Symptomatic Progression of Knee and Hip Osteoarthritis in Primary Care

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Progressie van symptomen in knie- en heupartrose in de eerste lijn

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Chapter 1

General introduction

OSTEOARTHRITIS OF THE KNEE AND HIP

Osteoarthritis (OA) is one of the most common chronic diseases and is one of the leading causes of pain and disability worldwide. OA can occur in many joints in the body, but patient consultation rates due to knee and hip OA are the highest in primary care. The main symptoms of both knee and hip OA are joint pain and stiffness, varying from mild to severe or disabling symptoms. Consequently, patients are restricted in their daily activities which has an impact on an individual's quality of life. Until recently, the available evidence showed that only physical work load is a risk factor for incident knee OA. Obesity, occupational factors, physical sporting activity and hip dysplasia are risk factors for incident hip OA.[1, 2] Known prognostic factors for knee OA are serum hyaluronic acid levels, generalized OA and malalignment. For hip OA these are superolateral migration of the hip, decreased joint space width and atrophic bone response.[1] However, the evidence for the majority of these factors is nearly a decade old and is often not based on primary care patients with OA or those in an early symptomatic phase of the disease. These were the main reasons to write this thesis.

EPIDEMIOLOGY OF KNEE AND HIP OA IN THE NETHERLANDS

Primary care physicians or general practitioners (GPs) have high consultation rates for OA related symptoms and they see large variability in the evolution of the disease.[3] In the Netherlands, incidence and prevalence of disease as registered in primary care can be accurately estimated from GP registry systems using the International Classification of Primary Care (ICPC) codes registered for each episode of patient care. In 2011 in the Netherlands, the prevalence of knee OA was 2,8% in men and 4,4% in women. The incidence of knee OA was 0,3% in men and 0,4% in women. The prevalence of hip OA was 1,6% in men and 2,7% in women. The incidence of hip OA was 0,2% in men and 0,3% in women. [4] The incidence and prevalence will increase due to the current aging of the general population.[5]

In 2011, over €1,1 billion in medical costs were made due to all OA related symptoms in Netherlands, which was 1,2% of the total national health care costs.[4] Noteworthy is that approximately €50 million (only 5%) was attributable to primary care. In 2014 in The Netherlands, 21,557 individuals underwent knee replacement surgery due to knee OA (average age 68 years) and 23,479 individuals underwent hip replacement surgery due to hip OA (average age 69 years).[6] These numbers all underline the vastness of the disease and the growing urgency to look for better preventive strategies or interventions in patients with OA. If these strategies are available, the prevention of disease progression should already start in primary care.

CLINICAL OR RADIOGRAPHIC OA

There are various ways to classify knee OA or hip OA, the two main varieties being clinical and radiographic OA. According to the American College of Rheumatology (ACR), clinical OA can be diagnosed if a patient fulfills a specific set of symptoms. For knee OA this is: pain in the knee, and at least 3 of the following symptoms: 1) over 50 years of age; 2) less than 30 minutes of morning stiffness; 3) crepitus on active motion; 4) bony tenderness; 5) bony enlargement; 6) no palpable warmth or synovium.[7] Regarding hip OA this is: hip pain and all of the following criteria under 1) or 2): 1) hip internal rotation greater than or equal to 15^0, pain present on internal rotation of the hip, morning stiffness of the hip for less than or equal to 60 minutes and age greater than 50 years; 2) hip internal rotation less than 15^0 and hip flexion less than or equal to 115^0.[8] These criteria are interpreted or applied differently by various medical associations, in particular in primary care settings.[9-11] For instance, the Dutch College of General Practitioners regards knee OA likely when the patient has the following criteria: 1) age over 45 years; 2) knee pain during activities; 3) no or less than 30 minutes morning stiffness. The diagnosis is more likely with the following symptoms: reduced knee flexion or extension; crepitus; joint space tenderness; bony enlargement of the joint.[9] Many studies (and clinicians) also focus on radiographic features to diagnose or assess progression of knee or hip OA,[12] despite an established discordance between radiographic and symptomatic knee OA.[13] In summary, there are various types of OA diagnoses used in clinical or research settings.

PAIN IN PATIENTS WITH KNEE OR HIP OA

Pain is the primary symptom in individuals with OA.[14] But pain due to knee or hip OA is known to fluctuate, characterized by periods of severe joint pain and periods with less or even no pain in the affected joint.[15] Assessing the average pain severity in an individual with OA can be challenging, because it is so time dependent. Multiple assessments of pain over time therefore could provide a better indication of an individual's course of pain throughout the disease than one single pain assessment during the course of follow up. This course of pain, or pain trajectory, might be a more accurate representation of clinical disease severity or clinical disease progression. In this thesis, we define distinct pain trajectories in individuals with early symptomatic knee and hip OA. Furthermore, individuals with OA use various strategies to cope with their pain. These strategies play an essential part in pain experience.[15-18] In this thesis will also study the effect of numerous pain coping strategies in individuals with early symptomatic knee and hip OA.

THE CHECK STUDY

Many of the data in this thesis were obtained from participants enrolled in the Cohort Hip & Cohort Knee (CHECK) study. The CHECK study is a nationwide prospective, ten-year follow-up cohort of 1,002 participants with early symptomatic knee and/or hip OA, who were referred for to the study centres by their general practitioners if they were eligible for inclusion in the study. The inclusion period ran from October 2002 until September 2005. Inclusion criteria for the CHECK study were: pain and/or stiffness of the knee and/or hip; age between 45 and 65 years; and never before, or less than six months prior to entry of the study, consulted a physician for these symptoms. CHECK is funded by the Dutch Arthritis Foundation (*het Reumafonds*), led by a steering committee comprising 16 members with expertise in different fields of osteoarthritis. Participants were excluded from the CHECK study if they had any other known pathological condition that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plicasyndrome, Baker's cyst); co morbidity that did not allow physical evaluation and/or follow-up of at least ten years; malignancy in the past five years; and inability to understand the Dutch language.[19, 20]

PROGRESSION OF KNEE AND HIP OA AND AIM OF THIS THESIS

As mentioned, an increasing number of (older) patients are at risk for progression of knee and hip OA, leading to an increase in health care usage, pain medication consumption, an increase in disability and in many cases ultimately to total joint replacement surgery.[5] However, not all patients with lower joint OA undergo surgery, suggesting that OA progression is dependent on patient characteristics and/or varies between so called phenotypes of OA.[21] Also, there is variability between surgeons in when to offer surgery.[22] OA is a chronic disease and thus far cannot be cured, hence the management of OA patients primarily focusses on managing symptoms, sustain doing daily activities and, if possible, preventing progression. The ability to predict symptom progression in an early stage of disease therefore could guide the clinician and patient in choosing preventive activities for further pain progression. The general aim of this thesis was to determine patient- and disease characteristics that are associated with progression of early symptomatic knee and hip OA in a primary care setting.

OVERVIEW OF THE CONTENTS OF THIS THESIS

Chapter 2 contains a systematic review of all available evidence for prognostic factors for the clinical progression of knee OA. This is one of the first systematic reviews of its kind.

Chapter 3 reviews the evidence for prognostic factors for radiographic progression of knee OA. This is an update of a systematic review, previously published in 2007. However, the literature search of the original review had been performed up to December 2003 and many articles studying radiographic progression of knee OA have been published in the decade thereafter.

