 4.4
Unilateral	Referent		Referent		Referent		Referent	
Hip internal rotation								
<15°	2.5	0.7 to 8.6	**5.0**	**1.6 to 15.4**	1.5	0.5 to 5.0	2.5	0.8 to 7.7
≥ 15°	Referent		Referent		Referent		Referent	
Hip flexion								
<115°	**3.0**	**1.2 to 7.3**	**8.9**	**3.1 to 26.1**	**2.3**	**1.1 to 4.9**	**2.2**	**1.0 to 4.8**
≥ 115°	Referent		Referent		Referent		Referent	
Concurrent knee pain								
Present	2.1	0.8 to 5.8	1.7	0.6 to 5.0	**3.3**	**1.4 to 7.9**	2.4	0.9 to 6.0
Absent	Referent		Referent		Referent		Referent	
Concurrent back pain								
Present	**6.2**	**2.1 to 18.2**	**15.5**	**3.4 to 71.0**	1.9	0.9 to 4.0	**2.6**	**1.1 to 5.9**
Absent	Referent		Referent		Referent		Referent	
Concurrent trochanteric pain								
Present	**2.9**	**1.2 to 7.1**	**4.5**	**1.7 to 12.0**	**2.3**	**1.1 to 4.9**	1.0	0.5 to 2.2
Absent	Referent		Referent		Referent		Referent	
Treatment allocation								
Glucosamine	1.9	0.8 to 4.5	1.5	0.6 to 3.5	0.9	0.5 to 2.0	0.6	0.3 to 1.3
Placebo	Referent		Referent		Referent		Referent	

DISCUSSION

The present study classified 222 patients with hip OA into five distinct trajectories of pain using LCGA. Most patients are classified into a trajectory consisting of 'mild pain'. Compared with the 'mild pain' group, patients in the 'always pain' group were more likely to be less educated, have a higher BMI, have a higher Kellgren and Lawrence score of the hip, have a longer duration of complaints, have morning stiffness of the hip, have generalized complaints, have a decreased range of motion and have concurrent back and trochanteric pain. The 'highly progressing' group was more likely to have a higher BMI, a higher Kellgren and Lawrence score of the hip, a longer duration of complaints, morning stiffness of the hip and concurrent back pain.

To our knowledge, this is the first study to use LCGA to examine the course of pain in patients with OA. Studies on the course of pain are scarce, have mainly focused on pain at group level and report that pain worsens slowly over time.[3-4] Two studies showed a large individual variability in pain.[5-6] One study[8] used cluster analyses to examine the patterns of change in an ongoing cohort of patients with OA; four different patterns of change emerged: 1) regularly increasing, 2) regularly decreasing, 3) stable over time, or 4) highly unstable. Our results are partially in line with these latter findings. We found two groups of patients in whom pain increased over time ('regularly progressing' and 'highly progressing') and two groups whose pain remained stable over time ('always pain' and 'mild pain'). However, no trajectory emerged for patients with a decreasing level of pain or for highly unstable patients.

We had expected a trajectory consisting of patients with highly unstable pain, as such a trajectory was observed with simple statistical analysis. However, although not found, almost all our patients fluctuated within their trajectory (Figure 3). Patients with decreasing levels of pain might be absent because our study population consisted of prevalent patients who did not consult their GP at the time of study inclusion. Discrepancy between our results and that of Leffondré et al.[8] might be due to our small study population with relatively mild OA. Also, our study population consisted of patients with hip OA only, whereas Leffondré et al.[8] included patients with knee and hip OA. A systematic review on heterogeneity reported that it might be better to present results of hip and knee OA separately, as moderate heterogeneity was found in trials that included both knee and hip OA.[18]

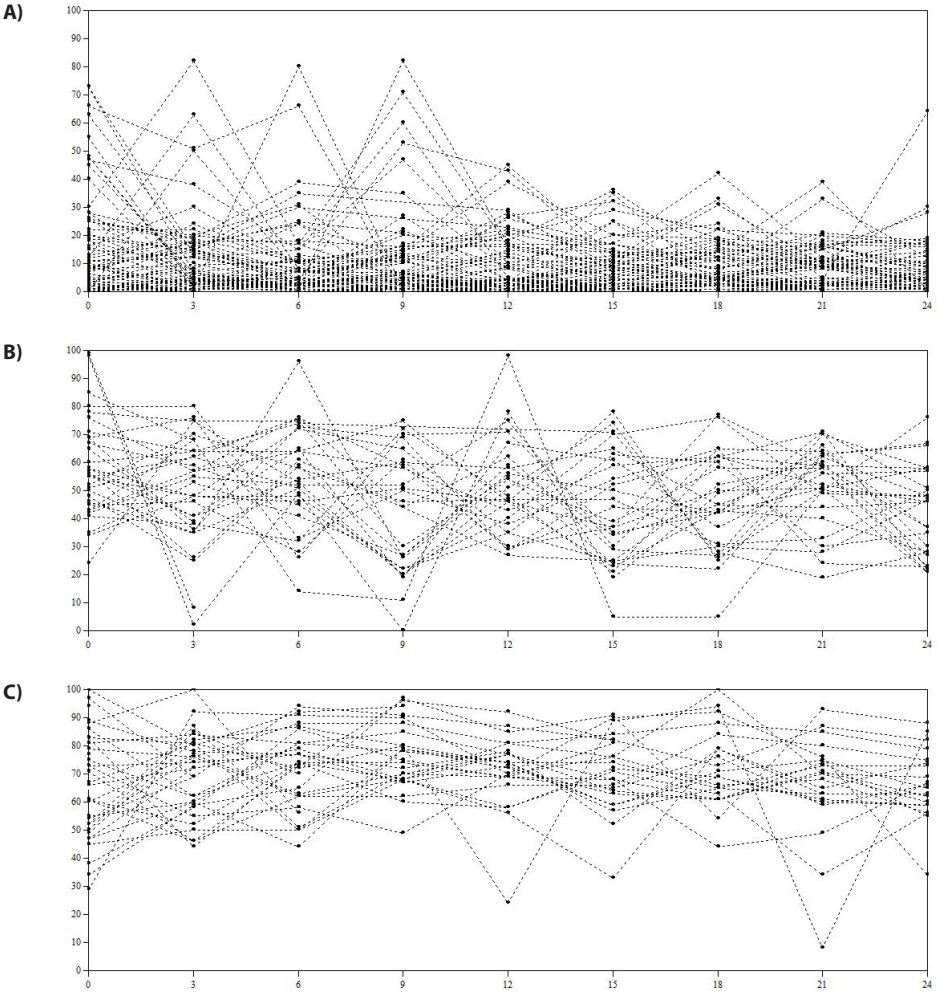

Figure 3A-C. Individual fluctuations of the visual analogue scale (VAS) scores within each trajectory of pain. **A)** class 1: Mild pain; **B)** class 2: Moderate pain; **C)** class 3: Always pain; **D)** class 4: Regularly progressing; **E)** class 5: Highly progressing

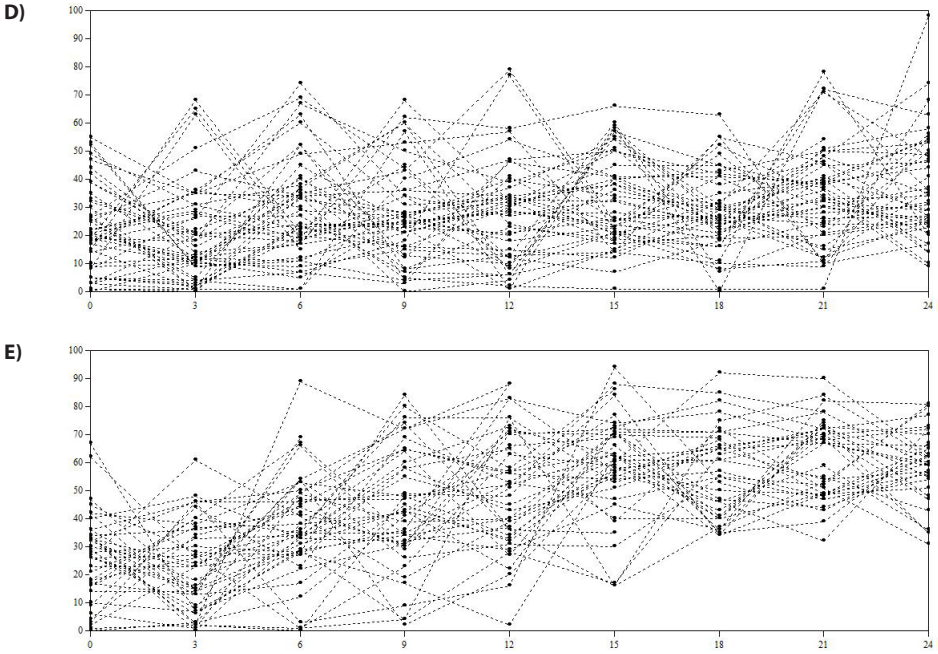

Figure 3D-E. Individual fluctuations of the visual analogue scale (VAS) scores within each trajectory of pain. **A)** class 1: Mild pain; **B)** class 2: Moderate pain; **C)** class 3: Always pain; **D)** class 4: Regularly progressing; **E)** class 5: Highly progressing

It might be possible that patients within the 'always pain' group have more characteristics of the 'neuropathic pain' syndrome.[19-20] Unfortunately, these pain characteristics were not measured in the study. What we do see is that patients within this group are more likely to have back complaints and trochanteric pain. Yet, compared with the 'mild pain' group, they did not have knee complaints more often. Also, they showed a decreased range of motion, morning stiffness, a longer duration of complaints and a higher Kellgren and Lawrence score, which might suggest that the hip OA has been there for years and may have led to more sensitized pain. Future studies about pain trajectories should incorporate questionnaires that measure components of neuropathic pain or central sensitization.

The present study reports the results of the VAS scores only, although we also performed LCGA on WOMAC scores. Based on the indices of fit, the quadratic four-group model was selected as the optimal model. Two trajectories consisted of patients who had stable mild levels of pain. One trajectory consisted of stable moderate pain. The fourth trajectory consisted of patients with stable severe levels of pain (data not shown). The pain subscale of WOMAC seems less sensitive to change than VAS. This was not caused by the summarization of the five pain items into one pain score, as LCGA analysis yielded the same trajectories for each individual pain item. In addition, the same trajectories were found when WOMAC pain was divided into weight-bearing

and non-weight-bearing pain as proposed by Stratford et al.[21]

The strengths of this study include the use of a longitudinal design with nine measurements over a 2-year period. Also, patients are classified into one of the five trajectories according to their highest probability of membership. For all patients, the probability of belonging to their trajectory was 84% or higher, suggesting that most patients were correctly allocated. Additional analysis excluded one or more of the nine measurements and still yielded the same trajectories (data not shown).

This study also has some limitations. First, although the present study was originally designed as an RCT, we described the present study as a cohort study. We believe that this description is feasible, as the original RCT showed that glucosamine sulphate was not more effective than placebo in reducing the symptoms and progression of hip OA. The original RCT showed a small placebo effect after 3 months, but remission of pain was not significantly different between placebo use and glucosamine use after 3-months. Also, treatment allocation was not found to be a predictor for one of the trajectories. Therefore, we expect the small placebo effect equally presented in all five trajectories. Nevertheless, patients in an RCT might represent a selected population. Second, our study population of 222 patients is relatively small when performing LCGA. Third, although our patients had relatively mild OA, these patients visited their GP with complaints. Therefore, it is important to determine the distinct trajectories of OA pain for these 'mild' patients to be able to offer GPs relevant information for treating individual patients with hip OA. A fourth limitation is the fit of our model. Although, LCGA is a well-established method for making distinct trajectories, the decision regarding the optimal number of classes is arbitrary.[14-15] Adding an additional trajectory seems to improve most indices of fit. However, the six-group solution does not improve the usefulness of the latent classes in practice as it adds a small trajectory of patients.

In conclusion, using LCGA, the present study reveals five distinct trajectories of pain in hip OA. These five subgroups of patients may need different types of information/education and/or treatment. More studies are needed to externally validate these findings. Future studies should also identify trajectories of pain in patients with knee, back and hand OA.

REFERENCES

1. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-97.
2. **Woolf AD**, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-656.
3. **Dieppe P**, Cushnaghan J, Tucker M, Browning S, Shepstone L. The Bristol 'OA500 study': progression and impact of the disease after 8 years. *Osteoarthritis Cartilage* 2000;8:63-68.
4. **van Dijk GM**, Dekker J, Veenhof C, van den Ende CH, Carpa Study G. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. *Arthritis Rheum* 2006;55:779-785.
5. **Paradowski PT**, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. *Health Qual Life Outcomes* 2005;3:59.
6. **Hutchings A**, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *J Rheumatol* 2007;34:2291-2300.
7. **Jung T**, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Social and personality psychology compass* 2008;2:302-317.
8. **Leffondre K**, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *J Clin Epidemiol* 2004;57:1049-1062.
9. **Rozendaal RM**, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008;148:268-277.
10. **Rozendaal RM**, Koes BW, Weinans H, Uitterlinden EJ, van Osch GJ, Ginai AZ, et al. The effect of glucosamine sulphate on osteoarthritis: design of a long-term randomised clinical trialISRCTN54513166. *BMC Musculoskelet Disord* 2005;6:20.
11. **Collins SL**, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain* 1997;72:95-97.
12. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
13. **Muthén B**. Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. *Handbook of quantitative methodology for the social sciences*. Newbury Park, CA: Sage Publications;2004:345-368.
14. **Connell AM**, Frye AA. Growth mixture modelling in developmental psychology: Overview and demonstration of heterogeneity in developmental trajectories of adolescent antisocial behavior. *Infant and child development* 2006;15:609-621.
15. **Nylund KL**, Asparouhov T, Muthén B. Deciding on the number of classes in latent class analysis and growth mixture modeling. A Monte Carlo simulation study. *Structural Equation Modeling* 2007;14:535-569.
16. **Muthen B**, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 2000;24:882-891.
17. Mplus. 6.1 ed 1998-2010.
18. **Verkleij SP**, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM. NSAIDs vs acetaminophen in

knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis Cartilage* 2011;19:921-929.

19. **Hochman JR**, French MR, Bermingham SL, Hawker GA. The nerve of osteoarthritis pain. *Arthritis Care Res (Hoboken)* 2010;62:1019-1023.
20. **Hochman JR**, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis Cartilage* 2011;19:647-654.
21. **Stratford PW**, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266-272.

CHAPTER 6

Defining pain trajectories in early hip osteoarthritis over a 5-year time period; the CHECK cohort

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Submitted

ABSTRACT

Background: Distinguishing different pain patterns over time could be important to optimize treatment in osteoarthritis (OA). A recent study found 5 distinct trajectories of pain in patients with hip OA.

Objectives: To identify and reproduce longitudinal trajectories of hip pain over a 5-year follow-up period.

Methods: Data from the CHECK cohort were used to identify trajectories of pain in 208 participants that fulfilled the radiographic/clinical American College of Rheumatology (ACR) criteria of hip OA (n=208) at baseline. Questionnaires were filled out each year to assess pain severity during the previous week using an 11-point numerical rating scale. A score of 1-3 was considered as mild pain, 4-6 as moderate pain and 7-10 as severe pain. Latent class growth analyses (LCGA) were used to identify pain trajectories. Multinomial regression analysis was used to predict membership probability to one of the trajectories.

Results: In 208 participants with radiographic/clinical hip OA, LCGA yielded 4 trajectories. Trajectory 1 consists of participants who had 'mild pain' (n=78). Participants in trajectory 2 had 'moderate pain' (n=76). Two trajectories consisted of fewer participants with 'decreasing pain' (n=22) or 'always pain' (n=32). Compared with the 'mild pain' group, the 'always pain' group included more women and concurrent knee OA and back complaints were more frequent.

Conclusions: During the 5-year follow-up, LCGA identified 4 distinct trajectories of pain. Compared with an earlier report, we identified three very similar trajectories (mild pain, moderate pain and always pain), as well as one new trajectory of participants with decreasing pain.

INTRODUCTION

Osteoarthritis (OA) is one of the most important joint diseases in the elderly.[1-2] Treatment of OA is mainly symptom driven and focused on relieving pain, but has only minor to moderate effects.[3] For adequate treatment strategies it is important to distinguish patients with different pain trajectories over time[4] because individual patient data shows that OA pain can fluctuate (substantially) over time.[5-7]

A recent study identified 5 trajectories over a 2-year period ('mild pain', 'regularly progressing', 'highly progressing', 'moderate pain' and 'always pain') among patients with hip OA in a primary care setting.[7] Compared with patients of the 'mild pain' group, patients of the 'always pain' group were more likely to have a lower education level, a higher body mass index (BMI), a higher Kellgren and Lawrence (K&L) score of radiographic hip OA, a longer duration of hip complaints, morning stiffness of the hip, a decreased range of motion and concurrent back and trochanteric pain. Compared with the 'mild pain' group, the 'highly progressing' group was more likely to have a higher K&L score of the hip and morning stiffness of the hip.

It is valuable to reproduce these initial findings in a (slightly) different population with clinical and/or radiographic hip OA over a longer follow-up period to assess the robustness of these trajectories. Therefore, the present study used data of a prospective inception cohort of participants with recent onset of hip complaints with the aim to identify distinct trajectories in men and women.