Chapter 4 presents patient- and disease characteristics associated with pain progression in individuals with early symptomatic knee OA during a 5-year follow-up period. *Latent Class Growth Analyses* were used to create pain trajectories obtained from multiple knee pain assessments over time. Data for this chapter were obtained from the CHECK study.

Chapter 5 describes patient- and disease characteristics associated with pain progression in individuals with early symptomatic hip OA during a 5-year follow-up period. *Latent Class Growth Analyses* were used to create pain trajectories obtained from multiple hip pain assessments over time. Data for this chapter were also obtained from the CHECK study.

Chapter 6 presents risk factors for rapid symptomatic progression of knee and hip OA, leading to undergoing total joint replacement surgery of the knee and/or hip within six years after first presentation of symptoms to a physician. Data for this chapter were obtained from the CHECK study.

Chapter 7 tests the hypothesis using *Structural Equation Modeling* that pain coping behavior plays a role in the causal pathway, i.e. acts as a mediating factor between pain severity and role limitations in patients with lower limb OA over a 5-year follow-up period. Substantial benefit could be achieved by focusing on pain coping behavior in the management of symptomatic knee or hip OA. Data for this chapter were obtained from the CHECK study.

Chapter 8 discusses the results, recommendations for future research and implications for clinical practice of this thesis.

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Chapter 2

Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies

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Arthritis Research & Therapy. 2015 Jun 8;17:152. Review.

ABSTRACT

Introduction

We performed a systematic review of prognostic factors for the progression of symptomatic knee osteoarthritis (OA), defined as increase in pain, decline in physical function or total joint replacement.

Method

We searched for available observational studies up to January 2015 in Medline and Embase according to a specified search strategy. Studies that fulfilled our initial inclusion criteria were assessed for methodological quality. Data were extracted and the results were pooled, or if necessary summarized according to a best evidence synthesis.

Results

Of 1,392 articles identified, 30 articles met the inclusion criteria and 38 determinants were investigated. Pooling was not possible due to large heterogeneity between studies. The best evidence synthesis showed strong evidence that age, ethnicity, body mass index (BMI), co morbidity count, magnetic resonance imaging (MRI)-detected infrapatellar synovitis, joint effusion and baseline OA severity (both radiographic and clinical) are associated with clinical knee OA progression. There was moderate evidence showing that education level, vitality, pain-coping subscale resting, MRI-detected medial femorotibial cartilage loss and general bone marrow lesions are associated with clinical knee OA progression. However, evidence for the majority of determinants was limited (including knee range of motion or markers) or conflicting (including age, gender and joint line tenderness).

Conclusion

Strong evidence was found for multiple prognostic factors for progression of clinical knee OA. A large variety in definitions of clinical knee OA (progression) remains, which makes it impossible to summarize the evidence through meta-analyses. More research on prognostic factors for knee OA is needed using symptom progression as outcome measure. The pathophysiology of radiographic factors and their relation with symptoms should be further explored.

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic diseases and is one of the leading causes of pain and disability worldwide. Amongst patients with OA, the incidence and prevalence of knee OA is the highest [1]. Consequently, many studies have been and are being performed to determine prognostic factors for knee OA. Previously, Belo et al. [2] published a systematic review determining all prognostic factors for knee OA. Their literature search was performed up to 2003 and none of the included articles had used clinical outcome measures to assess knee OA progression. An update of the review by Belo et al. [2] has recently been performed by the same authors as this current review, but again only focusses on radiographic progression of knee OA when a clear discordance between radiographic and symptomatic knee OA has formerly been established [3]. Also, symptomatic progression of knee OA is most relevant for the patient and the physician in clinical practice. Therefore, we have chosen to perform a systematic review of prognostic factors for the symptomatic (i.e. clinical) progression of knee OA. To our knowledge, this is the first systematic review of its kind.

MATERIALS AND METHODS

Literature search

Our search was performed in Medline and Embase up to January 2015. The key words used were: knee, osteoarthritis (or arthritis, or arthrosis, or degenerative joint disease), progression (or prognosis, or precipitate, or predictive), clinical (or symptomatic) and case-control (or cohort, or longitudinal, or follow-up). All abstracts and if necessary full texts of the identified references were reviewed for inclusion independently by two authors (ANB and JR or JNB). The following inclusion criteria were used: ≥85% of the patients used in the analyses for OA progression had clinical (i.e. American College of Rheumatology (ACR) or Osteoarthritis Research Society International (OARSI) criteria) or radiographic evidence of knee OA at baseline (equivalent to a Kellgren and Lawrence (K/L) score ≥2 at baseline); the study investigated determinants associated with the clinical progression of knee OA; a specific clinical outcome measure was appointed, i.e. pain, function or knee joint replacement; the study had either a case-control or cohort design with a minimal follow-up period of one year; the full text of the article was available; the study was written in English, Dutch, German or French. Studies that merely observed incidence of knee OA were excluded. Studies determining magnetic resonance imaging (MRI) features as prognostic factors were included as long as a clinical outcome measure was applied. Another reason for exclusion was if the study population had an underlying pathology (e.g. rheumatoid arthritis, bacterial infection) of the joint. Finally, inclusion of

articles was extended if a relevant article was detected when screening the references of included articles.

Methodological quality

The methodological quality assessment criteria were based on previously described criteria by Lievense et al. [4], Scholten-Peeters et al. [5], and Altman [6] (Table 1). All included articles were scored independently by two authors (ANB and JR or JNB) with a maximum score of 13 points. In case of disagreement, the authors arranged an appointment to achieve consensus. Noteworthy is that we only scored the articles based on the data that were published in the manuscripts, hence characteristics of the selected population under study that were published elsewhere were not incorporated in the quality score.

Table 1. Methodological quality assessment criteria

Quality criteria	*Score*
Study population	
A) Description of source population	1
B) Valid inclusion and exclusion criteria	1
C) Sufficient description of baseline characteristics	1
Follow-up	
D) Follow-up at least one year	1
E) Prospective or retrospective data collection	1
F) Loss to follow-up ≤ 20%	1
G) Information about loss to follow-up (selective for age, sex or severity)	1
Exposure	
H) Exposure assessment blinded for the outcome	1
I) Exposure measured identically in the studied population at baseline and follow-up	1
Outcome	
J) Outcome assessment blinded for exposure	1
K) Outcome measured identically in the studied population at baseline and follow-up	1
Analysis	
L) Measure of association or measures of variance given	1
M) Adjusted for age, sex and severity	1

Data extraction

Study population characteristics, observed risk factors, definitions of knee OA progression and measures of association or correlations, including odds ratios (OR), relative risks (RR), hazard ratios (HR) or regression coefficients and their 95% confidence intervals (CI) were extracted and are presented in this review.

Evidence synthesis

OR, RR or HR were pooled when clinical homogeneity in study population, measured determinants and assessed outcome was assumed (using *Review Manager* (*RevMan*). Version

5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In the absence of clinical homogeneity, a best evidence synthesis was used to summarize the data. The level of evidence was based on the updated guidelines by Furlan et al. [7] and was divided into the following levels: A) strong evidence, i.e. consistent (>75%) findings amongst multiple (≥2) high-quality studies; B) moderate evidence, i.e. findings in 1 high-quality study and consistent (>75%) findings in ≥2 low-quality studies; C) limited, evidence, i.e. findings in 1 high-quality study or consistent findings in ≥3 low-quality studies; and D) conflicting or inconclusive evidence, i.e. <75% of the studies reported consistent findings, or the results were only based on one study. Articles were scored as high quality when they had a quality score ≥9 (>65% of the maximal attainable score). Only statistically significant associations were considered as associated prognostic factors in the best evidence synthesis.