METHODS

Study design

The present study used 5-year follow-up data from the inception Cohort Hip and Cohort Knee (CHECK) study. This cohort collected data on 1,002 participants in the Netherlands with pain and/or stiffness of the knee and/or hip between October 2002 and September 2005. For the present study, we included all participants who indicated to have hip pain at baseline (n=588). The aim of the CHECK cohort study is to investigate the progression of OA over a period of at least 10 years.

The study was approved by the Medical Ethics committee of all participating centers and all participants gave written informed consent. A detailed description of the CHECK cohort is published elsewhere.[8]

STUDY POPULATION

General practitioners (GP) were invited to refer eligible individuals to 10 general and university Dutch hospitals. All participants visited their GP on their own initiative. In addition, 75% of the participants were recruited through advertisements in local newspapers and placed on the Dutch Arthritis Association website.

Individuals were eligible to participate if they had pain and/or stiffness of the knee and/or hip, were aged 45-65 years and had not visited their GP or had consulted them ≤ 6 months ago for their knee/hip complaints.

Exclusion criteria were 1) any other pathological condition that could explain the

existing complaints (e.g. other rheumatic disease, previous hip/knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome and Baker cyst), 2) co-morbidities that did not allow physical examination and/or follow-up of at least 10 years, 3) malignancy in the past 5 years and 4) inability to understand the Dutch language.

Data collection

Over the 5-year follow-up, participants of the CHECK cohort filled out questionnaires at baseline, and at 1, 2, 3, 4 and 5-years follow-up and underwent a yearly physical examination. At baseline, data on patient characteristics (age, gender, body mass index (BMI) and education) were collected. Also collected every year were data on co-morbidity, range of motion and physical activity. Furthermore, X-rays of hips and knees were made at baseline and at 2 and 5-year follow-up.

Pain

Pain severity was measured during the previous week on an 11-point numeric rating scale (NRS; 0-10). Based on previous studies we defined a score of 1-3 as mild pain, 4-6 as moderate pain, and 7-10 as severe pain.[9-11] Severity of knee and/or hip pain was measured with the Western Ontario McMaster osteoarthritis index (WOMAC) on a 0-100 scale with a higher score indicating worse pain.[12]

Clinical and radiographic ACR-criteria of the hip

Presence of hip OA at baseline was determined as meeting the clinical and/or radiographic ACR criteria. The clinical ACR criteria of hip OA were defined as the presence of hip pain and 1) hip internal rotation of < 15° and hip flexion of ≤115° or 2) hip internal rotation ≥ 15°, pain on internal rotation, morning stiffness of the hip ≤ 60 minutes and age > 50 years.[13] We used the K&L classification criteria to determine the presence of radiographic hip OA. These criteria are based on the presence of joint space narrowing, osteophytes, sclerosis, and deformity of bony ends.[14] Presence of radiographic hip OA was defined as having hip pain and having a K&L score of ≥ 2 as independently assessed by 5 observers (4 medical students, 1 physician).

Statistical analyses

Latent class growth analysis (LCGA) was performed for participants with radiographic/clinical hip OA (n=208) and for those who do not fulfill these criteria (n=380). The most optimal model was determined based on a combination of indices of fit and the interpretability of the model. The indices of fit used were 1) Bayesian information criteria; 2) Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRT) and the bootstrap LRT; and 3) Entropy indices.[15-17]

After determining the number of trajectories by the indices of fit, the best possible model was determined by the usefulness of the latent classes in practice. This was

examined by the trajectory shapes, the number of individuals in each class, the number of estimated parameters, and the differences in predictions of consequences based on the different numbers of classes.[15-18] The fit of the pain trajectories was tested for 2 to 7 trajectories. Also tested was whether the course of pain was best described by linear, quadratic, or cubic trajectories. After determining the best possible model, the characteristics of class membership were tabulated. Hereafter, multinomial regression analyses were used to predict the effect of patient characteristics and the probability of membership to one of the trajectories. The mild pain group was used as the reference group. Results of multinomial regression analysis are presented as odds ratios (ORs) and their 95% confidence intervals (95% CI). A p-value of <0.05 is considered statistically significant.

LCGA was performed using M-plus software (version 6.12, Mplus, Los Angeles, CA, USA). Description of patient characteristics of class membership and multinomial regression analyses were performed using SPSS software (version 17, SPSS Inc., Chicago, IL, USA).

RESULTS

Study characteristics

Of the 1,002 participants included in the CHECK cohort, 588 patients had hip pain at baseline of which 208 had clinical and/or radiographic hip OA. Table 1 presents the baseline characteristics of all 588 participants with hip pain, stratified for those with and without clinical/radiographic hip OA. Compared with all participants with hip pain, both with and without hip OA, participants with hip OA are slightly older men, have a decreased range of motion and more often have morning stiffness of the hip. In addition, at 5-year follow-up patients with hip OA more often received a total hip replacement.

Table 1. Baseline characteristics of all participants with hip pain.

	All participants with hip complaints (n=588)	With clinical/ radiographic hip OA (n=208)	Without clinical/ radiographic hip OA (n=380)
Baseline characteristics			
Age in years: mean (SD)	55.8 (5.3)	57.3 (4.8)	54.9 (5.4)
Gender (women, %)	475 (80.8)	161 (77.4)	314 (82.6)
Low education level (%)	418 (71.1)	152 (73.1)	266 (70.0)
Body mass index (SD)	26.1 (4.1)	26.2 (4.2)	26.0 (4.1)
WOMAC pain (SD)	27.2 (17.1)	31.0 (18.5)	25.1 (15.9)
WOMAC function (SD)	25.3 (17.6)	29.8 (18.4)	22.9 (16.7)
WOMAC Stiffness (SD)	34.8 (21.2)	40.0 (20.2)	32 (21.3)
NRS (SD)	3.7 (2.1)	4.1 (2.2)	3.5 (2.0)
Kellgren and Lawrence of the hip ≥ 2 (%)	61 (10.4)	61 (29.3)	0
Fullfilling clinical ACR criteria of the hip (%)	175 (29.8)	175 (84.1)	0
Morning stiffness of the hip (%)	326 (55.4)	172 (82.7)	154 (40.5)
Bilateral hip complaints (%)	208 (35.4)	77 (37.0)	131 (34.5)
Hip flexion, degrees	116.6 (11.6)	112.3 (12.3)	118.9 (10.6)
Internal hip rotation, degrees	28.8 (9.2)	25.0 (9.7)	30.9 (8.1)
Presence of concurrent knee pain (%)	415 (70.6)	135 (64.9)	280 (73.3)
Kellgren and Lawrence of the knee ≥ 2 (%)	20 (3.4)	12 (6.3)	8 (2.3)
Fulfilling clinical ACR criteria of the knee	342 (58.2)	122 (58.7)	220 (57.9)
Presence of concurrent back complaints (%)	120 (20.8)	54 (26.3)	66 (17.7)
Characteristics at 5-year follow-up			
Total hip replacements n, (%)	42 (7.1)	34 (16.3)	8 (2.1)

Pain trajectories in clinical/radiographic hip OA

Based on the indices of fit and the usefulness of the classes in practice, we chose the quadratic 4-group model as the most optimal classification for participants with hip OA at baseline (n=208) (Figure 1). Trajectory 1 consists of participants with 'mild pain' (n=78). The second trajectory includes 76 participants with 'moderate pain' and the smallest trajectory consists of participants with 'decreasing pain' (n=22). Trajectory 4 consists of participants with constant levels of severe pain ('always pain') (n=32). Table 2 presents the baseline characteristics for each trajectory of hip pain severity measured on NRS.

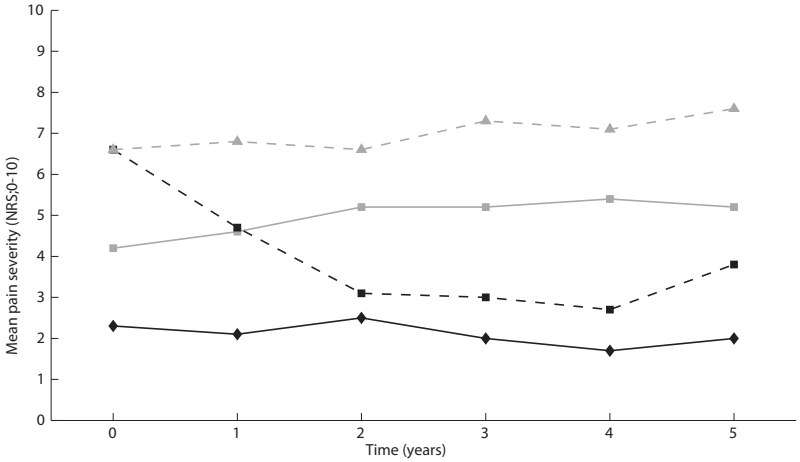

Figure 1. Trajectories of NRS hip pain severity for participants *with clinical/radiographic hip osteoarthritis* (n=208) at baseline. ◆ Mild pain (n=78) ■ Moderate pain (n=76), ■ Decreasing pain (n=22), ▲ Always pain (n=32)

Multinomial regression analyses showed that, compared with participants in the 'mild pain' group, participants in the 'always pain' group were more likely to be women (OR: 4.3; 95% CI: 1.2-15.5), more often fulfilled the clinical ACR criteria of the knee (OR: 2.7; 95% CI: 1.1-6.5) and more often had concurrent back complaints (OR: 3.0; 95% CI: 1.2-7.6) (Table 3). The 'moderate pain' group was more likely to have a higher BMI (OR: 1.2; 95% CI: 1.1-1.3), morning stiffness of the hip (OR: 2.9; 95% CI: 1.2-7.1) and decreased flexion of the hip (OR: 3.0; 95% CI: 1.6-5.9), more often fulfilled the clinical ACR criteria of the knee (OR: 3.2; 95% CI: 1.6-6.3) and more often had concurrent knee pain (OR: 2.4; 95% CI: 1.2-4.8). Patients in the 'decreasing pain' group more often had concurrent back complaints (OR: 3.7; 95% CI: 1.3-10.2).

Table 2. Baseline characteristics for participants (n=208) in each trajectory with clinically/ radiographic hip OA at baseline

	Class 1: Mild pain (n=78)	**Class 2: Moderate pain (n=76)**	**Class 3: Decreasing pain (n=22)**	**Class 4: Always pain (n=32)**
Age in years: mean (SD)	57.1 (4.6)	57.3 (4.6)	58.5 (5.9)	56.9 (4.6)
Gender (women, %)	54 (69.2)	58 (76.3)	20 (90.9)	29 (90.6)
Low education level (%)a	50 (64.1)	59 (77.6)	18 (81.8)	25 (78.1)
Body mass index (SD)	25.0 (3.1)	27.4 (4.8)	26.3 (4.7)	26.2 (3.9)
WOMAC				
Pain (SD)	15.1 (10.1)	35.3 (13.9)	46.1 (16.1)	48.5 (15.2)
Function (SD)	15.8 (11.0)	33.0 (14.6)	40.1 (17.6)	48.8 (16.0)
Stiffness (SD)	26.6 (17.4)	44.3 (16.5)	50.6 (20.9)	54.4 (15.3)
NRS (SD)	2.1 (1.1)	4.3 (1.4)	6.6 (1.4)	6.8 (1.3)
K&L score of the hip ≥ 2 (%)	23 (29.5)	18 (23.7)	9 (40.9)	11 (34.4)
Fulfilling clinical ACR criteria of the hip (%)	61 (78.2)	70 (92.1)	16 (72.7)	28 (87.5)
Presence of morning stiffness of the hip (%)	58 (74.4)	68 (89.5)	18 (81.8)	28 (87.5)
Bilateral hip complaints (%)	26 (33.3)	29 (38.2)	8 (36.4)	14 (43.8)
Hip flexion, degrees	115.9 (11.1)	109.7 (11.6)	110.6 (12.5)	110.9 (14.6)
Internal hip rotation, degrees	25.8 (9.5)	24.1 (9.5)	26.6 (11.9)	24.2 (9.4)
Presence of concurrent knee pain (%)	43 (55.1)	57 (75)	13 (59.1)	22 (68.8)
K&L score of the knee ≥ 2 (%)	3 (4.4)	6 (8.7)	0	3 (10)
Fulfilling clinical ACR criteria of the knee (%)	35 (44.9)	55 (72.4)	10 (45.5)	22 (68.8)
Presence of concurrent back complaints (%)	14 (18.4)	17 (22.7)	10 (45.5)	13 (40.6)
Total hip replacements after 5 years (%)	7 (9.0)	16 (21.1)	0	11 (34.4)

Table 3. Multinomial regression analysis for univariate predictors at baseline for each trajectory of pain (mild pain group (n=78) used as reference group) for all participants with clinical/ radiographic hip OA at baseline

	Moderate pain (n=76)		**Decreasing pain (n=22)**		**Always pain (n=32)**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age	1.0	0.9 to 1.1	1.1	1.0 to 1.2	1.0	0.9 to 1.1
Gender						
Women	1.4	0.7 to 2.9	4.4	1.0 to 20.5	**4.3**	**1.2 to 15.5**
Men	Referent		Referent		Referent	
Education level						
Low	1.8	0.9 to 3.8	2.3	0.7 to 7.4	1.8	0.7 to 4.7
High	Referent		Referent		Referent	
Body mass index	**1.2**	**1.1 to 1.3**	1.1	1.0 to 1.3	1.1	1.0 to 1.2
Kellgren and Lawrence						
grade ≥ 2	0.7	0.4 to 1.5	1.7	0.6 to 4.4	1.3	0.5 to 3.0
grade 0 or 1	Referent		Referent		Referent	
Morning stiffness of the hip						
Present	**2.9**	**1.2 to 7.1**	1.6	0.5 to 5.1	2.4	0.8 to 7.7
Absent	Referent		Referent		Referent	
Side of hip complaints						
Bilateral	1.2	0.6 to 2.4	1.1	0.4 to 3.1	1.6	0.7 to 3.6
Unilateral	Referent		Referent		Referent	
Hip internal rotation						
<15°	0.9	0.4 to 2.3	0.6	0.1 to 2.7	0.4	0.1 to 1.7
≥ 15°	Referent		Referent		Referent	
Hip flexion						
<115°	**3.0**	**1.6 to 5.9**	2.2	0.8 to 5.7	1.9	0.8 to 4.5
≥ 115°	Referent		Referent		Referent	
Fulfilling clinical knee ACR criteria						
Yes	**3.2**	**1.6 to 6.3**	1.1	0.4 to 2.9)	**2.7**	**1.1 to 6.5**
No	Referent		Referent		Referent	
Concurrent knee pain						
Present	**2.4**	**1.2 to 4.8**	1.2	0.5 to 3.1	1.8	0.8 to 4.3
Absent	Referent		Referent		Referent	
Concurrent back complaints						
Present	1.3	0.6 to 2.9	**3.7**	**1.3 to 10.2**	**3.0**	**1.2 to 7.6**
Absent	Referent		Referent		Referent	

Pain trajectories without clinical/radiographic hip OA

For those participants with pain but without clinical/radiographic hip OA (n=380), LCGA identified 4 trajectories of pain (Figure 2).This model yielded participants with 'mild pain' (n=126), 'moderate pain' (n=90), 'always pain' (n=118), and 'progressing pain' (n=46).

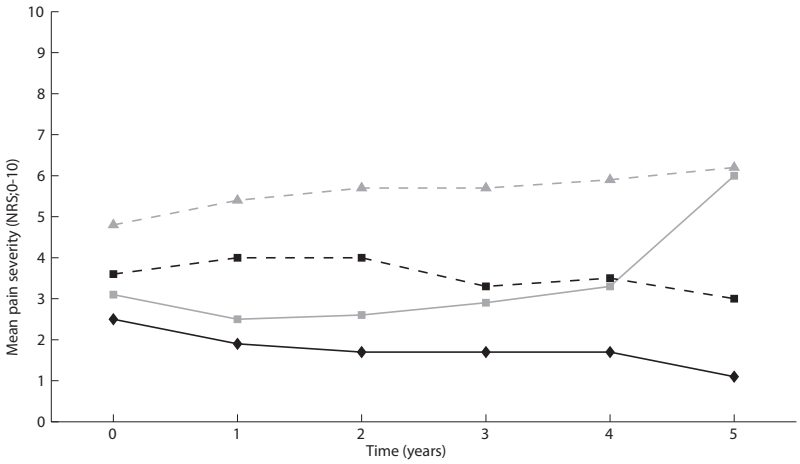

Figure 2. Trajectories of NRS hip pain of participants (n=380) *without clinical/radiographic* hip OA at baseline. ◆ Mild pain (n=126) ■ Progressing pain (n=46), ■ Moderate pain (n=90), ▲ Always pain (n=118).