Sensitivity analysis

If we were forced to perform a best evidence synthesis, we conducted a sensitivity analysis to check whether differences in sample size (cut-off N=200) could have altered our conclusions. Additionally we checked whether large variances in follow-up (cut-off 24 months) duration could have led to different conclusions. Lastly, we checked whether our conclusions could have been influenced by differences in definitions for clinical OA (cOA) progression in the included articles, for instance knee joint replacement as opposed to pain progression or function decline.

RESULTS

Studies included

Of the 1,392 articles identified using our search strategy, 30 articles met the inclusion criteria [8-37]. Three reviewers scored a total of 390 items for the methodological quality assessment and agreed on 351 items (90%; κ 0.71). The 39 disagreements were resolved in a single consensus meeting.

Of the 30 articles 20 were of high quality and scored in the range of 9-13. Almost all studies had a prospective research design. Three definitions of OA were used for the inclusion of participants: 17 studies used the K/L criteria, 11 articles applied the ACR criteria and 2 studies used the OARSI. 4 of the studied populations contained more men than women, all other studies contained more women. A full overview of these results, including study sample sizes and follow-up durations, is presented in Table 2. Fifteen different definitions were used to define progression of cOA, including knee joint replacement, symptom severity on the Western Ontario and McMasters osteoarthritis index (WOMAC) scales for pain, function or stiffness and visual analogue scale (VAS) for pain. The definitions for cOA progression are presented in the corresponding tables which are discussed below.

Table 2. Study characteristics of the included studies (n=30)

Author (ref.) year	*Follow-up month*	*Definition OA for inclusion*	*Age, years*	*Women, %*	*No. of patients*	*Quality score*	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*
Amin [9] 2009	30	ACR criteria	69	42	265	13	1	1	1	1	1	1	1	1	1	1	1	1	1
Tanamas [34] 2010	24	K/L	63.2 ± 10.3	51	109	13	1	1	1	1	1	1	1	1	1	1	1	1	1
Cicuttini [13] 2004	24	K/L	63.1 ± 10.3	58	113	12	1	1	1	1	1	1	0	1	1	1	1	1	1
Hill [18] 2007	30	ACR criteria	66.7 ± 9.2	41	233	12	1	1	1	1	1	1	0	1	1	1	1	1	1
Holla [20] 2014	60	ACR criteria	56.0 ± 5.1	81.3	697	12	1	1	1	1	1	1	1	0	1	1	1	1	1
Tanamas [35] 2010	24	ACR criteria	63.2 ± 10.3	70	109	12	1	1	1	1	1	1	1	0	1	1	1	1	1
Berry [11] 2010	24	ACR criteria	63.7 ± 10.3	58	117	11	1	1	1	1	1	1	1	0	1	0	1	1	1
Henriksen [17] 2013	12	K/L	63	82	157	11	1	0	1	1	1	1	1	1	1	0	1	1	1
Yang [37] 2014	36	K/L	43% >65	58	1625	11	1	0	1	1	1	1	0	1	1	1	1	1	1
Alschuler [8] 2013	12	K/L	65.3 ± 9.0	59	797	10	1	1	1	1	1	0	0	0	1	1	1	1	1
Amin [10] 2008	30	ACR criteria	67 ± 9	43	265	10	1	1	1	1	1	1	1	0	1	0	1	1	1
Collins [14] 2014	72	K/L	62 ± 9	59	1753	10	1	0	1	1	1	0	0	1	1	1	1	1	1
Holla [19] 2010	24	ACR criteria	56.0 ± 5.1	80	832	10	1	1	1	1	1	1	1	0	1	0	1	1	1
Lapane [21] 2014	48	K/L	70	58	1846	10	1	0	1	1	1	0	0	1	1	1	1	1	1
Larsson [22] 2012	90	OARSI	50 (32-73)	18	74	10	1	1	1	1	1	1	0	0	1	1	1	1	1
Laslett [23] 2014	60	K/L	61	100	323	10	1	1	1	1	1	0	0	1	1	0	1	1	1
Muraki [24] 2012	40	K/L	68.7 ± 11.3	75	1313	10	1	1	1	1	1	1	0	0	1	1	1	1	1
Podsiadlo [27] 2014	72	ACR criteria	63.9	57	114	10	1	0	1	1	1	1	1	0	1	0	1	1	1
Riddle [29] 2012	48	OARSI	62	58	4670	10	1	1	1	1	1	1	1	0	1	0	1	1	1
Roemer [31] 2014	60	K/L	64.2 ± 8.4	58	398	10	1	1	1	1	1	0	0	1	1	1	1	1	0
Bruyere [12] 2005	45.6	ACR criteria	64.7 ± 7.0	70	139	9	1	0	1	1	1	1	1	0	1	0	1	1	0
Conaghan [15] 2010	36	K/L	67 ± 10	73	531	9	1	1	1	1	1	1	0	0	1	0	1	1	0
Sharma [33] 2003	36	K/L	68.6 ± 10.8	73	236	9	1	1	1	1	1	1	0	0	1	0	1	1	0
Eckstein [16] 2012	48	K/L	58	64	97	8	1	0	1	1	1	0	1	0	1	1	1	0	0
Oak [25] 2013	48	K/L	61.2 ± 9.1	53	942	8	1	0	1	1	1	0	0	0	1	0	1	1	1
Riddle [28] 2009	24	K/L	61.6 ± 9.3	60	778	8	1	1	1	1	1	0	0	0	1	0	1	1	0
Scher [32] 2008	36	K/L	51	63	73	8	1	0	0	1	1	1	0	0	1	1	1	1	0
Van Dijk [36] 2011	36	ACR criteria	65.9 ± 8.3	74	174	8	1	0	1	1	1	1	0	0	1	0	1	1	0
Pisters [26] 2012	60	ACR criteria	66.1 ± 8.5	74	216	7	1	0	1	1	1	0	0	0	1	0	1	1	0
Riddle [30] 2013	33	K/L	62.7 ± 8.6	63	1410	7	1	0	1	1	1	0	0	0	1	0	1	1	0

ACR: American College of Rheumatology, K/L: Kellgren and Lawrence score, OARSI: Osteoarthritis Research Society International atlas

Study results

38 different determinants were obtained. We grouped our findings into two pragmatically chosen categories: patient characteristics and disease characteristics. A full overview of the determinants and their potential associations to clinical knee OA progression are presented in Tables 3 and 4. Some authors reported statistically significant associations to OA progression, but used p-values as indications of association. We chose to only present OR, RR, HR or regression coefficients as measures of associations in our tables, but we have tabulated whether there was a significant association found in an article or not. All measures of association were eventually included in the evidence syntheses.

Patient characteristics

Patient characteristics are shown in Table 3. Two studies found significant positive associations between age and cOA progression [28, 29]. One study [24] found no association and three studies [14, 19, 20], two of which are from the same cohort, found a slight negative association.

Muraki et al. found no association between gender and cOA progression [24]. Collins et al. found significant associations for low moderate, high moderate and severe pain trajectories compared to no pain trajectory (not all data in Table 3) [14].

Holla et al. determined a significantly increased risk for symptom progression in non-Western participants compared to Western participants [19]. Collins et al. found similar results comparing Whites with non-Whites [14]. They also found increased risks for cOA progression for a lower education level, as did Riddle et al. [28].

Six authors performed analyses determining the association between body mass index (BMI) and cOA progression [14, 19, 20, 24, 28, 33]. Five out of six analyses found statistically significant positive associations [14, 19, 20, 24, 28]. Sharma et al. found no association [33].

Riddle and Stratford investigated the influence of body weight change, either a reduction or gain, and cOA progression [30]. They found that only at least 10% change in bodyweight significantly influences the risk of cOA progression. Henriksen et al. found no association for change in peak knee joint compressive forces and cOA progression [17]. A decrease in peak knee force (or unloader) was defined as decrease in body mass, unchanged walking speed, and a decreased knee extensor moment.

Five authors studied co morbidity as a determinant for cOA progression [14, 19, 20, 26, 36]. Holla et al. found no association for co morbidity count in one study [19], but found an association in another study within the same cohort [20]. Collins et al. [14], Pisters et al. [26] and Van Dijk et al. [36] found that an increase in co morbidity count led to a significant increase in cOA progression.

Table 3. Patient characteristics studied as determinants for clinical knee OA progression in the included studies

Determinant	Author,[ref.] year	Instrument of measurement	Definition of knee OA progression	OR / RR / HR / β (95% CI)	Association with OA prog ‡
Age	Muraki [24] 2012	Per 5 years increase	Incident knee pain at follow-up (baseline K/L ≥2)	OR 1.01 (0.95-1.07)	o
(N = 10043)	Holla [19] 2010	Continuous (years)	Progressing/remaining in poor WOMAC-PF quintiles	OR 0.97 (0.94-1.00)	-
	Holla [20] 2014	Continuous (years)	Poor vs Good outcome WOMAC-PF trajectory	OR 0.94 (0.88-1.00)	-
	Collins [14] 2014	Continuous (years)	Severe vs no pain WOMAC pain trajectory	OR 0.92 (0.89-0.96)	-
	Riddle [28] 2009	Continuous (years)	Knee joint surgery	OR 1.07 (1.02-1.11)	+
	Riddle [29] 2012	Continuous (years)	Knee joint surgery	RR 1.04 (1.01-1.23)	+
Female sex	Collins [14] 2014	Female vs male	Severe vs no pain WOMAC pain trajectory	OR 3.0 (1.5-6.2)	+
(N = 3066)	Muraki [24] 2012	Female vs male	Incident knee pain at follow-up (baseline K/L ≥2)	OR 1.32 (0.94-1.84)	o
Ethnicity	Collins [14] 2014	Non-White vs White	Severe vs no pain WOMAC pain trajectory	OR 3.3 (1.7-6.6)	+
(N = 2585)	Holla [19] 2010	Non-Western vs Western	Progressing/remaining in poor WOMAC-PF quintiles	OR 4.03 (1.06-15.4)	+
Education level	Collins [14] 2014	< college ≥ college	Severe vs no pain WOMAC pain trajectory	OR 5.1 (2.3-11.2)	+
(N = 2531)	Riddle [28] 2009	≤ high school graduate	Knee joint surgery	OR 2.40 (1.09-5.28)	+
Body mass index (BMI) (N = 4857)	Holla [19] 2010	Continuous	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.06 (1.02-1.11)	+
	Sharma [33] 2003	Per 5 unit increase	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.15 (0.89-1.46)	o
	Collins [14] 2014	Obese vs non-obese	Severe vs no pain WOMAC pain trajectory	OR 2.3 (1.2-4.4)	+
	Holla [20] 2014	Continuous	Moderate vs Good outcome WOMAC-PF trajectory	OR 1.12 (1.07-1.18)	+
	Muraki [24] 2012	Per 5 units increase	Incident knee pain at follow-up (baseline K/L ≥2)	OR 1.54 (1.90-1.82)	+
	Riddle [28] 2009	≤30 vs >30 kg/m^2	Knee joint surgery	OR 2.66 (1.20-5.92)	+

Table 3. Patient characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Instrument of measurement	Definition of knee OA progression	OR / RR / HR / β (95% CI)	Association with OA prog ‡
Bodyweight change	Riddle [30] 2013	≥-10% vs -4.9 to +4.9%	Increase self-reported limitations (WOMAC-PF)	β 4.07 (1.49-6.65)	-
(N = 1410)		-9.9 to -5% vs -4.9 to +4.9%	Increase in pain (WOMAC); similar results, not tabulated	β 0.01 (-1.87-1.89)	o
		+5 to +9.9% vs -4.9 to +4.9%		β 1.08 (-0.91-3.07)	o
		≥+10% vs -4.9 to +4.9%		β -5.36 (-8.74- -2.00)	+
Knee compression force	Henriksen [17] 2013	Change in peak knee joint compressive force	Change in KOOS-4	LSMD -2.4 (-6.8-1.9)	o
(N= 157)			Change in walking speed, m/s	LSMD -0.01 (-0.05-0.03)	o
Co morbidity count	Holla [19] 2010	≥ 3 vs none	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.53 (0.93-2.53)	o
(N = 3672)	Holla [20] 2014	≥ 3 vs < 3	Poor vs Good outcome WOMAC-PF trajectory	OR 3.28 (1.62-6.64)	+
	Collins [14] 2014	≥ 1 vs 0	Severe vs no pain WOMAC pain trajectory	OR 2.0 (1.0-3.9)	+
	Pisters [26] 2012	Per unit CIRS increase	Increase in self-reported limitations (WOMAC-PF)	β 3.69 (1.66-8.23)	+
	Van Dijk [36] 2011	Per unit CIRS increase	Increase in self-reported limitations (WOMAC-PF)	β -0.147 (not provided)	+
			Increase in performance-based limitations (TWT)	β 0.150 (not provided)	+
Mental health	Collins [14] 2014	CES-D ≥16 vs CES-D < 16	Severe vs no pain WOMAC pain trajectory	OR 8.8 (3.1-25.2)	+
(N = 6659)	Sharma [33] 2003	Per 5 points score	Progressing/remaining in poor WOMAC-PF quintiles	OR 0.58 (0.39-0.86)	-

Table 3. Patient characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Instrument of measurement	Definition of knee OA progression	OR / RR / HR / β (95% CI)	Association with OA prog ‡
	Riddle [29] 2012	Per unit SF-12 MCS score	Knee joint surgery	RR 1.07 (1.04-1.10)	+
Vitality	Holla [20] 2014	Per unit SF-36 HS score	Poor vs Good outcome WOMAC-PF trajectory	OR 0.96 (0.94-0.98)	-
(N = 871)	Van Dijk [36] 2011	Per unit SF-36 MOS score	Increase in self-reported limitations (WOMAC-PF)	β 0.157 (not provided)	-
			Increase in performance-based limitations (TWT)	β -0.229 (not provided)	-
Pain coping (N = 1048)	Alschuler [8] 2013	CSQ subscale praying or hoping	≥20% change in combined NRS and WOMAC-PF score	Not provided	+
		CSQ subscale catastrophizing	≥20% change in combined NRS or WOMAC-PF score	Not provided	+
	Holla [19] 2010	PCI subscale distraction	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.26 (0.98-1.62)	o
		PCI subscale worrying		OR 0.63 (0.66-0.73)	-
	Holla [20] 2014	PCI subscale resting	Poor vs Good outcome WOMAC-PF trajectory	OR 1.16 (1.02-1.31)	+
	Pisters [26] 2012	PCI subscale resting	Increase in self-reported limitations (WOMAC-PF)	β 23.3 (1.93-280.7)	+
			Increase in performance-based limitations (TWT)	β 3.13 (1.95-5.03)	+
Morning stiffness (N = 832)	Holla [19] 2010	<30 min, yes vs no	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.37 (0.99-1.88)	o
Knee injury (N = 1313)	Muraki [24] 2012	Previous knee injury	Incident knee pain at follow-up (baseline K/L ≥2)	OR 2.91 (1.26-6.82)	+
Knee surgery (N = 4670)	Riddle [29] 2012	History of knee surgery	Knee joint surgery	RR 2.04 (1.33-3.13)	+