Multinomial regression analysis revealed that, compared with the 'mild pain' group, the 'always pain' group was more likely to have a lower education level (OR: 4.1; 95% CI: 2.2-7.6), a higher BMI (OR: 1.1; 95% CI: 1.1-1.2), decreased hip flexion (OR: 2.5; 95% CI: 1.4-4.4) and more often have concurrent knee pain (OR: 2.8; 95% CI: 1.6-5.1) and back complaints (OR: 2.5; 1.2-5.2). Compared with the 'mild pain' group the 'moderate pain' group was more likely to have a lower education level (OR: 1.8; 95% CI: 1.0-3.3) and more often have concurrent knee pain (OR: 2.5; 95% CI: 1.3-4.8) and back complaints (OR: 2.3; 95% CI: 1.1-4.9). The 'progressing pain' group was more likely to have a lower education level (OR: 5.0; 95% CI: 2.0-12.7), a higher BMI (OR: 1.1; 95% CI: 1.0-1.2) and more often have morning stiffness (OR: 2.5; 95% CI: 1.2-4.9) and decreased flexion of the hip (OR: 2.3; 95% CI: 1.1-4.7) (Table 4).

Table 4. Multinomial regression analysis for univariate predictors at baseline for each trajectory of pain (mild pain group (n=126) used as reference group) for all participants without clinical/ radiographic hip OA at baseline

	Progressing pain (n=46)		**Moderate pain (n=90)**		**Always pain (n=118)**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age	1.0	0.9 to 1.0	1.0	1.0 to 1.1	1.0	0.9 to 1.0
Gender						
Women	1.2	0.5 to 3.0	1.0	0.5 to 2.0	1.0	0.5 to 1.9
Men	Referent		Referent		Referent	
Education level						
Low	**5.0**	**2.0 to 12.7**	**1.8**	**1.0 to 3.3**	**4.1**	**2.2 to 7.6**
High	Referent		Referent		Referent	
Body mass index	**1.1**	**1.0 to 1.2**	1.0	0.9 to 1.1	**1.1**	**1.1 to 1.2**
Morning stiffness of the hip						
Present	**2.5**	**1.2 to 4.9**	1.4	0.8 to 2.4	1.6	1.0 to 2.7
Absent	Referent		Referent		Referent	
Side of hip complaints						
Bilateral	1.1	0.5 to 2.2	1.2	0.7 to 2.1	1.4	0.8 to 2.4
Unilateral	Referent		Referent		Referent	
Hip internal rotation*	1.0	0.9 to 1.0	1.0	1.0 to 1.1	1.0	0.9 to 1.0
Hip flexion						
<115°	**2.3**	**1.1 to 4.7**	1.3	0.7 to 2.4	**2.5**	**1.4 to 4.4**
≥ 115°	Referent		Referent		Referent	
Fulfilling clinical knee ACR criteria						
Yes	3.8	0.6 to 23.2	0.6	0.1 to 7.0)	1.0	0.1 to 7.3
No	Referent		Referent		Referent	
Concurrent knee pain						
Present	1.6	0.7 to 3.3	**2.5**	**1.3 to 4.8**	**2.8**	**1.6 to 5.1**
Absent	Referent		Referent		Referent	
Concurrent back complaints						
Present	1.5	0.6 to 4.2	**2.3**	**1.1 to 4.9**	**2.5**	**1.2 to 5.2**
Absent	Referent		Referent		Referent	

*hip internal rotation was analysed as a continuous variable because of small numbers of participants with a decreased internal rotation.

DISCUSSION

In this study, LCGA of the 208 participants with clinical/radiographic hip OA yielded four distinct trajectories of pain. Most participants were classified as having 'mild pain' and 'moderate pain'. Two smaller trajectories comprised the 'decreasing group' and the 'always pain' group. Probability for membership in the 'always pain' group was higher for female participants, having knee OA and concurrent back complaints. For the 'moderate pain' group membership was related to higher BMI, morning stiffness of the hip, decreased hip flexion, clinical knee OA and concurrent knee pain. The 'decreasing pain' group more often had concurrent back complaints.

Pain trajectories with radiographic/clinical hip OA

Some of our identified trajectories in the current CHECK cohort were similar to those found in our previous study on 222 participants with radiographic/clinical hip OA.[7] Again, we identified a trajectory of 'mild pain', 'moderate pain' and 'always pain'. However, we also identified a trajectory of participants with 'decreasing pain'. In contrast to the previous study, we did not found a trajectory with 'progressing pain'.

Some important differences between these two studies may account for this. First, in the present study all participants were included based on pain in their hip and/or knee at baseline (which might be due to symptomatic OA) and we then identified participants with radiographic/clinical hip OA. In the older study participants had to fulfil the clinical and/or radiographic ACR criteria to enter the study. This might suggest that the present study consisted of participants with an early phase of OA. Indeed, of the 208 patients who met the ACR criteria almost 30% had a K&L grade of ≥ 2, compared to almost 50% in our previous study. Second, the present study measured pain only once per year (average pain intensity over the past week) during the 5-year follow-up, compared with every 3 months (average pain intensity over past week) during the 2-year follow-up in the previous study. Third, most participants in the CHECK cohort had not visited their GP, or had visited the GP ≤ 6 months ago; moreover, 75% of all included participants were recruited through advertisements in local newspapers and on the Dutch Arthritis Association website. In the older study all participants had visited their GP.

Leffondré et al.[19] described a 'decreasing pain' trajectory in their study using cluster analysis, and identified trajectories with stable levels of pain over time which resemble the 'mild pain' and 'moderate pain' trajectories in our study. Furthermore, they also reported a fluctuating trajectory, which was not found in our study. Perhaps our yearly measurements were not suitable to distinguish fluctuations in pain. Fluctuations in pain intensity are better detected based on short-term recall, because retrospective pain assessments are influenced by current pain intensity at the end of the period.[20] Nevertheless, in the present study individual pain scores fluctuated within each trajectory (Figure 3), as also found in our previous study.[7]

Although we expected to find differences in baseline patient characteristics between the 'decreasing pain' and 'always pain' group, no such differences were found.

However, after 5 years none of the participants in the 'decreasing group' received a total hip replacement compared with 11 (34.4%) in the 'always pain' group. It is possible that this 'decreasing pain' group experienced flare ups at baseline, whereas the 'always pain' group has a more sensitized type of pain. Also, the numbers of participants in these two groups were probably too small to detect differences between them.

It is suggested that pain due to OA gradually worsens over time.[21] Based on the present findings this does not seem to hold, at least not after this 5-year follow-up in participants with early hip OA complaints.

Finding unique predictors for group membership based on individual characteristics and levels of pain at baseline alone was difficult, probably because of our small sample size. Nevertheless, all the trends were in the same direction as in our previous study.[7] For now, we recommend that clinicians follow their patients for a longer period to provide them with more individually-tailored therapy.

Pain trajectories without clinical/radiographic hip OA

Besides finding trajectories of pain in participants with clinical/radiographic hip OA, we also performed LCGA on participants with hip pain at baseline but who do not fulfil the clinical and radiographic ACR criteria. This analysis also yielded a 4-group model. Similar to our model with clinical/radiographic hip OA, we found a trajectory of 'mild pain', 'moderate pain' and 'always pain'. The fourth trajectory consisted of participants with 'progressing pain'. Again, individual pain scores fluctuated within each trajectory (Figure 4).

Some differences emerged in the trajectories of participants with and without clinical/radiographic hip OA. First, the mean hip pain of participants who do not fulfil the ACR criteria was lower and most pronounced in the 'always pain' group. Second, while the OA model comprised a 'decreasing pain' group, the model without clinical/radiographic hip OA yielded a 'progressing pain' group. This latter group is interesting because their pain suddenly increases at 4-year follow-up. We hypothesized that they might have developed clinical/radiographic hip OA at some time during follow-up. However, at 5-year follow-up 9% of the participants in this 'progressing' group developed radiographic hip OA and none of them received a total hip replacement.

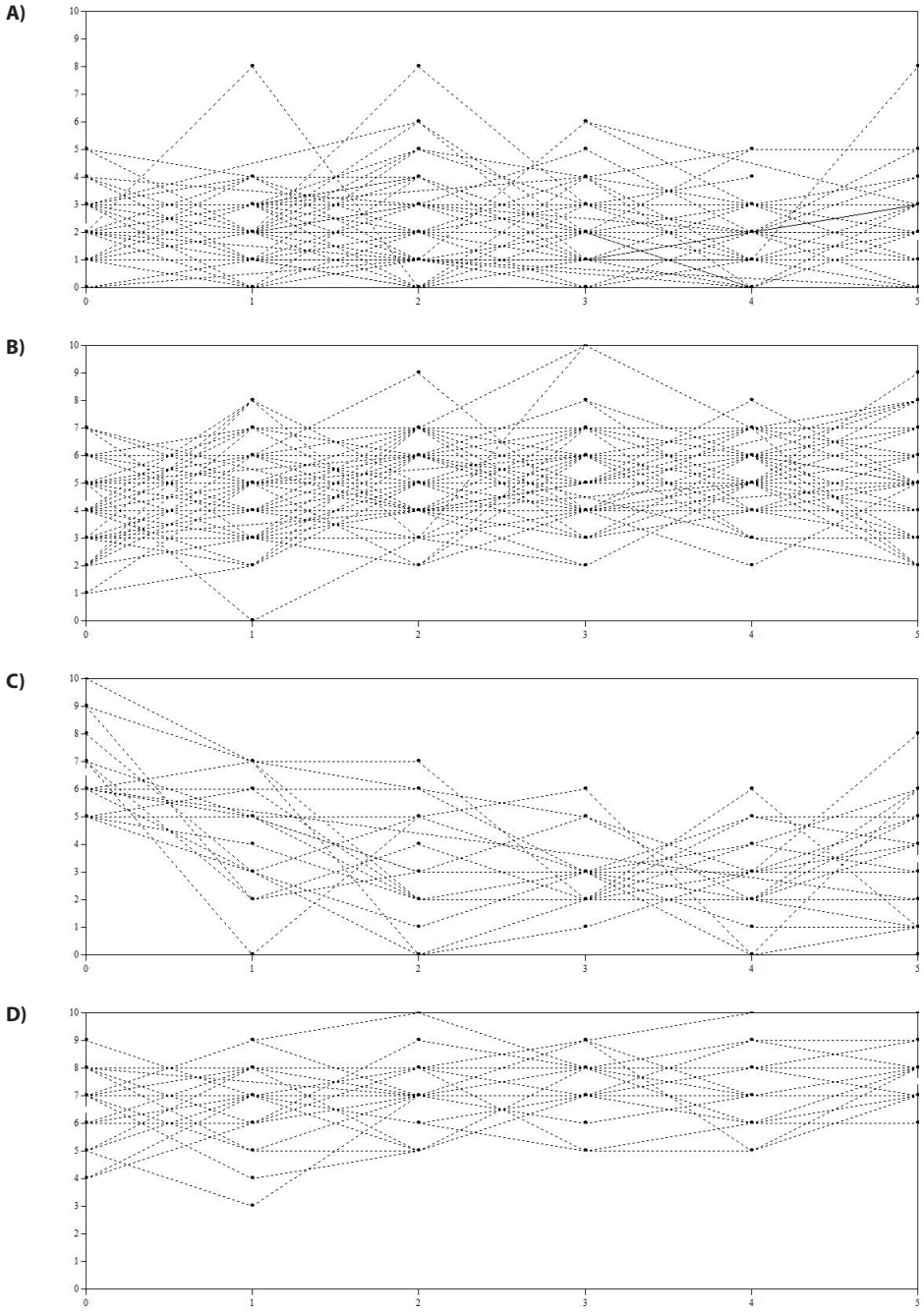

Figure 3. Individual pain fluctuations within each trajectory of hip pain due to clinical/radiographic hip OA. **A)** Mild pain; **B)** Moderate pain; **C)** Decreasing pain; **D)** Always pain.

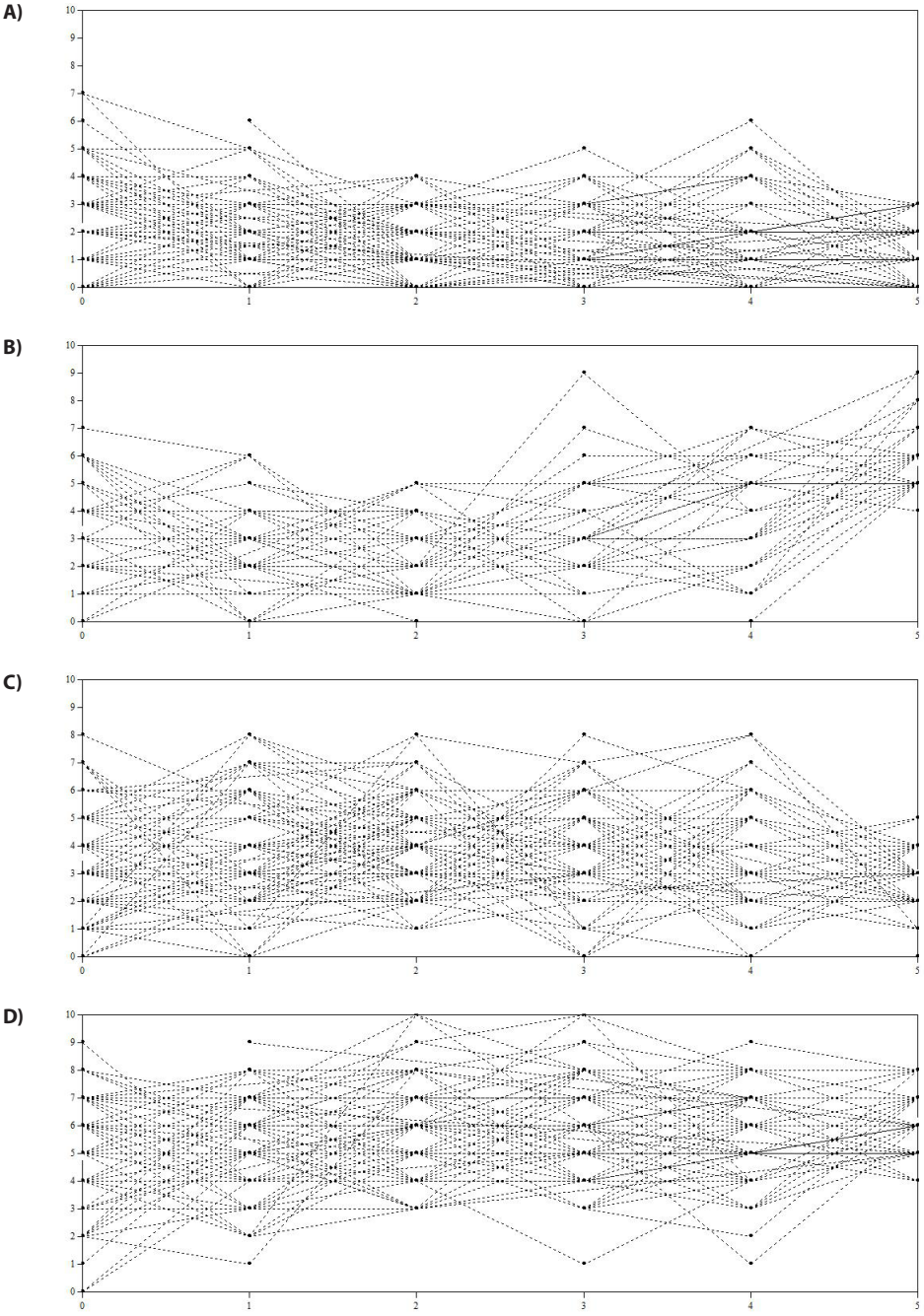

Figure 4. Individual pain fluctuations within each trajectory of hip pain without clinical/radiographic hip OA. **A)** Mild pain; **B)** Progressing pain; **C)** Moderate pain; **D)** Always pain

Strengths and Limitations

An important strength of the present study is the fit of our model. The probability of membership is 83% or higher, meaning that the majority of the participants were correctly allocated. A limitation is that the study population was rather small to perform LCGA. Also, due to the small trajectories we were unable to perform multivariate multinomial regression analysis. Until now, we are unable to identify unique baseline characteristics of membership and more studies are needed to identify such characteristics. Another limitation concerns the decision of choosing the most optimal number of classes. Previous studies found this decision to be arbitrary.[15,17] However, in our study most indices of fit deteriorated by adding an extra trajectory. Moreover, the 5-group model solution also yielded one very small group (n=8). A final limitation is that the CHECK cohort did not measure neuropathic or sensitized pain during the first 5 years. Pain due to OA has long been considered as nociceptive pain, sometimes with local inflammatory processes; however, there is increasing evidence that neuropathic and central sensitized pain mechanisms are also involved in OA.[22] The participants in our 'always pain' group may have had more extensive neuropathic pain compared with the other groups.

Conclusion

This present study offers new data on the course of pain in patients with and without clinical/radiographic hip OA. We have reproduced the trajectories of 'mild pain', 'moderate pain' and 'always pain' which were identified earlier.[7] Moreover, we also found a trajectory of 'decreasing pain'.