Table 3. Patient characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Instrument of measurement	Definition of knee OA progression	OR / RR / HR / β (95% CI)	Association with OA prog ‡
Pain medication use	Riddle [29] 2012	For pain, aching or stiffness	Knee joint surgery	RR 1.64 (0.87-3.12)	o
(N= 6516)	Lapane [21] 2014	NSAID usage vs not	MICD of WOMAC pain	β -0.88 (-2.22-0.46)	o
			MICD of WOMAC-PF	β -4.27 (-8.84-0.31)	o
			MICD of WOMAC stiffness	β -0.72 (-1.56-0.12)	o
Bisphosphonate use	Laslett [23] 2014	Yes vs no	Decrease in WOMAC pain	β 0.69 (-0.54-1.92)	o
(N= 323)			Decrease in WOMAC function	β 0.05 (-3.85-3.95)	o
			Decrease in WOMAC stiffness	β -0.24 (-0.75-0.27)	o
			Decrease in NRS after 3 and 4 years, but not 5 years	β -1.15 (-1.94- -0.36)	+
Glucosamine / chondroitin use	Yang [37] 2014	Yes vs no	MICD of WOMAC pain	β 0.68 (-0.16-1.53)	o
			MICD of WOMAC-PF	β 1.28 (-1.23-3.79)	o
(N= 1625)			MICD of WOMAC stiffness	β 0.41 (0-0.82)	o
History of HRS	Riddle [29] 2012	Yes vs no	Knee joint surgery	RR 2.73 (0.93-8.07)	o
(N = 4670)					

OA: Osteoarthritis, CI: Confidence Interval, K/L: Kellgren and Lawrence score, WOMAC-PF: Physical Function scale of the Western Ontario and McMaster osteoarthritis index, KOOS-4: Knee injury and Osteoarthritis Outcome Score for pain, symptoms, function and quality of life, CIRS: Cumulative Illness Rating Scale, TWT: Timed Walking Test, CES-D: Center for Epidemiologic Studies Depression scale, SF-12 MCS: Short Form survey instrument for the Mental Component Summary, SF-36 HS / MOS: SF-36 Heatlth Survey / Medical Outcome Study, PCI: Pain Coping Inventory, CSQ: Coping Strategies Questionnaire, NRS: Numeric Rating Scale, NSAID: Non-Steroidal Anti-Inflammatory Drug, MICD: minimally important clinical Difference, HRS: Hip Replacement Surgery, OR: Odds Ratio, RR: Relative Risk, HR: Hazard Ratio, β: regression coefficient, LSMD: Least Squares Means Difference.
N = combined sample size
‡ Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable)

Collins et al. found that depression (CES-D ≥16) increased the risk for a unfavourable pain trajectory [14]. Sharma et al.studied the association between a mental health survey score and the progression of limitations in physical functioning [33]. A higher mental health score (i.e. better mental health) was associated with a decreased risk for a poor outcome on the WOMAC-PF scale. Riddle et al. found a reversed association per unit SF-12 MCS score and knee joint surgery [29].

Van Dijk et al. [36] and Holla et al. [20] reported a favorable effect of high vitality on cOA progression. Alschuler et al. found associations for the coping strategy catastrophizing and praying or hoping (not all data presented in Table 3) [8]. Holla et al. found no association for frequent use of the pain coping strategy distraction, but found a significant association for infrequent use of the pain coping strategy worrying [19]. Pisters et al. [26] and Holla et al. [20] found significant associations for cOA progression when applying the pain coping strategy resting (i.e. avoidance of activity).

Holla et al. found an association between morning stiffness of the knee joint (<30 minutes) and a poor outcome on the WOMAC-PF scale [19]. Muraki et al. found a significant association between previous knee injury and incident knee pain at follow-up in patients with K/L ≥2 at baseline [24].

Riddle et al. determined a significant association for participants with a history of knee surgery, but no associations for history of hip replacement surgery [29]. Riddle et al. [29] and Lapane et al. [21] found no associations for frequent medication use. Laslett et al. found an association between bisphosphonate use and decrease in NRS after 3 and 4 years, but not after 5 years, however medication compliance did drop remarkably in this study by the fifth year [23]. They found no association for WOMAC scores. Yang et al. found no clinically significant differences between users and non-users of glucosamine and/or chondroitin in WOMAC pain, stiffness or function [37].

Disease characteristic

Disease characteristics are shown in Table 4. Multiple studies were performed determining the associations for baseline radiographic or clinical severity of OA [8, 12, 14, 20, 25, 26, 29, 33]. Bruyere et al. found an increased risk for knee joint surgery in patients with an increased rate of joint space narrowing per 3 years [12]. Collins et al. [14], Riddle et al. [29] and Oak et al. [25] found significant associations for both baseline radiographic severity and baseline pain. Alschuler et al. found associations for baseline pain and function scores [8]. Pisters et al. found a significant association between baseline pain intensity and self-reported limitations on the WOMAC-PF scale [26]. Sharma et al. determined a significantly positive association for baseline VAS pain score [33]. Holla et al. found significant associations for baseline osteophytosis and NRS for pain [20].

Table 4. Disease characteristics studied as determinants for clinical knee OA progression in the included studies

Determinant	Author,[ref.] year	Analysis of determinant	Definition of knee OA progression	OR / RR / HR/ β (95% CI)	Association with OA prog ‡
Severity					
Radiographic	Bruyere [12] 2005	JSN ≥0.5 mm/3 yrs	Knee joint surgery	RR 4.61 (1.65-12.8)	+
(N = 8201)	Riddle [29] 2012	Per grade (0-4 grade scale)	Knee joint surgery	RR 2.09 (1.63-2.69)	+
	Collins [14] 2014	K/L 3 vs K/L 2 §	Severe vs no pain WOMAC pain trajectory	OR 4.3 (2.1-8.6)	+
	Holla [20] 2014	Osteophytosis	Poor vs Good outcome WOMAC-PF trajectory	OR 5.68 (2.57-12.55)	+
	Oak [25] 2013	Baseline JSW (mm)	Decrease KOOS pain (KOOS symptom and quality of life show similar regression coefficients)	β 1.94 (1.19-2.69)	+
		JSN over 4 years (mm)		β 2.31 (1.18-3.44)	+
Clinical	Alschuler [8] 2013	NRS of past 7 days §	≥20% change in combined NRS and WOMAC-PF score	Not provided	+
(N = 7558)		WOMAC-PF §		Not provided	+
	Holla [20] 2014	NRS for knee pain §	Poor vs Good outcome WOMAC-PF trajectory	OR 1.81 (1.51-2.16)	+
	Oak [25] 2013	Baseline KOOS value	Decrease KOOS pain (KOOS symptom and quality of life show similar regression coefficients)	β 0.49 (0.43-0.59)	+
	Pisters [26] 2012	Per cm increase VAS §	Increase in self-reported limitations (WOMAC-PF)	β 5.99 (2.90-12.4)	+
	Sharma [33] 2003	Per 20mm VAS increase	Progressing/remaining in poor WOMAC-PF quintiles	OR 1.48 (1.12-1.95)	+
	Riddle [29] 2012	NRS of past 30 days §	Knee joint surgery	RR 1.12 (1.02-1.22)	+
Painful knee flexion	Riddle [29] 2012	Yes vs no	Knee joint surgery	RR 1.58 (1.04-2.39)	+
(N = 4670)					
Joint line tenderness	Holla [20] 2014	Yes vs no	Poor vs Good outcome WOMAC-PF trajectory	OR 2.63 (1.38-5.02)	+
(N = 5367)	Riddle [29] 2012	Yes vs no	Knee joint surgery	RR 0.71 (0.43-1.18)	o
Flexion contracture	Riddle [29] 2012	Knee flexion contracture (°)	Knee joint surgery	RR 1.06 (1.02-1.11)	+
(N = 4670)					

Table 4. Disease characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Analysis of determinant	Definition of knee OA progression	OR / RR / HR/ β (95% CI)	Association with OA prog ‡
Knee ROM	Holla [20] 2014	Active ROM in degrees	Poos vs Good outcome WOMAC-PF trajectory	OR 0.96 (0.93-1.00)	-
(N = 913)	Pisters [26] 2012	Mean extension	Increase in performance-based limitations (TWT)	β 0.92 (0.86-0.98)	-
Hand grip strength (muscle strength)	Muraki [24] 2012	Per 1 kg strength increase	Incident knee pain at follow-up (baseline K/L ≥2)	OR 1.00 (0.98-1.02)	o
(N = 1313)					
Quadriceps strength	Amin [9] 2009	Low vs middle	Increase in knee specific VAS pain score	Not provided	o
(N = 5151)		vs high strength	Increase in self-reported limitations (WOMAC-PF)	Not provided	o
	Pisters [26] 2012	Continuous in Newton/kg	Increase in self-reported limitations (WOMAC-PF)	β 0.11 (0.01-1.36)	o
			Increase in performance-based limitations (TWT)	β 0.60 (0.37-1.03)	o
	Riddle [29] 2012	Normalized to bodyweight	Knee joint surgery	RR 0.79 (0.65-0.96)	-
Bone marrow lesions/ edema (BMLs / BME)	Roemer [31] 2014	≥2 subregions vs 0-1	Knee joint surgery	OR 4.00 (1.75-9.16)	+
		Grade ≥1 vs grade 0		OR 4.00 (0.85-18.84)	o
	Scher [32] 2008	Global BME vs none	Knee joint surgery	OR 15.2 (2.38-97.1)	+
(N = 580)	Tanamas [34] 2010	BMLs, present vs absent	Knee joint surgery	OR 1.57 (1.04-2.35)	+
		Medial BMLs vs absent	Knee joint surgery	OR 1.78 (1.16-2.74)	+
		Lateral BMLs vs absent	Knee joint surgery	OR 0.82 (0.43-1.54)	o
Subchondral bone cysts (MRI)	Tanamas [35] 2010	Medial, per grade of severity	Knee joint surgery	OR 1.99 (1.01-3.90)	+
		Lateral, per grade of severity	Knee joint surgery	OR 0.96 (0.48-1.94)	o
(N = 109)					

Table 4. Disease characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Analysis of determinant	Definition of knee OA progression	OR / RR / HR/ β (95% CI)	Association with OA prog ‡
Cartilage loss (MRI)	Cicuttini [13] 2004	Rate 3-8% per annum	Knee joint surgery	OR 2.3 (0.4-12.2)	o
(N = 681)		Rate >8% per annum		OR 7.1 (1.4-36.5)	+
	Eckstein [16] 2012	Change in cMFTC.ThC	Knee joint surgery	Not provided	+
		Change in MFTC.ThC		Not provided	+
		Change in LFTC.ThC		Not provided	o
	Roemer [31] 2014*	Grade 3 vs <3 (whole knee)		OR 4.00 (2.23-7.18)	+
		Grade 3 vs 0 (MFTC)	Knee joint surgery	OR 3.01 (1.52-5.95)	+
		Grade 3 vs 0 (LFTC)		OR 1.69 (0.94-3.02)	o
	Scher [32] 2008	≥50% vs <50% loss	Knee joint surgery	OR 2.06 (0.74-5.70)	o
Meniscal extrusion (MRI)	Roemer [31] 2014	≥5 mm vs <5 mm (medial)	Knee joint surgery	OR 1.00 (0.60-1.67)	o
		≥5 mm vs <5 mm (lateral)		OR 1.42 (0.54-3.75)	o
(N= 398)					
Meniscal damage (MRI)	Roemer [31] 2014	Grade 6-8 vs 0-1(medial)	Knee joint surgery	OR 1.84 (1.13-2.99)	o
(N= 398)		Grade 6-8 vs 0-1 (lateral)		OR 1.10 (0.68-1.77)	o
Anterior cruciate ligament tear	Amin [10] 2008	Complete tear on MRI	Increase in knee specific VAS pain score	Not provided	o
		Complete tear on MRI	Increase in self-reported limitations (WOMAC-PF)	Not provided	o
(N = 265)					
Synovitis	Roemer [31] 2014	Infrapatellar fat pad on MRI	Knee joint surgery	OR 2.17 (1.33-3.56)	+
(N = 764)	Hill [18] 2007	Infrapatellar fat pad on MRI	Increase in knee specific VAS pain score	β 4.89 (0.42-9.36)	+
		Intercondylar on MRI		β 5.74 (0.34-11.14)	+

Table 4. Disease characteristics studied as determinants for clinical knee OA progression in the included studies (*continued*)

Determinant	Author,[ref.] year	Analysis of determinant	Definition of knee OA progression	OR / RR / HR/ β (95% CI)	Association with OA prog ‡
		Suprapatellar on MRI		β 3.35 (-0.34-7.05)	o
	Conaghan [15] 2010	Present on US	Knee joint surgery	HR 1.54 (0.95-2.50)	o
Joint effusion	Conaghan [15] 2010	Present on US	Knee joint surgery	HR 3.06 (2.00-4.69)	+
(N = 5979)	Riddle [28] 2009	Positive bulge sign	Knee joint surgery	OR 2.53 (1.13-5.56)	+
	Riddle [29] 2012	Positive bulge sign	Knee joint surgery	RR 1.58 (1.04-2.40)	+
	Roemer [31] 2014	Present on MRI (grade 1-3)	Knee joint surgery	OR 4.75 (2.55-8.85)	+
Trabecular bone texture	Podsiadlo [27] 2014	FD_{mean} on FSA, medial	Knee joint surgery	OR 0.23 (0.06-0.82)	+
(N=114)		FD_{mean} on FSA, lateral		OR 0.33 (0.09-1.22)	o
C2C (serum)	Berry [11] 2009	High level vs low	Knee joint surgery	OR 1.01 (0.94-1.08)	o
(N = 117)					
COMP (serum)	Berry [11] 2010	High level vs low	Knee joint surgery	OR 0.77 (0.15-3.81)	o
(N = 117)					
PIIANP (serum)	Berry [11] 2010	Natural log baseline levels	Knee joint surgery	OR 0.28 (0.10-0.93)	-
(N = 117)					
ARGS (synovial) (N = 74)	Larsson [22] 2012	Baseline level ARGS > follow-up level ARGS	≥10 units progression KOOS Pain	OR 3.66 (1.01-13.2)	+
			≥10 units progression KOOS Function of daily living	OR 1.11 (0.26-4.80)	o