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REFERENCES

1. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-97.
2. **Woolf AD**, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-656.
3. **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.
4. **Bierma-Zeinstra SM**, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. *Arthritis Res Ther* 2011;13:213.
5. **Hutchings A**, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *J Rheumatol* 2007;34:2291-2300.
6. **Paradowski PT**, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. *Health Qual Life Outcomes* 2005;3:59.
7. **Verkleij SP**, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. *Ann Rheum Dis* 2012.
8. **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.
9. **Fejer R**, Jordan A, Hartvigsen J. Categorising the severity of neck pain: establishment of cut-points for use in clinical and epidemiological research. *Pain* 2005;119:176-182.
10. **Krebs EE**, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med* 2007;22:1453-1458.
11. **Turner JA**, Franklin G, Heagerty PJ, Wu R, Egan K, Fulton-Kehoe D, et al. The association between pain and disability. *Pain* 2004;112:307-314.
12. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
13. **Altman R**, Alarcon 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;34:505-514.
14. **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
15. **Connell AM**, Frye AA. Growth mixture modelling in developmental psychology: Overview and demonstration of heterogeneity in developmental trajectories of adolescent antisocial behavior. *Infant Child Develop* 2006;15:609-621.
16. **Jung T**, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personality Psychol Compass* 2008;2:302-317.
17. **Nylund KL**, Asparouhov T, Muthén B. Deciding on the number of classes in latent class analysis and growth mixture modeling. A Monte Carlo simulation study. *Structural Equation Modeling* 2007;14:535-569.

18. **Muthen B**, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 2000;24:882-891.
19. **Leffondre K**, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *J Clin Epidemiol* 2004;57:1049-1062.
20. **Perrot S**, Rozenberg S, Moyse D, Legout V, Marty M, cercle d'etude de douleur en r. Comparison of daily, weekly or monthly pain assessments in hip and knee osteoarthritis. A 29-day prospective study. *Joint Bone Spine* 2011;78:510-515.
21. **van Dijk GM**, Dekker J, Veenhof C, van den Ende CH, Carpa Study G. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. *Arthritis Rheum* 2006;55:779-785.
22. **Mease PJ**, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol* 2011;38:1546-1551.

CHAPTER 7

Are weight-bearing and non-weight-bearing knee pain associated with MRI findings?

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ABSTRACT

Objective: To examine whether weight-bearing and non-weight-bearing knee pain are (equally) associated with specific features in both the patello-femoral joint and tibio-femoral joint assessed with magnetic resonance imaging (MRI) in middle-aged women with or without evident knee OA.

Methods: In an open population cohort study, 891 women received an MRI scan of both knees to assess the presence of bone marrow lesions (BMLs), joint effusions, osteophytes and cartilage defects using the Knee Osteoarthritis Scoring System (KOSS). Knee pain during the previous week was measured using the Western Ontario McMaster Osteoarthritis index (WOMAC). Because the WOMAC pain items were highly correlated, we classified them into non-weight-bearing (pain at night and at rest) and weight-bearing pain (pain on walking, on climbing stairs and on standing). Associations were tested using logistic generalized estimation equations.

Results: Of all women, 161 had weight-bearing and 88 had non-weight-bearing pain. BMLs were associated with weight-bearing (odds ratio (OR):1.9; 95% confidence interval (95%CI): 1.3 to 2.7) and non-weight-bearing pain (OR:1.7; 95%CI: 1.1 to 2.7). Cartilage defects in the knee were associated with non-weight-bearing pain (OR:2.0; 95%CI: 1.2 to 3.4). In the tibio-femoral joint, BMLs were associated with weight-bearing pain (OR:1.5; 95%CI: 1.1 to 2.2). Cartilage defects in the patello-femoral joint were also associated with weight-bearing pain (OR:1.5; 95%CI: 1.0 to 2.3).

Conclusion: In these middle-aged women, knee pain was associated with BMLs and cartilage defects seen on MRI. Regarding the magnitude of these associations, almost no differences were found between weight-bearing and non-weight-bearing knee pain.

INTRODUCTION

Osteoarthritis (OA) is the most common chronic joint disease of especially the hip and knee.[1-3] The most prominent characteristic of OA is pain, which is an important reason for seeking medical care[3] and is widely used as a primary outcome in trials on OA.
It is thought that pain in OA is of multifactorial origin.[4-9] A systematic review indeed showed that knee pain in OA is associated with bone marrow lesions (BMLs) and joint effusions found on magnetic resonance imaging (MRI), but the level of evidence is moderate.[10] Data on other MRI findings remain inconsistent and inconclusive.

These conflicting results might be caused by difficulties in measuring pain. Pain severity is often presented as one summary score, whereas it may in fact comprise different items of pain (e.g. pain on walking, on climbing stairs, on standing, at night and at rest). One study questioned this summation of the five pain items measured with the Western Ontario McMaster Osteoarthritis index (WOMAC).[11] The authors proposed to either separately interpret each pain item, or to classify them according to homogeneity into: 1) weight-bearing pain items (pain on walking, on climbing stairs and on standing), and 2) non-weight-bearing pain items (pain at night and at rest).

The present study examines whether weight-bearing and non-weight-bearing pain items are (equally) associated with BMLs, joint effusions, osteophytes and cartilage defects in the knee, as assessed with MRI in women with or without evident knee OA who participated in an open population cohort. Because it has been suggested that (in a symptomatic population) isolated OA in the patello-femoral joint (PFJ) may be a marker for future development of OA in the tibio-femoral joint (TFJ),[12] we also analysed these two joints separately in addition to the whole knee.

METHODS

Rotterdam Study

For the present study, we used a subpopulation of the Rotterdam Study (RS-III-1),[13] a population-based cohort study to investigate the incidence and risk factors for chronic disabling diseases.

Study population

The RS-III-1 cohort was initiated in 2006 and included 3,932 participants aged 45 years and over, and living in Rotterdam. Participants were included between 2006 and 2008.[13] Women in the RS-III-1 cohort who were aged between 45 and 60 years were invited to join a sub-study investigating the early signs of knee OA. These women (n=1,116) were screened for contra-indications for MRI; of this latter group, 891 were recruited and underwent an MRI scan of both knees.

The Medical Ethics committee of the Erasmus Medical Center approved the study and all participants gave written consent.

Data collection

Clinical data

All participants were interviewed for demographic details and received a physical examination of the knee. Age was calculated from birth date to date of MRI. Body mass index (BMI) was calculated from measured height and weight (kg/m^2).

Pain

Severity of knee pain over the previous week was measured using the Western Ontario McMaster Osteoarthritis index (WOMAC).[14] The separate WOMAC pain items (pain on walking, on climbing stairs, on standing, at night and at rest) were measured on a 5-point Likert scale: none (0), slight (1), moderate (2), severe (3) and extreme (4), and were dichotomized into: no/slight pain (0) and moderate/severe/extreme pain (1) for the purpose of the statistical analysis. As the five pain items were highly correlated (Table 1) they were classified, in accordance with previous research,[11] into non-weight-bearing (pain at night and at rest) and weight-bearing pain (pain on walking, on climbing stairs and on standing).

Table 1. Correlations of the five WOMAC pain items

	On walking	On climbing stairs	On standing	At night	At rest
On walking	1	0.51	0.71	0.40	0.43
On climbing stairs	0.51	1	0.51	0.45	0.44
On standing	0.71	0.51	1	0.48	0.49
At night	0.4	0.45	0.48	1	0.64
At rest	0.43	0.44	0.49	0.64	1

Magnetic resonance imaging (MRI)

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

A trained reader, who was blinded for any clinical or radiographic data, scored all MRIs of the knees. BMLs (grade 0-3), joint effusion (grade 0-3), osteophytes (grade 0-3)

and cartilage defects (graded as diffuse or focal defects) were scored using the semi-quantitative grading of the Knee Osteoarthritis Scoring System (KOSS); this system has good intra- and inter-observer reliability and is described in detail by Kornaat et al.[15]

BMLs, osteophytes and cartilage defects were scored at five locations of the PFJ: 1) crista patellae; 2) medial patellar facet; 3) lateral patellar facet; 4) medial trochlear facet; and 5) lateral trochlear facet; and four locations of the TFJ: 1) medial femoral condyle; 2) lateral femoral condyle; 3) medial tibial plateau; and 4) lateral tibial plateau. To simplify the KOSS scores, we dichotomized BMLs and osteophytes into present (1; score of ≥ 1 in original scoring) and absent (0) per knee and per joint of the knee (PFJ and TFJ). Diffuse and focal cartilage defects were summed together and these scores were also dichotomized into present (1; score of ≥ 1) and absent (0) per knee and per joint (PFJ and TFJ). We dichotomized joint effusion into present (1; score of ≥ 2 in original scoring) and absent (0; score ≤ 1 in original scoring).

Radiographs

Weight-bearing antero-posterior radiographs of both knees were taken. Two independent readers, who were blinded for any clinical or MRI data, scored the radiographs for the presence of OA using the Kellgren and Lawrence (K&L) classification criteria.[16] Knee alignment was also scored.

Statistical analyses

We used logistic generalized estimation equations (GEE) to analyse, cross-sectionally, if weight-bearing and non-weight-bearing pain was associated with BMLs, joint effusion, osteophytes and cartilage defects. GEE takes into account the correlation between the right and left knee. Consecutively, weight-bearing and non-weight-bearing pain were used as dependent variables. BML, effusion, osteophytes and cartilage defects assessed with MRI were used as independent variables. In addition, analyses were performed for the PFJ and TFJ separately.

All analyses were adjusted for age, BMI, MRI findings and K&L scores assessed with radiography. Results are presented as odds ratios (ORs) and their 95% confidence intervals (95% CI). A p-value of <0.05 is considered statistically significant. All analyses were performed using SPSS software (version 17, SPSS Inc., Chicago, IL,USA).

RESULTS

Of the 891 women (1782 knees) that were recruited, we excluded four women for whom we lacked data on age, BMI and/or side of knee pain. Furthermore, as the WOMAC questionnaire was not measured for both knees, we excluded data of the contra-lateral knee if women indicated to have uni-lateral knee pain (n=118). Characteristics of the remaining 887 women (1656 knees) are shown in Table 2. Mean age of all women was 53.7 standard deviation (SD): 3.8 years. Of all women, 181 reported to have pain on one or more of the five WOMAC pain items. Of these, 161 reported weight-bearing pain and 88 non-weight-bearing pain. Compared to women without pain, in women

with knee pain BMLs, effusions, osteophytes and cartilage defects were more often present. Also, women who reported to have knee pain, more often had a K&L grade of two or higher.

Table 2. Characteristics of the study population (n=887)

	With pain in one or both knees*			Without pain			All women		
Participants	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**N**	**Mean**	**SD**
Age in years	181	54.3	3.5	706	53.6	3.9	887	53.7	3.8
Body mass index	181	28.8	5.2	706	26.6	4.6	887	27.0	4.8
Knees	**297**	**n**	**%**	**1359**	**n**	**%**	**1656**	**n**	**%**
Womac pain									
Pain on walking ≥ 2	297	81	27.3	-	-		1656	81	4.9
Pain on climbing stairs ≥ 2	297	261	87.9	-	-		1656	261	15.8
Pain on standing ≥ 2	297	87	29.3	-	-		1656	87	5.3
Pain at night ≥ 2,	297	101	34.0	-	-		1656	101	6.1
Pain at rest ≥ 2,	295	97	32.9	-	-		1654	97	5.9
Presence of bone marrow lesions									
Whole knee joint	292	150	51.4	1347	413	30.7	1639	563	34.4
Tibio-femoral joint	292	90	30.8	1347	240	17.8	1639	330	20.1
Patello-femoral joint	292	96	32.9	1347	263	19.5	1639	359	21.9
Presence of effusions	293	29	9.9	1348	68	5.0	1641	97	5.9
Presence of osteophytes									
Whole knee joint	296	174	58.8	1353	594	43.9	1649	768	46.6
Tibio-femoral joint	295	142	48.1	1353	402	29.7	1648	544	33.0
Patello-femoral joint	296	137	46.3	1350	421	31.2	1646	558	33.9
Presence of cartilage defects									
Whole knee joint	294	147	50	1353	403	29.8	1647	550	33.4
Tibio-femoral joint	294	75	25.5	1353	207	15.3	1647	282	17.1
Patello-femoral joint	294	113	38.4	1348	263	19.5	1642	376	22.9
Kellgren and Lawrence grade ≥ 2	296	48	16.2	1353	53	3.9	1649	101	6.1

SD = Standard deviation; * Knee pain was defined as having pain on one or more of the Womac pain items. WOMAC: Western Ontario McMaster Osteoarthritis index.

MRI features and their associations with (non-)weight-bearing pain

Univariate analysis showed that weight-bearing and non-weight-bearing pain were significantly associated with BMLs, effusion, osteophytes and cartilage defects (Table 3).

After adjusting, BMLs were significantly and equally associated with both weight-bearing (OR: 1.9; 95% CI: 1.3 to 2.7) and non-weight-bearing pain (OR: 1.7; 95% CI: 1.1 to 2.7). Cartilage defects were significantly associated with non-weight-bearing pain (OR: 2.0; 95% CI: 1.2 to 3.4) but not with weight-bearing pain. Joint effusion and osteophytes were not significantly associated with either weight-bearing or non-weight-bearing pain (Table 4).

Table 3. Data on univariate regression regarding MRI features and weight-bearing and non-weight-bearing knee pain

	Weight-bearing pain		**Non-weight-bearing pain**	
MRI features in whole knee	**OR**	**95% CI**	**OR**	**95% CI**
Bone marrow lesions	**2.5**	**1.8 to 3.4**	**2.6**	**1.7 to 3.9**
Effusions	**2.3**	**1.3 to 3.9**	**2.1**	**1.0 to 4.2**
Osteophytes	**2.0**	**1.5 to 2.7**	**2.0**	**1.3 to 3.1**
Cartilage defects	**2.3**	**1.7 to 3.2**	**3.2**	**2.1 to 5.0**

OR = Odds ratio; 95% CI = 95% confidence interval; Printed bold: differences are significant

Table 4. Data on multivariate GEE analyses regarding MRI features and weight-bearing and non-weight-bearing knee pain

	Weight-bearing pain		**Non-weight-bearing pain**	
MRI features in whole knee	**OR**	**95% CI**	**OR**	**95% CI**
Bone marrow lesions	**1.9**	**1.3 to 2.7**	**1.7**	**1.1 to 2.7**
Effusions	1.2	0.7 to 2.2	1.1	0.5 to 2.3
Osteophytes	1.1	0.8 to 1.6	0.9	0.5 to 1.5
Cartilage defects	1.2	0.9 to 1.8	**2.0**	**1.2 to 3.4**

Adjusted for age, BMI, the other three MRI features (e.g., for BML analysis, results were adjusted for effusions, osteophytes and cartilage defects) and Kellgren and Lawrence scores; OR = Odds ratio; 95% CI = 95% confidence interval; Printed bold: differences are significant

Patello-femoral joint (PFJ) and tibio-femoral joint (TFJ)

Multivariate analyses showed that weight-bearing pain was significantly associated with BMLs in the TFJ (OR: 1.5; 95% CI: 1.1 to 2.2) and with cartilage defects in the PFJ (OR: 1.5; 95% CI: 1.0 to 2.3). No associations were found for non-weight-bearing pain (Table 5).

Table 5. Data on multivariate GEE analyses regarding MRI features and weight-bearing and non-weight-bearing knee pain stratified for patello-femoral and tibio-femoral joint

	Weight-bearing pain				**Non-weight-bearing pain**			
	Patello-femoral		**Tibio-femoral**		**Patello-femoral**		**Tibio-femoral**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Bone marrow lesions	1.4	0.9 to 2.1	**1.5**	**1.1 to 2.2**	1.4	0.8 to 2.4	1.2	0.8 to 1.9
Osteophytes	1.1	0.7 to 1.5	1.2	0.8 to 1.7	0.9	0.6 to 1.4	1.4	0.9 to 2.2
Cartilage defects	**1.5**	**1.0 to 2.3**	0.9	0.6 to 1.3	1.7	1.0 to 2.9	1.6	1.0 to 2.7

Adjusted for age, BMI, the other three MRI features (e.g., for presence of BML in the patello-femoral joint, results were adjusted for effusions, osteophytes and cartilage defects) and Kellgren and Lawrence scores; OR = Odds ratio; 95% CI = 95% confidence interval; Printed bold: differences are significant

DISCUSSION

In this cross-sectional cohort study of 887 middle-aged women, BMLs were significantly associated with both weight-bearing and non-weight-bearing knee pain. Cartilage defects within the knee were significantly associated with non-weight-bearing pain. When discriminating for the PFJ and the TFJ, BMLs in the TFJ and cartilage defects in the PFJ were significantly associated with weight-bearing pain.

Except for cartilage defects within the knee, no differences were found regarding the magnitude of the associations between weight-bearing versus non-weight-bearing pain in women with or without evident knee OA. We expected to find a smaller magnitude of the association for non-weight-bearing pain, as this present cohort study investigates early signs of OA. Also, the presence of night pain (a part of non-weight-bearing pain) is most often used as an indication for disease severity.[17-18] An earlier cross-sectional study found that weight-bearing pain was associated with BMLs and effusions, but less so with non-weight-bearing pain8. However, whereas the latter study included patients with at least one knee with both radiographic evidence of knee OA and symptoms (pain, aching or stiffness),[8] we focused on women with and without evident knee OA. In our study, only 61 (6.8%) women had a K&L grade of two or higher. We showed a small difference in the magnitude of the associations for cartilage defects and weight-bearing vs. non-weight-bearing pain. A higher magnitude was found for non-weight-bearing pain. Comparison of our results with others is difficult as most authors described pain as one single construct. We recommend that future studies distinguish between the different pain items, rather than analysing them as one summary score.