JSN: Joint Space Narrowing, JSW: Joint Space Width, VAS: Visual Analogue Scale, ROM: range of motion, (c)MFTC.ThC: (central) Medial Femorotibial Compartment Cartilage Thickness (in mm), LFTC: Lateral FTC, US: ultrasonography, FD_{mean}: mean Fractal Dimension, FSA: Fractal Signal Analysis, C2C: Collagen type-II Cleavage, COMP: Cartilage Oligomeric Matrix Protein, PIIANP: N-Propeptide of type IIA collagen, ARGS: Aggrecan neoepitope amino acid Sequence, KOOS: Knee injury and Osteoarthritis Outcome Score. See Table 3 for other abbreviations.

N = combined sample size. § Assessed at baseline, * Similar results found when measuring compartment cartilage thickness

‡ Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable)

Riddle et al. found that a painful knee flexion and a flexion contracture were significantly associated with future knee joint surgery, but knee joint line tenderness was not associated [29]. Holla et al. did find an association for bony tenderness [20]. Pisters et al. [26] and Holla et al. [20] reported that a larger baseline knee range of motion (ROM) was significantly associated with less knee cOA progression. Muraki et al. studied hand grip strength in participants with knee cOA progression, as an indication of general muscle strength, and found no significant associations [24].

Three authors studied the association between quadriceps strength and cOA progression [9, 26, 29]. Only one study found an association, describing significantly lower mean baseline quadriceps strength in patients with cOA progression [29].

Scher et al. found a significant association for MRI-detected global bone marrow edema [32]. Roemer et al. found an association in knees with more than two subregions with bone marrow lesions (BMLs), but no association when scoring BMLs [31]. Tanamas et al. investigated the association for BMLs in the tibiofemoral joint [34]. They found significant associations for the total presence of BMLs and for medial BMLs. The association for lateral BMLs was not statistically significant. The authors also found an association for MRI detected subchondral bone cysts in the medial tibiofemoral compartment, but not for the lateral compartment [35].

MRI-detected cartilage loss and the risk of cOA progression was studied by four authors [13, 16, 31, 32]. Cicuttini et al. reported a significant association bewteen cartilage loss rate >8% per annum and knee joint surgery [13]. Eckstein et al. found significant positive associations for increased cartilage thickness loss in the medial tibiofemoral compartment [16]. They found no significant association in the lateral compartment. Similar significant associations were found in their analyses when calculating the percentage denuded area of subchondral bone in the medial compartment (data not presented in this review). Roemer et al. found elevated risks in knees that exhibited ≥2 compartments with severe cartilage loss on MRI [31]. Scher et al. found no significant associations [32].

Roemer et al. found an association with knee joint surgery in knees with MRI detected medial meniscus maceration, but not for lateral maceration or meniscal extrusion [31]. Amin et al. found no significant association for MRI-detected anterior cruciate ligament (ACL) tear [10].

Hill et al. found significant correlations for the presence of MRI-detected infrapatellar and intercondylar synovitis at baseline [18]. The correlation for suprapatellar synovitis was non-significant. Conaghan et al. found no association for synovitis detected by ultrasonography (US) [15]. They did report a significant association for US detected joint effusion [15]. Riddle et al. also reported significant associations for clinically detected joint effusion (positive bulge sign) [28, 29]. Roemer et al. found associations for both MRI-detected effusion and synovitis [31].

Podsiadlo et al. found that an increase in overall roughness of medial tibial trabecular bone texture, or fractal dimension (FD_{mean}), detected on Fractal Signal Analysis led to a risk reduction for knee joint surgery [27]. All other FD regions of interest showed non-significant associations (data not presented in Table 4).

Berry et al. studied the associations between three serum markers and cOA progression [11]. They found no association for serum collagen type-II cleavage (C2C) or for serum levels of cartilage oligometric matrix protein (COMP). They did find that serum N-propeptide of type II collagen (PIIANP) was associated with a significantly reduced risk for knee joint replacement.

Larsson et al. found an association between synovial fluid aggrecan neoepitope amino acid sequence (ARGS) levels and pain progression, but not between ARGS levels and function of daily living [22].

Best evidence synthesis

Pooling was not possible due to heterogeneity, hence we were forced to apply a best evidence synthesis (Table 5), which demonstrated strong evidence that age, ethnicity, BMI, co morbidity count, MRI-detected infrapatellar synovitis, joint effusion and baseline OA severity (both radiographic and clinical) are associated with the progression of clinical knee OA. There was moderate evidence showing that education level, vitality, pain-coping subscale resting, MRI-detected medial femorotibial cartilage loss and general BMLs are associated with knee cOA progression.

There is limited evidence that pain coping subscales worrying, hoping and catastrophizing, knee injury, knee surgery, bisphosphonate usage, painful knee flexion, flexion contracture, knee ROM, medial BMLs, medial subchondral bone cysts and medial trabecular bone texture are associated with the cOA progression. There is also limited evidence that there is no association between clinical knee OA progression and knee compression force, pain-coping subscale distraction, morning stiffness, pain medication usage, glucosamine or chondroitin usage, hip replacement surgery, joint line tenderness, muscle strength, lateral BMLs, lateral subchondral bone cysts, lateral femorotibial cartilage loss, meniscal extrusion or damage, anterior cruciate ligament tear, synovitis other than infrapatellar, lateral trabecular bone texture, serum markers C2C and COMP.

Conflicting evidence was found for the associations between clinical knee OA progression and gender, mental health, bisphosphonate usage, joint line tenderness, quadriceps strength, MRI-detected whole knee cartilage loss and synovial marker ARGS. There was inconclusive evidence for the associations found between cOA progression and bodyweight change.