The present study found that BMLs were associated with both weight-bearing and non-weight-bearing knee pain; this is in accordance with previous work.[7,9,19] It is reported that BMLs can change over time and are often found in knees with and without OA;[20-23] therefore, future research should also focus on longitudinal associations.

We found that cartilage defects are associated with non-weight-bearing pain. A recent review found conflicting results regarding the association between cartilage

defects and pain.[10] Also, it is suggested that because cartilage is not innervated, it is incapable of directly causing pain.[24] A possible explanation for our findings might be that during rest, inflammatory responses are released into the joint which might cause pain.

We found no significant associations for joint effusions, in contrast to others who did.[6,8-9,19] However, these latter studies included older patients with clinically or radiographically determined OA; also, the total number of effusions was probably too low to detect a significant association, as only 5.9% of all women had an effusion. In our analysis, we dichotomized effusions as present if they had a score of ≥ 2 in the original scoring. We think this classification is justifiable, as the present study investigates early signs of OA which should exclude large abnormalities. Also, additional analysis showed that if we dichotomized effusions as present with a score of ≥ 1, the associations were still not significant.

Furthermore, we found no associations between pain and osteophytes, which is in accordance with others.[7,9,19] In our analyses, we adjusted for K&L scores, which may have caused the lack of association. However, additional analysis without adjusting for K&L scores did not change our results.

Earlier studies on knee OA mainly focused on the TFJ, whilst OA within the PFJ is very common.[25-26] OA of the PFJ is reported to be more prevalent than OA of the TFJ, especially in women with early symptomatic knee OA.[12,27] In our relatively young and healthy study population, MRI findings within the PFJ were more prevalent than within the TFJ. In the TFJ, we found significant associations for BMLs and weight-bearing pain. In the PFJ, cartilage defects were associated with weight-bearing pain. Future research should also focus on differences between the TFJ and PFJ, as differences may exist with regard to complaints due to knee OA.

Most of our women with pain reported to have pain during climbing stairs (87.9%). Climbing stairs results in a higher patello-femoral pressure, more lateral force distribution on the trochlea and a lateral tilt of the patella, which may be an explanation for pain during stair climbing.[28]

In our study, because pain was not measured knee specific, we excluded all contralateral knees of those women who indicated to have unilateral knee pain (n=118). In additional analysis, for those 118 contralateral knees we set all pain scores at zero, which yielded more or less the same associations.

An important strength of this study is its design. As this cross-sectional cohort study was unselected for OA, it was possible to study which early structural changes are associated with knee pain. Recognizing these early changes within the knee can help prevent further damage of the joint,[20] which will have important implications in disease progression.[29] The next step is to reproduce our findings based on longitudinal data.

Our study also has some limitations. First, because the number of women reporting knee pain was small (n=181; 20.4%), the associations may have been found by chance. Nevertheless, women with pain showed more abnormalities on MRI than women

without pain (Table 2). Second, based on previous studies, we decided to include BMLs, joint effusion, osteophytes and cartilage defects in our analyses, as we expected these to be associated with pain; it is possible that we missed features that could have influenced our results. However, a recent systematic review showed that knee pain due to OA is only associated with BMLs and effusions;[10] from this viewpoint we can justify not including all MRI features. Third, knee pain and MRI features were analyzed as being present or absent; due to the small numbers it was not possible to measure these features as categorical or continuous variables.

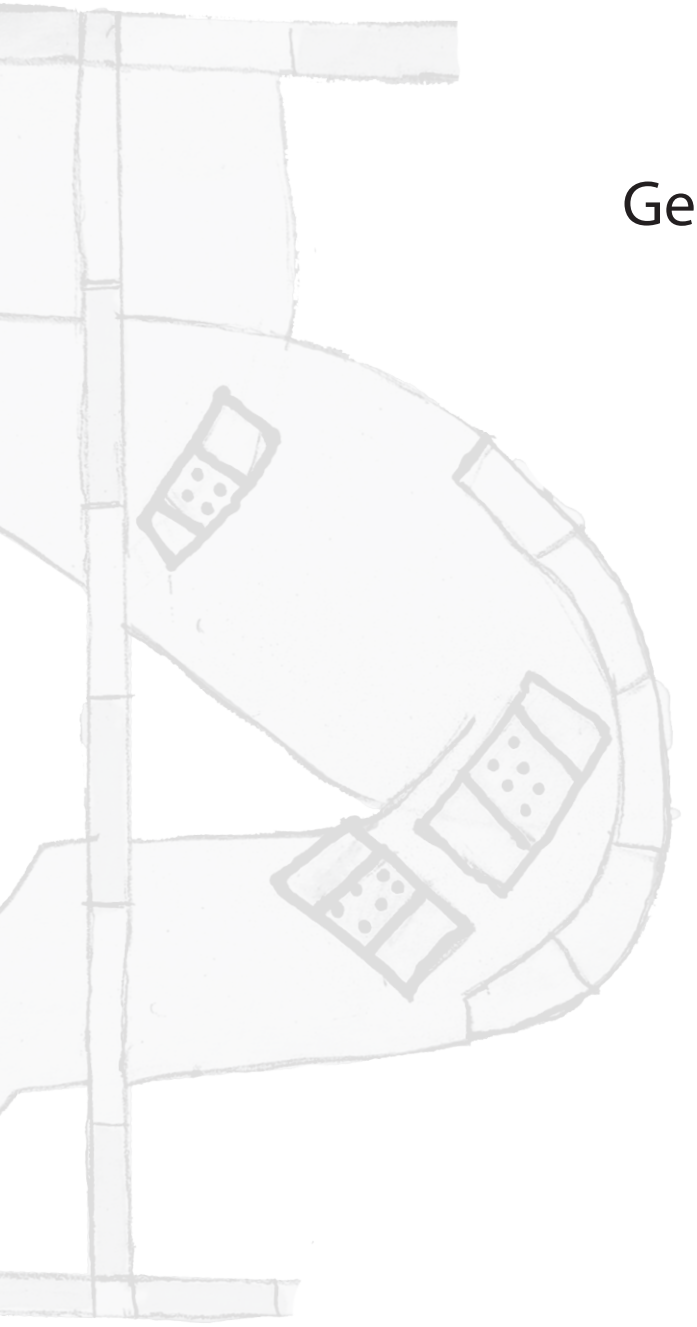
In summary, the present study shows that BMLs are significantly associated with (non-) weight-bearing knee pain. Also, cartilage defects are associated with non-weight-bearing knee pain. Moreover, BMLs in the TFJ and cartilage defects in the PFJ are associated with weight-bearing pain. Except for cartilage defects, the magnitude of these associations showed no difference between weight-bearing and non-weight-bearing knee pain in women with and without OA.

REFERENCES

1. **Felson DT**, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635-46.
2. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-7.
3. **Woolf AD**, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646-56.
4. **Felson DT**, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 2001;134:541-9.
5. **Hernandez-Molina G**, Neogi T, Hunter DJ, Niu J, Guermazi A, Reichenbach S, et al. The association of bone attrition with knee pain and other MRI features of osteoarthritis. *Ann Rheum Dis* 2008;67:43-7.
6. **Hill CL**, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. *J Rheumatol* 2001;28:1330-7.
7. **Link TM**, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 2003;226:373-81.
8. **Lo GH**, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2009;17:1562-9.
9. **Torres L**, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage* 2006;14:1033-40.
10. **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;70:60-7.
11. **Stratford PW**, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266-72.
12. **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;70:1944-8.
13. **Hofman A**, van Duijn CM, Franco OH, Ikram MA, Janssen HL, Klaver CC, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol* 2011;26:657-86.
14. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-41.
15. **Kornaat PR**, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO, et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. *Skeletal Radiol* 2005;34:95-102.
16. **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
17. **Hawker GA**, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:415-22.
18. **Woolhead G**, Gooberman-Hill R, Dieppe P, Hawker G. Night pain in hip and knee osteoarthritis: a focus group study. *Arthritis Care Res (Hoboken)* 2010;62:944-9.
19. **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;239:811-7.
20. **Ding C**, Jones G, Wluka AE, Cicuttini F. What can we learn about osteoarthritis by studying a healthy

person against a person with early onset of disease? *Curr Opin Rheumatol* 2010;22:520-7.

21. **Felson DT**, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum* 2007;56:2986-92.
22. **Kornaat PR**, Kloppenburg M, Sharma R, Botha-Scheepers SA, Le Graverand MP, Coene LN, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol* 2007;17:3073-8.
23. **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;63:691-9.
24. **Hunter DJ**, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Rheum Dis Clin North Am* 2008;34:623-43.
25. **Duncan R**, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? *Osteoarthritis Cartilage* 2009;17:1151-5.
26. **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.
27. **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.
28. **Goudakos IG**, Konig C, Schottle PB, Taylor WR, Singh NB, Roberts I, et al. Stair climbing results in more challenging patellofemoral contact mechanics and kinematics than walking at early knee flexion under physiological-like quadriceps loading. *J Biomech* 2009;42:2590-6.
29. **Roemer FW**, Crema MD, Trattnig S, Guermazi A. Advances in imaging of osteoarthritis and cartilage. *Radiology* 2011;260:332-54.



CHAPTER 8

General discussion

Pain is the most common complaint in osteoarthritis (OA)[1] and is therefore often used as an outcome in clinical studies. Because the exact etiology of OA is unknown and curable treatments are still lacking, general practitioners (GPs) and other clinicians can only apply symptom-driven treatment options to postpone the moment of total joint replacement. Moreover, because OA results in a heterogeneous expression of clinical complaints, it is difficult to apply effective individually-tailored treatment. The overall aim of this thesis was to improve the knowledge on: i) which medication to use as first choice in treating knee pain due to clinical OA in general practice, ii) the course of pain due to OA and its predictors and iii) which structural features in the knee are related to different dimensions of reported knee pain.

In this chapter we discuss the main findings and place them in a broader perspective. In addition, we focus on the course of pain due to OA and the various methods used to measure it. Then, we present a more detailed description of the different approaches used in the trials exploring the use of acetaminophen and NSAIDs. Finally, we discuss implications for general practice and make some recommendations for further research on pain due to OA.

Main findings of this thesis

In Chapters 2 and 3 we present our pragmatic randomized controlled trial of 104 primary care patients with knee OA. The results show no significant differences in knee pain and function at 3, 6, 9 and 12 weeks between the acetaminophen and diclofenac groups. However, some benefit was found in the use of diclofenac compared with acetaminophen from day 5 to day 12. In Chapter 4 we evaluate the heterogeneity of studies assessing the effectiveness of acetaminophen versus non-steroidal anti-inflammatory drugs (NSAIDs). We found moderate clinical heterogeneity for those studies that included patients with both hip and knee OA versus knee OA alone. In Chapter 5 we identified 5 trajectories of pain in 222 primary care patients with hip OA. Most patients were classified into the 'mild pain' (stable low levels of pain) group. Furthermore, we found a trajectory of patients with 'moderate pain', 'regularly progressing pain', 'highly progressing pain' and 'always pain' (permanent severe levels of pain). Predictors for membership in the 'always pain' group were low level of education, higher BMI, higher Kellgren and Lawrence (K&L) score of the hip, a longer duration of complaints, morning stiffness of the hip, generalized complaints, a decreased internal rotation and flexion and concurrent back and trochanteric pain. Predictors in the 'highly progressing pain' group were a higher K&L score of the hip and morning stiffness of the hip. The aim of the study in Chapter 6 was to investigate if these trajectories were also present in a different study population with a longer follow-up period. We revealed 4 distinct trajectories. Again, we found a group of 'mild pain', 'moderate pain' and 'always pain'. Moreover, we also identified a 'decreasing pain' group. Predictors for membership in the 'always pain' group were female participants, knee OA and concurrent back complaints. Predictors for membership in the 'moderate pain' group were higher BMI, morning stiffness of the hip, decreased hip flexion,

clinical knee OA and concurrent knee pain. Predictors for the 'decreasing pain' group were concurrent back complaints.

In Chapter 7 we found that bone marrow lesions were equally associated with both weight-bearing and non-weight-bearing knee pain. Cartilage defects were associated with non-weight-bearing knee pain. Weight-bearing pain was also associated with bone marrow lesions in the tibio-femoral joint and cartilage defects in the patello-femoral joint.

Pain in OA

Etiology of pain

Because the precise etiology of OA pain has not yet been established the optimal treatment for individual patients remains difficult, as does the application of adequate strategies for symptomatic prevention. It is reported that bone marrow lesions and joint effusion are associated with knee pain.[2] In Chapter 7, we investigated whether MRI findings are associated with knee pain. Based on a previous study,[3] we classified pain into weight-bearing pain and non-weight bearing pain. We hypothesized that we would find differences in the magnitude of the associations for weight-bearing pain versus non-weight-bearing pain as this was reported earlier.[4] In addition, because we used data from a study that investigated early signs of OA, and because (for example) pain at night is often used as an indication for disease severity, we anticipated that we would find smaller magnitudes for non-weight-bearing pain. In this study we found that bone marrow lesions were significantly and equally associated with both weight-bearing and non-weight-bearing knee pain. However, in contrast to others,[4-7] we found no significant associations for joint effusions. In our analysis, we chose to dichotomize effusions as present if they had a score of ≥ 2 (moderate/severe) on the original scoring, which resulted in a low total number of effusions with which to detect a significant association, i.e. from the entire cohort, in only 5.9% was an effusion seen on MRI. When dichotomizing effusions as being present with a score of ≥ 1 the associations were still not significant. Until now, there is conflicting evidence regarding cartilage defects, meniscal lesions and bone attrition.[2] In the same study (Chapter 7) we found that cartilage defects in the knee were significantly associated with non-weight-bearing knee pain. It has been suggested that cartilage is not innervated and is therefore incapable of directly causing pain.[8] However, besides the degenerative process of OA, blood vessel outgrowth (angiogenesis) and subsequently sensory nerve growth is increased in the synovium, osteophytes and menisci, and this leads to ossification in osteophytes and the deep layers of articular cartilage.[9] The former assumption that articular cartilage is not innervated does possibly not hold in osteoarthritis patients. However, the mechanism by which blood vessel outgrowth and sensory nerve growth might contribute to the presence of pain in OA remains unclear. More advanced imaging, or harvesting of joint materials after joint replacement, are needed to study these blood and nerve growth processes in relation to the severity and type of pain.

Course of pain

Data on the course of pain in osteoarthritis is scarce. Moreover, data on prognostic factors to predict the clinical course of OA are also limited.[10,11] On the group level, pain due to OA slightly worsens over time[12,13] whereas at the individual level there are marked fluctuations in pain severity.[14] Unfortunately, earlier studies on the course of pain generally used only two or three measuring points over time to establish the trajectories of pain.[12,14] However, this method is probably too insensitive when assessing the course of pain because of the intra-individual fluctuations in pain severity. Therefore, it remains difficult to accurately identify prognostic variables.

Using cluster analysis, Leffondré and colleagues made a first attempt to identify longitudinal patterns of change in 835 patients with pain due to hip and/or knee OA by measuring over four time points. Using this approach, individuals within a group are more similar than individuals between groups.[15] Leffondré et al. identified their trajectories using the maximum absolute first difference, the slope, the proportion of variance R^2 explained by the linear model and the ratio of the maximum absolute second difference to the mean over time. They found four distinct subgroups based on their individual pain response pattern: 1) regularly increasing; 2) regularly decreasing; 3) stable over time; or 4) highly unstable.[16] Nevertheless, cluster analysis is a rather restrictive method and the subjectivity of the researchers may bias the decision regarding the most optimal number of classes, which increases the chance of misclassification.[17,18] Also, there is a lack of statistical indices to help decide on the optimal number of classes.[17] In contrast, latent class growth analysis (LCGA) is a more flexible technique.[17] With LCGA the variance and covariance estimates are assumed to be fixed to zero. Consequently, all individuals within a class are assumed to be homogeneous.[15] Similar to cluster analysis, with LCGA it is possible to assess heterogeneity in a population and to identify clinically meaningful groups of people that are similar in their response regarding relevant outcomes or growth trajectories.[19] However, LCGA outperforms cluster analysis, especially when true classifications are unknown.[17,18] The advantages of LCGA over cluster analysis are: 1) assistance in determining the number of classes, 2) calculation of probability values for confidence regarding the correct allocation of an individual to a class and 3) no need to standardize the variables.[18,20] In this thesis, we succeeded in finding distinct trajectories of pain in patients with hip OA using LCGA. Chapter 5 yielded 5 trajectories of pain in 222 patients with hip OA who were followed over nine time points over 2 years. In Chapter 6, we found 4 trajectories of pain in 208 participants with hip OA over six time points over a period of 5 years. Although both studies had important differences in design, population, number and length of follow-up measurements, three more or less similar trajectories over time were found in both studies ('mild pain', 'moderate pain' and 'always pain'). In both studies the probability of membership was high (≥80%) meaning that most participants were correctly allocated. An important limitation of both studies was the small study groups, which made it impossible to perform multivariate regression analyses to identify characteristics of group membership. Therefore, we only performed univariate regression analysis. Based on that analysis, being female, level of education, BMI, K&L score of the hip, duration of complaints, morning stiffness of the hip, decreased range of motion of the hip, generalized complaints and concurrent

back, knee and trochanteric complaints were found to be characteristics for group membership; however, they were not specific for one of the groups. This needs further investigation. In our studies, pain was measured at 3-monthly intervals (Chapter 5) and at yearly intervals (Chapter 6). Because it remains unknown which time interval is the most effective to identify reliable trajectories of pain severity, more studies on this topic are needed. Also, more data are needed to elucidate predictors for an unfavorable and favorable course of pain as this may have implications for treatment strategies.

Pain questionnaires

Because pain is a subjective outcome it is difficult to measure. Also, in various studies different time intervals between the measurements are used to assess pain severity. It has also been shown that weekly or monthly retrospective pain assessments are influenced by current pain intensity at the end of the period,[21] even though patients were asked to report their pain intensity over the whole period. Therefore, daily pain measures may lead to a more accurate pain assessment. However, no data are available on the most optimal time interval between measurements. In addition, a wide variety of questionnaires are used to assess the severity of OA pain, all of which measure pain in a slightly different way.[22] Nevertheless, all these questionnaires seem to have comparable psychometric properties.[23]

Western Ontario McMaster Universities Osteoarthritis Index

The Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)[24] is a validated questionnaire assessing 5 different pain items (pain on walking, on climbing stairs, on standing, at night and at rest). Previous studies most often presented pain as one summary score,[7,25-32] while it is probably better to either interpret each pain item separately, or to classify them according to homogeneity into: 1) weight-bearing pain items (pain on walking, on climbing stairs and on standing), and 2) non-weight-bearing pain items (pain at night and at rest).[3] Indeed, in Chapter 7 we found that the three weight-bearing pain subscales were highly correlated with each other, as were the two non-weight-bearing pain subscales. Therefore, we used weight-bearing and non-weight-bearing pain for our analyses. A previous study found that weight-bearing pain was associated with MRI findings (bone marrow lesions and effusions), but less so with non-weight-bearing pain.[4] In contrast to this previous study, we found a slightly higher magnitude for the associations of cartilage defects and non-weight-bearing compared to weight-bearing pain.

In Chapter 7, most of the women with pain reported to have pain during climbing stairs (87.9%). It is known that knee OA patients show differences in their lower extremity joint kinematics when ascending and descending stairs compared with healthy controls.[33] Regrettably, the WOMAC does not distinguish between stair ascending and descending. However, such a distinction would be valuable as a higher patello-femoral pressure has been found during stair ascent.[34,35]

In Chapter 5, the WOMAC pain subscale was also used for the latent class growth analysis. We found four trajectories of pain: two of them consisted of patients with

stable mild levels of pain, one consisted of stable moderate pain levels, and the fourth trajectory consisted of patients with stable severe levels of pain (data not shown). We suggested that the WOMAC is less sensitive for change compared with the Visual Analogue Scale (VAS). This was not caused by the summation of the five pain items into one pain score, as LCGA yielded the same trajectories for each individual pain item (data not shown). In addition, the same (stable) trajectories were also found when the WOMAC pain was divided into weight-bearing and non-weight-bearing pain, as proposed by Stratford et al.[3]

A limitation of the WOMAC questionnaire is its high correlation between pain and physical function subscale scores.[36] For our trial (Chapter 3) we used the Knee Osteoarthritis Outcome Score (KOOS),[37] which is an extension of the WOMAC questionnaire and more suitable for younger and/or more active patients with knee injuries and/or OA, as it includes more questions on activities of daily living and sport and recreation. Another difference between the two questionnaires is that the WOMAC measures pain and function over the past 48 hours, whereas the KOOS measures pain and function over the past week. Compared to the WOMAC, the KOOS has improved validity and may be at least as responsive as the WOMAC.[38]

Constant and Intermittent Osteoarthritis Pain

Based on focus groups examining the pain experience of patients with hip/knee OA, a relatively new questionnaire (the ICOAP) has been developed including pain intensity, frequency and impact on mood, sleep and quality of life.[39,40] Two different types of pain are assessed with this questionnaire: a dull aching pain that is relatively constant over time; and intermittent pain which is a less frequent but more intense, unpredictable pain.[39,40] It is suggested that constant pain is more often a complaint later in the course of OA.[39] Indeed, in our primary care trial (Chapter 3) the participating patients scored higher on the intermittent pain scale than on the constant pain scale. The ICOAP was developed to measure the multidimensional pain experience and has a low correlation with physical functioning. This is in contrast to the WOMAC in which pain and function are highly correlated.[36] Until now, very few studies have incorporated the ICOAP as an outcome measure. Additional studies using this questionnaire are needed.

Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS)

Although the WOMAC is highly recommended and the most commonly used outcome instrument to measure pain and function[41] the VAS and NRS are often used in OA research to measure the severity of pain, and both are easy to use.[22] For patients, the NRS may be easier due to a simpler scoring and it can be used both verbally and in written form.[22] In Chapters 5 and 6, we used both the NRS and VAS pain to identify distinct trajectories and both seemed suitable for this purpose. For daily pain measures (as in Chapter 3) and for pain assessment in general practice the NRS seems the most practical. In addition, the NRS is also easy to use when using a short message service (SMS), which will probably be used more often to gather data on daily pain severity.

Treatment in OA

Treatment in OA is mainly symptom driven and consists of pharmacological and non-pharmacological treatments. Clinical guidelines[42-44] recommend a wide variety of multidisciplinary treatments to alleviate pain, and improve function and quality of life. In the Netherlands, to facilitate guideline implementation and optimize the tuning of non-surgical treatment, a stepped-care strategy with three phases was recently developed.[45] The first phase consists of education, lifestyle advice and medication (e.g. acetaminophen). Evaluation of this phase takes place after 3 months. Phase 2 consists of exercise therapy, dietary therapy and medication (e.g. NSAIDs). The final phase consists of referral to secondary care, multidisciplinary care, TENS and medication (e.g. opioid, intra-articular injection).[45]

In this stepped-care model and in the clinical guidelines, acetaminophen is recommended as the medication of first choice, mainly because of its good safety profile.[42-44] Despite this, studies have shown that most patients prefer to use NSAIDs as first choice medication.[46,47]

Trials assessing effectiveness of pain medication in OA

The results of our pragmatic randomized controlled trial (Chapter 3) are in line with clinical guidelines for treating knee OA, all of which recommend acetaminophen as first choice. However, previous reviews showed that acetaminophen is less effective than NSAIDs in relieving pain due to OA.[48-51] Effects sizes showed only small improvements in pain (range 0.2 to 0.37) in favor of NSAIDs. In our trial, we found almost no differences between diclofenac and acetaminophen when pain was measured every three weeks. However, our daily pain measures showed significant differences in effectiveness between the two groups from day 5 to day 12 in favor of patients allocated to diclofenac. It seems that these daily measures of pain severity provide a more precise description of the course of pain

Pragmatic design

Although we stress the fact that placebo-controlled trials are needed as proof of principle, pragmatic trials are also important as these provide a better reflection of daily practice[52] than previous studies that used wash-out periods[53-61] or a flare design[62-64] and/or used distinct favorable age categories.[53,64,65] Furthermore, they do not reflect daily practice in primary care because the far most studies were performed in secondary care.[53,58,65]

In Chapter 3 we present the results of our pragmatic trial which stayed as close as possible to actual daily practice, and the patients were aware which pain medication they were allocated to receive. Pain medication was prescribed for a period of two weeks and, if necessary, for another one to two weeks. This is in accordance with the Dutch guideline for non-traumatic knee complaints.[42] For our trial, we included patients aged ≥ 45 years without excluding the oldest patients, in contrast to some studies which excluded elders.[53,54,64,65]

In Chapter 3, acetaminophen dosage of 1000 mg per pill was used instead of the regular acetaminophen dosage of 500 mg per pill. This was done to enhance the user-friendliness of the medication.

A limitation of an (open-label) trial is the use of concurrent treatment, such as physiotherapy or other medications. It is possible that GPs and patients feel the need to use other therapies (e.g. physical therapy) besides the medication used in the study if they are not confident about the effectiveness of one of the two treatments. However, in our study 14.3% of the patients in the diclofenac group visited a physiotherapist in the first three weeks compared with 6.7% in the acetaminophen group. In the diclofenac group, 5.6% used co-medication (acetaminophen) compared with 1.9% in the acetaminophen group.

Flare design

The effectiveness of NSAIDs is often assessed in trials with a flare design.[66] In those studies, patients are included if their pain severity increases during a wash-out period of the medication (mostly NSAIDs) that they use. Studies using a flare of symptoms might overestimate the treatment effect that will be found in daily practice, because in a flare design only those patients are included in whom an NSAID was proven efficient before the screening for a study. In addition, with such a design, patients are more likely to tolerate the allocated treatment as they are already familiar with it. It has been shown that a flare design might raise the effect sizes found.[66-68] For instance, Bjordal and colleagues showed marked heterogeneity and an effect size for pain reduction of 0.32. In those 10 trials that did not use a flare design results were heterogeneous with an effect size for pain reduction of 0.23.[68]

A flare design may not be suitable to compare the effectiveness of medication in primary care patients, as many patients who visit their GP did not use medication previously. Remarkably, all guidelines are based on trials using a wash-out period or a flare design.[42-44] Our review (Chapter 4) that compared trials assessing effectiveness of acetaminophen with NSAIDs, found no differences in effect for studies with and without a flare design. It is possible that the number of studies with and without a flare was too low to detect any differences. Of the included studies, 3 of the 14 used a flare design.[62-64] In contrast, 10 studies used a wash-out period prior to the study.[53-61,65] With a wash-out period, patients need to stop the pain medication, but their pain severity does not have to increase. However, only one study included in our review used neither a wash-out period nor a flare design in their two-year follow-up trial assessing the effectiveness of naproxen and acetaminophen.[69] Patients in this latter study were prohibited from taking NSAIDs 3 months prior to the study. Concurrent corticosteroid treatment and injection were also not allowed 2 months prior to the study. This long-term study showed no differences in effectiveness of treatment with either acetaminophen or naproxen69. Although, Williams et al.[69] treated patients for 2 years, their results are in line with the findings of our trial at 12-week follow-up (Chapter 3).

Primary care versus secondary care

From the GP's perspective, an important drawback of most earlier studies is that most of them included patients from secondary care. We suggest that patients in secondary care more frequently have more severe pain and symptoms and might therefore respond better to an NSAID compared with acetaminophen.[60] In the Netherlands, the GP is generally the primary caregiver in OA. Surprisingly, in our review (Chapter 4), where we excluded n-of-1 trials, only one study, included patients from general practice;[54] they followed their patients for 14 days and concluded that ibuprofen was more effective than acetaminophen. In our study (Chapter 3), we found that diclofenac was also more effective from day 5 to day 12, but after that specific period no differences were found. Compared with our trial (Chapter 3), patients in the above-mentioned study had both hip and knee OA, were slightly older (average 66 years vs. 63 years), more likely to be women and had more severe pain. Moreover, 3% of their patients needed a wash-out period prior to randomization as they already used pain medication.[54] In our trial (Chapter 3) patients were excluded if they were already on pain medication prior to randomization.

Placebo-controlled versus active-controlled

Previous reviews found that acetaminophen is more effective than placebo, but slightly less effective than NSAIDs.[49,51] The trial described in this thesis (Chapter 3) aimed to stay as close to daily practice as possible. For this, we also investigated the effectiveness of diclofenac and acetaminophen in patients that were aware of which study medication they received, which implies that this is often accompanied by expectations. Because of this design, a placebo arm was not included in this study (Chapter 3). A drawback of placebo-controlled trials is the placebo effect which may hamper comparison with an effect of the active treatment.[70,71] Further, the placebo effect might be caused (in part) by the use of rescue drugs, which is generally acetaminophen.[70,71] Another explanations for this effect is regression to the mean.

Revealing the effectiveness in active controlled studies may be even more difficult, probably because the patients may have expectations and a preference for one of the two medications. As previous studies showed patients' preferences for NSAIDs over acetaminophen,[46,47] we expected that most of the patients in our study would prefer diclofenac. However, it appeared that most patients preferred acetaminophen (41.4%) to diclofenac (15.4%). Recently more attention has been paid to the possible side-effects of diclofenac, which might have hampered the preference for this medication.

N-of-1 studies

N-of-1 studies are randomized crossover trials in which patients are their own control; therefore, the generalizability of such studies is low. However, they do provide important data on the most appropriate treatment for the individual patient.[72-76] Previous N-of-1 studies found that acetaminophen was useful for most patients with chronic pain, whose optimal type of pain medication is not yet established.[73,76]

However, another study expressed doubts about this finding.[74] Wegman et al. found that the best treatment differed per person.[75] These results underline the need for an individually-tailored treatment, which is also emphasized in the EULAR guideline.[43] This implies that future studies need to identify predictors that indicate which patients will benefit from using acetaminophen and which will benefit from using another type of pain medication.

Subgroups of OA

Differences between hip and knee OA

In Chapter 4 we reported moderate clinical heterogeneity for studies that included patients with both hip and knee OA.[54,58-60,64] We found higher effect sizes in favor of NSAIDs in studies that included a higher percentage of patients with hip OA. Another study also found differences in effectiveness in patients with hip and knee OA in favor of naproxen. However, they found an improvement in patients with knee OA compared with hip OA.[77] Another study assessing the effectiveness of glucosamine versus placebo in hip OA, also found indications for differences in effect on pain between hip and knee OA.[78] They suggested that this might be caused by differences in the inflammatory component, which is thought to be higher in knees. Nevertheless, this latter suggestion does not explain our results in Chapter 4 showing higher effect sizes in studies with a higher percentage of patients with hip OA.

Until now, subgroup studies focused on comparing different trials and generally included only the active treatment. An important problem with subgroup analysis is that the studies are not predefined and therefore unreliable because they were not powered for subgroup testing. Using individual patient data from several randomized controlled trials would overcome the power problem.[79] However, this has not yet been done in studies assessing the effectiveness of NSAIDs versus acetaminophen in knee versus hip OA.

Tibio-femoral joint and patello-femoral joint

Earlier studies on knee OA mainly focused on the tibio-femoral joint (TFJ), whilst OA in the patello-femoral joint (PFJ) is very common.[80,81] OA of the PFJ is reported to be more prevalent than OA of the TFJ, especially in women with early symptomatic knee OA.[82,83] In our relatively young and healthy study population presented in Chapter 7, MRI findings in the PFJ were more prevalent than in the TFJ. We found significant associations for bone marrow lesions in the TFJ and weight-bearing pain. Cartilage defects in the PFJ were associated with weight-bearing pain. Future research should also focus on differences between the TFJ and PFJ, as differences may exist with regard to complaints due to knee OA.

Mild versus severe pain patients

It has been suggested that patients with more severe pain complaints react better to an NSAID compared with acetaminophen;[60] however, not everyone agrees with this.[84]

In Chapter 4 we assessed differences in effectiveness for those patients with severe pain (≥55 on a 0-100 VAS scale) versus moderate pain (<55) at baseline and found that patients with severe pain had lower effect sizes (ES -0.25; 95% CI: -0.35 to -0.16) than those reporting moderate pain (ES -0.37; 95% CI: -0.51 to -.024). This suggests that NSAIDs are not more effective in patients with more severe pain. However, the differences in effect were small and were not based on individual patient data. In Chapter 3 we reported that patients with moderate/severe pain (≥5 on a 0-10 NRS) at baseline (acetaminophen: n=32; diclofenac: n=35), had a greater reduction in knee pain in favor of diclofenac users from day 5 to day 10. At 3, 6, 9 and 12-weeks follow-up, no differences were found regarding knee pain and function between the diclofenac and acetaminophen group for moderate/high pain patients. Also, no differences in effect were found for mild pain (NRS <5) patients (acetaminophen: n=19; diclofenac: n=17), perhaps because of small numbers. Although there is a small benefit in using diclofenac in the first days of treatment for patients with moderate/severe pain, we still recommend to use acetaminophen as the medication of first choice. As we did not predefine our subgroup analysis, this may have consequences for a high risk of false results.[79] However, we did test the subgroup interaction effect which was highly significant (p=0.008).

Lasagna's Law

In Chapter 3 we reported that we originally planned to include 154 patients. After extending the inclusion period by an additional year, we managed to included only 104 patients. Recruiting eligible patients to participate in research is often a problem. This phenomenon is called Lasagna's Law and was studied in Dutch primary care.[85] They found that studies which included prevalent cases were more successful than studies which included incident cases. Therefore, to reinforce study inclusion we also searched GPs' electronic medical records for eligible patients. Of the 104 included patients, 33 patients (diclofenac: n=16; acetaminophen: n=17) were screened for the same inclusion/exclusion criteria and were included after searching the GPs' medical records. No differences between incident cases and prevalent cases were found regarding pain severity and disability at baseline. However, prevalent cases (not surprisingly) had a longer duration (complaints ≥3 months: 75.8%) of knee complaints than the incident cases (complaints ≥3 months: 47.1%).

Other pain medication used in primary care

An important disadvantage of oral NSAIDs is the high risk of developing gastrointestinal, cardiovascular and renal adverse events.[86,87] As an alternative, topical NSAIDs can be used. For OA in the superficial joints such as the hand and knee, topical NSAIDs have been shown to be more effective in relieving pain than placebo and similar to oral NSAIDs[88] and are especially useful in OA patients with only a view joints affected. In addition, topical NSAIDs have been associated with fewer adverse events compared with oral NSAIDs.[88] If topical NSAIDs are also effective in a deeper joint such as the hip

is unknown.

Tramadol which is a weak opioid is another pain medication that could be an alternative when acetaminophen does not provide enough pain relief in OA and NSAIDs are contraindicated or non-tolerated. Tramadol is effective in relieving pain in patients with moderate to severe OA. However, the benefits are small[89] and they must be used with caution in elderly patients because of central nervous system depression and in patients with a seizure disorder.[90] For both tramadol and topical NSAIDs, limited evidence is available for the effectiveness in primary care and future studies on this are needed.

Implications for general practice

The results of our open pragmatic trial implicate that acetaminophen should be used as the first choice medication in knee OA regardless of pain severity, since we found no difference between acetaminophen compared to diclofenac at 3, 6, 9 and 12-weeks follow-up and only a small differences in favor of diclofenac from day 5 to day 12. GPs now have more evidence that may help them in their advice to patients that acetaminophen is the medication of first choice, which could be effective if used in a sufficiently high dosage (≥ 3000 mg) for a period of 2 weeks and, if required, for another 1 to 2 weeks. If ineffective, patients and GPs may decide to switch to other pain medications (e.g. NSAIDs). Therefore, GPs can now be more confident about following the clinical guidelines.[42-44]

Recommendations for future research

Our study was one of the first pragmatic trials to assess the effectiveness of acetaminophen versus diclofenac in patients with knee OA in primary care. An important strength of our study is its generalizability to daily practice. Placebo-controlled trials are important as proof of principle, but pragmatic trials are also needed to assess the effectiveness of treatments in daily practice.

In order to identify different trajectories and their predictors of pain using latent class growth analysis, a larger cohort study is required. Predictors of group membership should be reproduced based on multivariate regression analyses. In addition, future studies should also focus on the favorable and unfavorable trajectories of pain as these subgroups of patients might require different treatments.

It is also worthwhile to establish the most optimal time interval at which to measure pain. The time interval between measurements can influence the results of a study. In addition, it is important to pay more attention to different types of pain, such as (non-) weight-bearing pain, intermittent pain and pain that comes and goes. Until now, most studies used the WOMAC pain subscale as a summary score to measure severity of pain.

In a cross-sectional study that was unselected for knee OA (Chapter 7) we found that bone marrow lesions and cartilage defects were associated with pain. These findings need to be reproduced in longitudinal studies. Also, future studies should

focus on differences between the TFJ and PFJ, as differences may exist with regard to complaints due to knee OA.

A final remark is that future studies should use reliable predefined subgroup analysis in patients with hip and knee OA, as the effectiveness of treatment might differ between patients with hip versus knee OA.

References

1. **Hunter DJ**, Felson DT. Osteoarthritis. *BMJ* 2006;332:639-642.
2. **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;70:60-67.
3. **Stratford PW**, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266-272.
4. **Lo GH**, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2009;17:1562-1569.
5. **Hill CL**, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. *The Journal of rheumatology* 2001;28:1330-1337.
6. **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.
7. **Torres L**, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage* 2006;14:1033-1040.
8. **Hunter DJ**, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Rheum Dis Clin North Am* 2008;34:623-643.
9. **Mapp PI**, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol* 2012.
10. **Belo JN**, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. *Arthritis Rheum* 2007;57:13-26.
11. **Lievense AM**, Bierma-Zeinstra SM, Verhagen AP, Verhaar JA, Koes BW. Prognostic factors of progress of hip osteoarthritis: a systematic review. *Arthritis Rheum* 2002;47:556-562.
12. **Dieppe P**, Cushnaghan J, Tucker M, Browning S, Shepstone L. The Bristol 'OA500 study': progression and impact of the disease after 8 years. *Osteoarthritis Cartilage* 2000;8:63-68.
13. **van Dijk GM**, Dekker J, Veenhof C, van den Ende CH, Carpa Study G. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. *Arthritis Rheum* 2006;55:779-785.
14. **Paradowski PT**, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. *Health Qual Life Outcomes* 2005;3:59.
15. **Jung T**, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Social and personality psychology compass* 2008;2:302-317.
16. **Leffondre K**, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *J Clin Epidemiol* 2004;57:1049-1062.
17. **DiStefano C**, Kamphaus RW. Investigating subtypes of child development. A comparison of cluster analysis and latent class cluster analysis in typology creation. Educational and Psychological Measurement 2006;66:778-794.
18. **Magidson J**, Vermunt JK. Latent class models for clustering: A comparison with K-means. *Canadian Journal of Marketing Research* 2002;20:37-44.

19. **Muthén B**. Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. *Handbook of quantitative methodology for the social sciences*. Newbury Park, CA: Sage Publications; 2004:345-368.
20. **Vermunt JK**, Magidson J. Latent class cluster analysis. *Applied latent class analysis*. Cambridge: Cambridge University press; 2002:89-106.
21. **Perrot S**, Rozenberg S, Moyse D, Legout V, Marty M, cercle d'etude de douleur en r. Comparison of daily, weekly or monthly pain assessments in hip and knee osteoarthritis. A 29-day prospective study. *Joint Bone Spine* 2011;78:510-515.
22. **Hawker GA**, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S240-252.
23. **Ruyssen-Witrand A**, Fernandez-Lopez CJ, Gossec L, Anract P, Courpied JP, Dougados M. Psychometric properties of the OARSI/OMERACT osteoarthritis pain and functional impairment scales: ICOAP, KOOS-PS and HOOS-PS. *Clin Exp Rheumatol* 2011;29:231-237.
24. **Bellamy N**, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. *Clin Rheumatol* 1986;5:231-241.
25. **Kornaat PR**, Kloppenburg M, Sharma R, Botha-Scheepers SA, Le Graverand MP, Coene LN, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol* 2007;17:3073-3078.
26. **Wildi LM**, Raynauld JP, Martel-Pelletier J, Abram F, Dorais M, Pelletier JP. Relationship between bone marrow lesions, cartilage loss and pain in knee osteoarthritis: results from a randomised controlled clinical trial using MRI. *Ann Rheum Dis* 2010;69:2118-2124.
27. **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;63:691-699.
28. **Dunn TC**, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. *Radiology* 2004;232:592-598.
29. **Link TM**, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 2003;226:373-381.
30. **Pelletier JP**, Raynauld JP, Berthiaume MJ, Abram F, Choquette D, Haraoui B, et al. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. *Arthritis Res Ther* 2007;9:R74.
31. **Phan CM**, Link TM, Blumenkrantz G, Dunn TC, Ries MD, Steinbach LS, et al. MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. *Eur Radiol* 2006;16:608-618.
32. **Wluka AE**, Wolfe R, Stuckey S, Cicuttini FM. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? *Ann Rheum Dis* 2004;63:264-268.
33. **Hicks-Little CA**, Peindl RD, Hubbard TJ, Scannell BP, Springer BD, Odum SM, et al. Lower extremity joint kinematics during stair climbing in knee osteoarthritis. *Med Sci Sports Exerc* 2011;43:516-524.
34. **Costigan PA**, Deluzio KJ, Wyss UP. Knee and hip kinetics during normal stair climbing. *Gait Posture* 2002;16:31-37.

35. **Goudakos IG**, Konig C, Schottle PB, Taylor WR, Singh NB, Roberts I, et al. Stair climbing results in more challenging patellofemoral contact mechanics and kinematics than walking at early knee flexion under physiological-like quadriceps loading. *J Biomech* 2009;42:2590-2596.
36. **Bond M**, Davis A, Lohmander S, Hawker G. Responsiveness of the OARSI-OMERACT osteoarthritis pain and function measures. *Osteoarthritis Cartilage* 2012;20:541-547.
37. **Roos EM**, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88-96.
38. **Roos EM**, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes* 2003;1:17.
39. **Hawker GA**, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:409-414.
40. **Hawker GA**, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16:415-422.
41. **Bellamy N**, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *The Journal of rheumatology* 1997;24:799-802.
42. **Belo JN**, Bierma-Zeinstra SMA, Raaijmakers AJ, van der Wissel F. NHG-Standaard niet-traumatische knieproblemen bij volwassenen. *Huisarts en Wetenschap* 2008;51:229-240.
43. **Jordan KM**, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, 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 tESCISIT). *Ann Rheum Dis* 2003;62:1145-1155.
44. **Zhang W**, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981-1000.
45. **Smink AJ**, van den Ende CH, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, 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;30:1623-1629.
46. **Pincus T**, Swearingen C, Cummins P, Callahan LF. Preference for nonsteroidal antiinflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. *The Journal of rheumatology* 2000;27:1020-1027.
47. **Wolfe F**, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum* 2000; 43:378-385.
48. **Lee C**, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004;51:746-754.
49. **Towheed TE**, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006:CD004257.

50. **Wegman A**, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *The Journal of rheumatology* 2004;31:344-354.
51. **Zhang W**, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004;63:901-907.
52. **Patsopoulos NA**. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci* 2011;13:217-224.
53. **Batlle-Gualda E**, Roman Ivorra J, Martin-Mola E, Carbonell Abello J, Linares Ferrando LF, Tornero Molina J, et al. Aceclofenac vs paracetamol in the management of symptomatic osteoarthritis of the knee: a double-blind 6-week randomized controlled trial. *Osteoarthritis Cartilage* 2007;15:900-908.
54. **Boureau F**, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004; 63:1028-1034.
55. **Bradley JD**, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med* 1991;325:87-91.
56. **Geba GP**, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, Vioxx ACTG. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002;287:64-71.
57. **Golden HE**, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. *Am J Ther* 2004;11:85-94.
58. **Lequesne M**, Fannius J, Reginster JY, Verdickt W, du Laurier MV. Floctafenin versus acetaminophen for pain control in patients with osteoarthritis in the lower limbs. Franco-Belgian Task Force. *Rev Rhum Engl Ed* 1997;64:327-333.
59. **Pincus T**, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004;63:931-939.
60. **Pincus T**, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;44:1587-1598.
61. **Shen H**, Sprott H, Aeschlimann A, Gay RE, Michel BA, Gay S, et al. Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2006;45:765-770.
62. **Schnitzer TJ**, Tesser JR, Cooper KM, Altman RD. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1-7.
63. **Schnitzer TJ**, Weaver AL, Polis AB, Petruschke RA, Geba GP, Groups V-aV-S. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee. A combined analysis of the VACT studies. *The Journal of rheumatology* 2005;32:1093-1105.
64. **Temple AR**, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6-12 months) safety of acetaminophen in adult patients with osteoarthritis. *Clin Ther* 2006;28:222-235.

65. **Case JP**, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169-178.
66. **Trijau S**, Avouac J, Escalas C, Gossec L, Dougados M. Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2010;18:1012-1018.
67. **Scott-Lennox JA**, McLaughlin-Miley C, Lennox RD, Bohlig AM, Cutler BL, Yan C, et al. Stratification of flare intensity identifies placebo responders in a treatment efficacy trial of patients with osteoarthritis. *Arthritis Rheum* 2001;44:1599-1607.
68. **Bjordal JM**, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004;329:1317.
69. **Williams HJ**, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis and Rheumatism* 1993;36:1196-1206.
70. **Zeidler H**. Paracetamol and the placebo effect in osteoarthritis trials: a missing link? *Pain Res Treat* 2011;2011:696791.
71. **Zhang W**, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008;67:1716-1723.
72. **March L**, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. n of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. *BMJ* 1994;309:1041-1045; discussion 1045-1046.
73. **Nikles CJ**, Yelland M, Glasziou PP, Del Mar C. Do individualized medication effectiveness tests (n-of-1 trials) change clinical decisions about which drugs to use for osteoarthritis and chronic pain? *Am J Ther* 2005;12:92-97.
74. **Pope JE**, Prashker M, Anderson J. The efficacy and cost effectiveness of N of 1 studies with diclofenac compared to standard treatment with nonsteroidal antiinflammatory drugs in osteoarthritis. *The Journal of rheumatology* 2004;31:140-149.
75. **Wegman AC**, van der Windt DA, de Haan M, Deville WL, Fo CT, de Vries TP. Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis. *Ann Rheum Dis* 2003;62:1156-1161.
76. **Yelland MJ**, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ, Brown RM. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. *Rheumatology (Oxford)* 2007;46:135-140.
77. **Svensson O**, Malmenas M, Fajutrao L, Roos EM, Lohmander LS. Greater reduction of knee than hip pain in osteoarthritis treated with naproxen, as evaluated by WOMAC and SF-36. *Ann Rheum Dis* 2006;65:781-784.
78. **Rozendaal RM**, Uitterlinden EJ, van Osch GJ, Garling EH, Willemsen SP, Ginai AZ, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. *Osteoarthritis Cartilage* 2009;17:427-432.
79. **Bierma-Zeinstra SM**, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. *Arthritis Res Ther* 2011;13:213.
80. **Duncan R**, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? *Osteoarthritis Cartilage* 2009;17:1151-1155.

81. **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.
82. **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.
83. **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.
84. **Bradley JD**, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an antiinflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. *The Journal of rheumatology* 2001;28:1073-1076.
85. **van der Wouden JC**, Blankenstein AH, Huibers MJ, van der Windt DA, Stalman WA, Verhagen AP. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. *J Clin Epidemiol* 2007;60:819-824.
86. **Laine L**, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Alimentary pharmacology & therapeutics* 2006;24:751-767.
87. **Ong CK**, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clinical medicine & research* 2007;5:19-34.
88. **Altman RD**, Barthel HR. Topical therapies for osteoarthritis. *Drugs* 2011;71:1259-1279.
89. **Cepeda MS**, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: a systematic review and metaanalysis. *The Journal of rheumatology* 2007;34:543-555.
90. **Harvey WF**, Hunter DJ. The role of analgesics and intra-articular injections in disease management. *Rheumatic diseases clinics of North America* 2008;34:777-788.

Summary

Osteoarthritis (OA) is of multifactorial origin, but the precise etiology remains unknown. Because pain is the most common complaint reported by patients with OA it is often used as the primary outcome in trials. In most of these trials, on the group level patients' reported pain severity deteriorates slowly over time regardless of the treatment. However, individually it is known to vary greatly over time. Until now, treatment options are mainly symptom driven and consist of pharmacological and non-pharmacological therapies. They are focused on alleviating perceived pain, maintenance of activities in daily life, enhancing quality of life and postponing the moment of total joint replacement.

The main aim of this thesis was to improve our understanding of pain due to OA.

The (inter)national guidelines recommend acetaminophen as the medication of first choice because of its safety profile. However, systematic reviews have shown that non-steroidal anti-inflammatory drugs (NSAIDs) are more effective. In addition, various studies have also shown that NSAIDs are preferred to acetaminophen. We have suggested that patients, as well as general practitioners (GP), do not have sufficient evidence to support the use of acetaminophen in OA. **Chapter 2** describes the study protocol of our open-label randomized controlled trial (RCT) assessing the effectiveness of acetaminophen versus diclofenac in primary care patients with knee OA. Patients aged 45 years or older consulting their GP for a new episode of non-traumatic knee pain, meeting the clinical American College of Rheumatology (ACR) criteria for knee OA and with a pain severity of 2 or higher (on a 0-10 scale), were randomly allocated to either acetaminophen (maximum daily dose of 3000 mg) or diclofenac (maximum daily dose of 150 mg) for 2 weeks and, if required, another 1-2 weeks, with a total follow-up period of 12 weeks. Primary outcomes were severity of pain and disability measured with the Knee Injury and Osteoarthritis (KOOS; 0-100) at baseline, and at 3, 6, 9 and 12-weeks follow-up, and daily knee pain severity using a numeric rating scale (NRS; 0-10) measured with a diary during 6 weeks. Secondary outcomes were patients' perceived recovery, 3-weekly measured severity of knee pain (NRS), quality of life, compliance to the therapy, co-interventions and adverse reactions.

Chapter 3 describes the results of the trial which included 104 patients: 52 randomly allocated to the acetaminophen group and 52 to the diclofenac group. After 3 weeks, severity of knee pain showed a significant reduction in both the diclofenac and acetaminophen group. At 3, 6, 9 and 12-weeks follow-up, no significant differences were found between the groups regarding severity of knee pain (KOOS) and disability (KOOS). However, we found a significant difference ($p<0.05$) in the course of knee pain between day 5 and 12 in favor of the diclofenac group (range effect sizes: 0.4 to 0.5). We concluded that, although there was a small significant difference in effectiveness in favor of the diclofenac group from day 5 to day 12, there were no clinically relevant differences between the acetaminophen and diclofenac group during the 3, 6, 9 and 12-week follow-up in patients with knee OA.

In trials assessing the effectiveness of acetaminophen versus NSAIDs in OA, many differences exist in their study design. To identify whether these different designs also lead to differences in reported height of effectiveness, we systematically reviewed all sources of heterogeneity in studies evaluating NSAIDs versus acetaminophen in patients with knee and hip OA (**Chapter 4**). A database search up to January 2010 yielded 15 RCTs, which included 21 comparisons of NSAIDs and acetaminophen. We found moderate clinical heterogeneity for the comparisons which included both hip and knee OA versus knee OA only. Furthermore, no significant methodological and statistical heterogeneity was found. In conclusion, because of the moderate clinical heterogeneity that was found, we recommend that future trials should present the results of hip and knee OA separately. Differences might well exist in the effectiveness of NSAIDs versus acetaminophen in patients with hip versus knee OA.

In **Chapter 5**, using latent class growth analysis, we identified distinct trajectories of pain due to hip OA in 222 patients that were followed for 2 years. Severity of pain over the past week was measured with a visual analogue scale (VAS; 0-100). Five trajectories of pain due to hip OA were identified. Trajectory 1 (mild pain; n=69) had stable mild pain. Trajectory 2 (moderate pain; n=31) fluctuated slightly within ranges of moderate to severe pain levels. Patients in trajectory 3 (always pain; n=32) had constant severe pain. In trajectory 4 (regularly progressing; n=48) patients started with mild pain and slowly progressed to moderate hip pain. Patients in trajectory 5 (highly progressing; n=42) also started with mild pain, but quickly progressed to severe hip pain. Compared with patients in the 'mild pain' group, patients in the 'always pain' group had more severe radiographic hip OA, morning stiffness of the hip and a decreased range of motion of the hip. The 'highly progressing' group also had more severe radiographic hip OA and morning stiffness.

The aim of **Chapter 6** was to reproduce the findings described in Chapter 5 by using the 5-year follow-up data from the CHECK cohort that included 1,002 participants with hip and knee pain. Of the 588 participants who had hip complaints at baseline, 208 had clinical and/or radiographic hip OA, and 380 had hip pain but no hip OA. Each year questionnaires were filled out by participants to assess pain severity over the previous week measured on an 11-point numerical rating scale. We reproduced 3 trajectories regarding hip pain severity. Trajectory 1 consisted of participants who had 'mild pain' (n=78). Participants in trajectory 2 had 'moderate pain' (n=76) and those in trajectory 3 had 'always pain' (n=32). We also identified a smaller group that had 'decreasing pain' (n=22). Probability for membership in the 'always pain' group was higher for female participants, having knee OA and concurrent back complaints. For the 'moderate pain' group membership was related to higher BMI, morning stiffness of the hip, decreased hip flexion, clinical knee OA and concurrent knee pain. The 'decreasing pain' group more often had concurrent back complaints.

In **Chapter 7** we measured severity of knee pain according to homogeneity into weight-bearing versus non-weight-bearing knee pain and examined whether they were (equally) associated with specific features in the patello-femoral and tibio-femoral joints assessed with magnetic resonance imaging (MRI), in 887 middle-aged women with or without knee OA. In this open population cohort study, women received an MRI scan of both knees to assess the presence of bone marrow lesions (BML), joint effusions, osteophytes and cartilage defects using the Knee Osteoarthritis Scoring System (KOSS). Knee pain severity during the previous week was measured using the Western Ontario McMaster Osteoarthritis index (WOMAC) and classified into weight-bearing knee pain (pain on walking, on climbing stairs and on standing) and non-weight-bearing knee pain (pain at night and at rest). We showed that BMLs were associated with weight-bearing painodds ratio (OR): 1.9; 95% confidence interval (95% CI): 1.3 to 2.7 and non-weight-bearing pain (OR: 1.7; 95% CI: 1.1 to 2.7). Cartilage defects were associated with non-weight-bearing pain (OR: 2.0; 95% CI: 1.2 to 3.4). In the tibio-femoral joint, BMLs were associated with weight-bearing pain (OR: 1.5; 95% CI: 1.1 to 2.2). Cartilage defects in the patello-femoral joint were also associated with weight-bearing knee pain (OR: 1.5; 95% CI: 1.0 to 2.3). Regarding the magnitude of the found associations, almost no differences were found between weight-bearing and non-weight-bearing knee pain.

Samenvatting

De oorsprong van artrose is multifactorieel, maar de precieze ontstaanswijze is nog steeds onbekend. Pijn is de meest voorkomende klacht waarmee patiënten hulp zoeken in de gezondheidszorg en wordt daarom vaak gebruikt als primaire uitkomstmaat in wetenschappelijk onderzoek. In de meeste onderzoeken wordt gerapporteerde ernst van de pijn vanwege artrose in de loop van de tijd (jaren) langzaam erger onafhankelijk van behandeling. Echter, individueel gezien fluctueert pijn vaak hevig over de tijd. Tot nu toe is behandeling van artrose gebaseerd op symptoom bestrijding bestaande uit farmacologische en niet-farmacologische therapieën. Deze zijn gericht op pijnvermindering, behoud van dagelijkse activiteiten, het verhogen of stabiliseren van de kwaliteit van leven en zo lang mogelijk uitstellen van een gewrichtsvervangende operatie.

Het doel van dit proefschrift was om de kennis wat betreft pijn als gevolg van artrose te vergroten.

De (inter)nationale richtlijnen adviseren paracetamol als het medicijn van eerste keuze bij de behandeling van pijn als gevolg van artrose vanwege het brede veiligheidsprofiel. Echter systematische literatuuronderzoeken tonen aan dat niet-steroïde anti-inflammatoire drugs (NSAIDs) effectiever zijn dan paracetamol. Daarnaast heeft een onderzoek aangetoond dat de meeste patiënten met artrose een voorkeur hebben voor NSAIDs. Wellicht hebben huisartsen en patiënten niet genoeg bewijs om paracetamol te gaan gebruiken bij artroseklachten. **Hoofdstuk 2** beschrijft het studieprotocol van de uitgevoerde pragmatische niet-geblindeerde gerandomiseerde gecontroleerde trial (RCT) naar de effectiviteit van paracetamol en diclofenac bij patiënten met knieartrose. Patiënten van 45 jaar of ouder die hun huisarts consulteerden vanwege een nieuwe episode van niet-traumatische kniepijn, voldeden aan de klinische American College of Rheumatology (ACR)-criteria voor knieartrose en een pijnscore hoger dan een 2 hadden op een 0-10 schaal kwamen in aanmerking voor deelname aan de RCT. Patiënten werden at random toegewezen aan of de paracetamol groep (maximale dagelijkse dosis van 3000 mg) of de diclofenac groep (maximale dagelijkse dosis van 150 mg). Medicatie werd voorgeschreven voor een periode van 2 weken en indien nodig nogmaals 1-2 weken. Patiënten werden gedurende 12 weken gevolgd. De primaire uitkomstmaten waren ernst van de kniepijn en beperkingen in functioneren als gevolg van knieklachten gemeten met de Knee Osteoarthritis Outcome Score (KOOS; 0-100) op baseline, 3, 6, 9 en 12 weken follow-up en dagelijkse ernst van de pijn gemeten met een numerieke rating schaal (NRS; 0-10) in een dagboek gedurende 6 weken. Secundaire uitkomstmaten waren de patiënt zijn of haar ervaren herstel, ernst van de kniepijn gemeten met een 3-wekelijkse NRS score (gemiddelde ernst afgelopen week), kwaliteit van leven, therapietrouw, co-interventie en bijwerkingen.

Hoofdstuk 3 beschrijft de resultaten van de RCT waarbij in totaal 104 patiënten werden gerandomiseerd: 52 in de paracetamol groep en 52 in diclofenac groep. Na 3 weken vonden we een significante afname in ernst van de kniepijn in beide groepen. Op 3, 6, 9 en 12 weken follow-up was er geen verschil in kniepijn tussen de beide groepen op basis van de scores van de KOOS pijn en functie. Echter, op basis van de dagboekgegevens vonden we statistisch significante verschillen ($p<0,05$) in ernst van de kniepijn van dag 5 tot en met dag 12 in het voordeel van de diclofenac groep. De grootte van het effect in 'effect sizes' ging van 0,4 tot 0,5. De conclusie van deze pragmatische niet-geblindeerde studie was dat we na 3, 6, 9 en 12 weken geen verschil vonden tussen paracetamol en diclofenac gebruikers ook al was er wel een klein statistisch significant verschil tussen de beide groepen van dag 5-12 in het voordeel voor patiënten die diclofenac toegewezen hadden gekregen.

Hoofdstuk 4 geeft de resultaten van het systematisch literatuuroverzicht naar de heterogeniteit van de studies naar de effectiviteit van NSAIDs vergeleken met paracetamol bij patiënten met knie en heup artrose. De grootste literatuurdatabases werden systematisch doorgezocht op relevante studies tot januari 2010. Uiteindelijk werden er 15 RCTs, bestaande uit totaal 21 vergelijkingen van paracetamol met NSAIDs in de review geïncludeerd. We vonden matige klinische heterogeniteit voor de studies die zowel patiënten met heup en knie artrose insloten. Het literatuuronderzoek vond geen methodologische of statistische heterogeniteit. Toekomstige studies zouden de gegevens van heup en knie artrose beter apart kunnen presenteren vanwege de gevonden aanwezige klinische heterogeniteit. Het zou mogelijk kunnen zijn dat er een verschil in effectiviteit bestaat tussen NSAIDs en paracetamol bij patiënten met heup versus knie artrose.

In **Hoofdstuk 5** hebben we met behulp van 'latent class growth analysis' (LCGA) verschillende trajecten van pijn vanwege heup artrose geïdentificeerd in 222 patiënten met klinische en radiografische heup artrose die gedurende 2 jaar werden gevolgd. Gemiddelde ernst van de heuppijn over de afgelopen week werd gemeten met een Visuele Analoge Schaal (VAS; 0-100). In totaal werden 5 pijn trajecten gevonden. Traject 1 (milde pijn; n=69) bestaat uit mensen met een stabiel pijn niveau. Traject 2 (matige pijn; n=31) bestaat uit patiënten die licht fluctueren rondom matige tot ernstige pijn. Patiënten in traject 3 (altijd pijn; n=32) hebben altijd een ernstige mate van pijn. In traject 4 (langzaam verergerend; n=48) hadden patiënten milde pijn op baseline en verergerden deze langzaam naar matige pijn. Patiënten in traject 5 (snel verergerend; n=42) hadden ook milde pijn op baseline en verergerden snel naar ernstige heuppijn. Vergeleken met patiënten in de 'milde pijn' groep hadden patiënten in de 'altijd pijn' groep vaker ernstigere radiografische heup artrose, vaker ochtendstijfheid van de heup en een verminderde beweeglijkheid van de heup. De 'snel verergerende' groep had ook meer ernstige radiografische heup artrose en ochtendstijfheid van de heup.

Het doel van **Hoofdstuk 6** was het reproduceren van de resultaten van hoofdstuk 5 in een andere studiepopulatie met een langere follow-up periode. Hiervoor gebruikten we de 5-jaars follow-up data van het CHECK cohort. CHECK bestaat uit 1002 deelnemers met heup en/of knieklachten. Van de 588 mensen die heupklachten aangaven hadden 208 klinische en/of radiologische heupartrose en overige 380 hadden wel heuppijn maar geen heupartrose. De gemiddelde ernst van de heuppijn over de afgelopen week werd jaarlijks gemeten met behulp van een NRS (0-10). Vergeleken met het onderzoek naar pijntrajecten beschreven in hoofdstuk 5, werden er 3 min of meer dezelfde beloop trajecten voor de heuppijn gevonden. Traject 1 bestaat uit mensen met 'milde pijn' (n=78). Traject 2 bestaat uit 'matige pijn' (n=76) en traject 3 heeft altijd een ernstige mate van pijn ('altijd pijn'; n=32). Traject 4 bestaat uit een kleinere groep met 'afnemende pijn' (n=22). Vergeleken met de 'milde pijn' groep bestaat de 'altijd pijn' groep vaker uit vrouwen en hadden zij ook vaker last van klinische knieartrose en rugklachten. In de 'matige pijn' groep zitten vaker mensen met een hoger BMI, ochtendstijfheid van de heup, verminderde heupflexie, klinische knieartrose en kniepijn. De 'afnemende pijn' groep heeft vaker last van rugklachten.

In **Hoofdstuk 7** hebben we onderzocht of kniepijn tijdens belasting en pijn tijdens rust gerelateerd zijn aan vroege kenmerken van artrose zichtbaar gemaakt middels Magnetic Resonance Imaging (MRI) in de patello-femorale en tibio-femorale gewrichten van vrouwen van middelbare leeftijd met en zonder knieartrose. Vrouwen ondergingen een MRI van beide knieën om beenmerg leasies (BML), gewrichtseffusie, osteofyten and kraakbeenschade te identificeren. Ernst van de kniepijn gemiddeld over de afgelopen week werd gemeten met behulp van de Western Ontario McMaster Osteoarthritis Index (WOMAC) en werd ingedeeld in kniepijn tijdens belasting (pijn tijdens lopen, traplopen en staan) en kniepijn tijdens rust (pijn in rust en 's nachts). We vonden dat BMLs geassocieerd waren met pijn tijdens belastingodds ratio (OR): 1,9; 95% betrouwbaarheidsinterval (95% BI): 1,3 tot 2,7 en pijn tijdens rust (OR: 1,7; 95% BI: 1,1 tot 2,7). Kraakbeenschade was geassocieerd met pijn tijdens rust (OR: 2,0; 95% BI: 1,2 tot 3,4). Verder vonden we dat pijn tijdens belasting geassocieerd was met BMLs in het tibio-femarale gewricht (OR: 1,5; 95% BI: 1,1 tot 2,2) en met kraakbeenschade in het patello-femorale gewricht (OR: 1,5; 95% BI: 1,0 tot 2,3). Er waren geen duidelijke relevante klinische verschillen zichtbaar wat betreft de grootte van de associaties tussen pijn tijdens belasting en kniepijn tijdens rust.

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CURRICULUM VITAE

Saskia Pauline Jantina Verkleij is op 16 februari 1981 geboren in Heemstede. Na het behalen van haar VWO diploma aan het Sancta Maria te haarlem is zij in 1999 begonnen aan de studie Psychologie aan de Universiteit van Amsterdam. Na het behalen van haar propedeuse is zij overgestapt naar de studie Fysiotherapie aan de Hogeschool van Leiden en hierna heeft zij de 2-jarige onderzoeks-master Gezondheidswetenschappen gevolgd en is in 2008, met als afstudeerrichting Preventie, afgestudeerd. Tijdens haar afstudeeronderzoek onderzocht zij bij het RIVM of er een effect was van 'Hartslag Limburg', een project om het aantal hart- en vaatziekte terug te dringen, op de kwaliteit van leven. Daarnaast onderzocht zij of er binnen 'Hartslag Limburg' een relatie was tussen verandering in gewicht en kwaliteit van leven over een periode van 5 jaar.

In oktober 2008 begon zij aan haar promotietraject als wetenschappelijk onderzoeker bij de afdeling Huisartsgeneeskunde van het Erasmus MC, waarbij zij werkte aan de in dit proefschrift beschreven project.

PHD PORTFOLIO

Courses	Year	Workload
BROK (basiscursus regelgeving en organisatie voor klinische onderzoekers)	2009	30 hours
Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2009	8 hours
Biomedical English Writing and Communication	2011	40 hours
Presentations		
International		
Primus Rotterdam, poster presentation	2010	16 hours
Eular Londen, poster presentation	2011	16 hours
KARMA Keele, oral presentation	2011	20 hours
OARSI San Diego, oral and poster presentation	2011	36 hours
OARSI Barcelona, 2 poster presentations	2012	32 hours
Eular Berlijn, oral presentation and poster presentation	2012	36 hours
National		
NHG wetenschapsdag	2009	8 hours
CHECK bijeenkomst Utrecht, 2 oral presentations	2012	40 hours
Department of General Practice, oral presentation	2012	20 hours
National collaborations		
Research visit at VU University, Amsterdam	2010	16 hours
Teaching activities		
Supervising medical student	2011	80 hours
Other activities		
Lay out ontwerp Limesurvey	2009	20 hours
Academische jaarprijs, NWO	2011	20 hours
Loopbaancursus	2011	20 hours
NLP practitioner and master practitioner	2011/2012	292 hours

LIST OF PUBLICATIONS

This thesis

Verkleij SPJ, Hoekstra T, Rozendaal RM et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. *Annals of Rheumatic Diseases*. 2012

Verkleij SPJ, Luijsterburg PAJ, Bohnen AM et al. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis Cartilage*. 2011;19:921-9.

Verkleij SPJ, Luijsterburg PAJ, Koes BW et al. Effectiveness of diclofenac versus acetaminophen versus acetaminophen in primary care patients with knee osteoarthritis:[NTR1485], DIPA-trial: design of a randomized clinical trial. *BMC Musculoskelet Disord*. 2010;11:7.

Other

Verkleij SPJ, Adriaanse MC, Wendel-Vos GCW, Schuit AJ. Longitudinal relation between weight change and quality of life in a community-based population: a prospective cohort study. *The European Journal of Public Health*. 2012

Verkleij SPJ, Adriaanse MC, Verschuren WMM et al. Five-year effect of community-based intervention Hartslag Limburg on quality of life: a longitudinal cohort study. *Health Qual Life Outcomes*. 2011;9:11.