Table 5. Results from the best evidence synthesis: associations with clinical knee OA progression

Determinants	Level of evidence
Age, ethnicity, BMI, co morbidity count, MRI detected infrapatellar synovitis, joint effusion and baseline OA severity (radiographic and clinical)	Strong evidence for association
Education level, vitality, pain coping subscale resting, MRI detected medial femorotibial cartilage loss and general BMLs	Moderate evidence for association
Pain coping subscales worrying, hoping and catastrophizing, knee injury, knee surgery, bisphosphonate usage, painful knee flexion, flexion contracture, knee ROM, medial BMLs, medial subchondral bone cysts and medial trabecular bone texture	Limited evidence for association
Knee compression force, pain coping subscale distraction, morning stiffness, pain medication usage, glucosamine or chondroitin usage, hip replacement surgery, joint line tenderness, muscle strength, lateral BMLs, lateral subchondral bone cysts, lateral femorotibial cartilage loss, meniscal extrusion or damage, anterior cruciate ligament tear, intercondylar or suprapatellar synovitis on MRI, synovitis on US, lateral trabecular bone texture serum markers C2C and COMP	Limited evidence for no association
Gender, mental health, bisphosphonate usage, joint line tenderness, quadriceps strength, MRI detected whole knee cartilage loss and synovial marker ARGS	Conflicting evidence
Bodyweight change	Inconclusive evidence

Sensitivity analysis

No conclusions were influenced or altered by differences in sample size or follow-up duration. When analysing the definitions for cOA progression, we found irregularity in the strong evidence found for age as a risk factor. Five out of six studies found significant associations with clinical knee OA progression. Three of these five associations were negative associations (i.e. lower baseline age resulted in higher risk for progression); the remaining two associations were positive associations. However, these two positive associations defined cOA progression as knee joint surgery, where the other three negative associations defined cOA progression by pain or function scores. By splitting these definitions of cOA progression, the evidence for age would remain strong, but lower age would be labeled as a risk factor for more severe symptom progression and higher age would be labeled as a risk factor for knee joint surgery due to OA.

DISCUSSION

There is strong evidence that age, ethnicity, BMI, co morbidity count, MRI-detected infrapatellar synovitis, joint effusion and both radiographic and clinical baseline OA severity are predictive for clinical knee OA progression. However, for the majority of studied determinants in our review the evidence is limited, conflicting or inconclusive.

More precise estimates of associations could have been given if pooling was possible, but this was not feasible due to large variation in criteria for defining disease (progression). Six different criteria were used for inclusion of OA (see Table 2) and nine definitions were applied for cOA progression (see Tables 3 and 4). Furthermore, variables under study were measured differently (continuous, dichotomous, or categorical with varying cut-off points).

Age has previously been recognized as a risk factor for progression on symptomatic knee OA by Van Dijk et al. [38] In this 2006 review determining prognostic factors for functional status in knee OA, the authors presented similar evidence on age as a risk factor. Oddly enough, as presented in our sensitivity analysis, a lower baseline age is associated with an increased risk of symptom progression, whereas a higher baseline age results in an increased risk for undergoing knee joint surgery due to knee OA. This inverse association is not properly understood yet and should be explored in future studies.

Overweight has previously been recognized as a risk factor for incident knee OA [39, 40]. The evidence for an association between overweight and progression of radiographic knee OA remains conflicting [2, 41], but this review shows strong evidence for the association between BMI and symptom progression which is in line earlier finding by Van Dijk et al. [38].

An association between knee pain and joint effusion has been found before in cross-sectional analysis, but the exact pathophysiology needs to be better understood [42]. Previous reviewers found similar results for MRI-detected effusion or synovitis, but these results are based on cross-sectional studies or on the same longitudinal studies included in this review [43]. Our results show that joint effusion, which is relatively easy and uncostly to ascertain in primary care by physical examination or US, seems to be a strong predictor of symptom progression and it underlines the importance of proper physical examination.

High baseline OA severity scores were associated with clinical knee OA progression. It seems logical that subjects with initial severe symptoms are prone to symptom progression, but there is a discrepancy in the evidence for radiographic OA severity and symptom severity [44]. In this 2009 review of the (mainly cross-sectional) literature the authors however state that many studies have not used X-ray views of all three compartments of the knee, which could have contributed to an underestimation of the association between radiographic knee OA and clinical symptoms [44].

We found notable overlap with the evidence for clinical hip OA progression in two large reviews, defining clinical hip OA progression as total hip arthroplasty (THA) [4, 45]. The authors presented conflicting evidence regarding age and gender, but consistent evidence for associations between both radiographic and clinical baseline severity with THA. Moreover, there was limited evidence for an association between BMI and no association between serum COMP with THA.

A point of discussion could be our choice of outcome measure inclusion, i.e. including and comparing pain progression, physical function decline and knee joint surgery. Although these measures are not the same, there exists a strong correlation between these outcomes. Moreover, presenting these results together provides a clear overview of all existing evidence regarding symptomatic knee OA progression. One observation that strongly becomes apparent is the lack of studies investigating risk factors for pain progression in knee OA, when pain has shown to be the number one complaint in patients with (knee) OA [1]. On the other hand, pain is an important indication for undergoing knee joint surgery, which will be further addressed below.

Our study may have limitations. Firstly, limitations to reviewing observational studies on disease progression has been addressed, stating that unlike randomized trials, observational studies of pre-existing disease are subject to various biases that may account for discrepancies found between risk factors for incidence and progression [46]. The hypothesis is that risk factors may exist for progressive knee OA, but that flaws in study design and the measure of disease progression may prevent true detection of risk factors [46]. Secondly, some outcome measures were only assessed once at follow-up, which consequently could have led to an incorrect assessment of true clinical OA progression. Pain and physical limitations due to OA fluctuate over time, hence multiple outcome measure assessments during follow-up would give a better depiction of disease progression [47]. Lastly, using knee joint surgery as an outcome measure for clinical knee OA progression might lead to discussion, considering orthopaedic surgeons would generally not operate on a knee that shows no sign of (progressed) radiographic OA. However, studies have shown that a key indicator for undergoing knee joint surgery in patients with knee OA is pain or disability [29, 48].

When comparing our results to the results found in the review by Belo [2], substantial differences in prognostic factors for cOA progression can be detected compared to risk factors for radiographic progression of knee OA. Belo et al. for instance, found strong evidence for no association for gender and quadriceps strength, when we found conflicting evidence for both determinants. Moreover, there are differences in the number of investigated possible risk factors. For example, Belo et al. found strong evidence for the association of serum levels of hyaluronic acid with radiographic knee OA progression, when no articles investigating hyaluronic acid were included in this current review. The abovementioned underlines the importance to distinguish (possible) risk factors

for clinical knee OA progression from (possible) risk factors for radiographic knee OA progression.

More research is needed on the true relationship between prognostic factors for symptomatic knee OA progression, especially regarding factors where conflicting, limited or inconclusive evidence was presented. It would be very convenient if a physician was enabled to closely monitor patients with symptomatic knee OA whom are at high risk for rapid or severe symptom progression. Moreover, potential risk factors which can be modified at an early stage of the disease, i.e. pain coping strategies or quadriceps strength could prove to have substantial benefit in the treatment of patients with knee OA. In addition, the aetiology and pathophysiology of radiographic OA features, joint effusion, BMLs and subchondral cysts in knee OA and their relation with clinical symptoms longitudinally should be further explored.

CONCLUSIONS

In conclusion, we have summarized the available evidence of prognostic factors for clinical knee OA progression. A large variety in definitions of clinical knee OA (progression) remains, which unfortunately makes it impossible to properly summarize the evidence through meta-analyses. More research on prognostic factors for knee OA is needed using symptom progression as an outcome measure. There are remarkably few studies that study pain progression in patients with knee OA.

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Chapter 3

What Are the Prognostic Factors for Radiographic progression of Knee Osteoarthritis? A Meta-analysis

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ABSTRACT

Background A previous systematic review on prognostic factors for knee osteoarthritis (OA) progression showed associations for generalized OA and hyaluronic acid levels. Knee pain, radiographic severity, sex, quadriceps strength, knee injury, and regular sport activities were not associated. It has been a decade since the literature search of that review and many studies have been performed since then investigating prognostic factors for radiographic knee OA progression.

Questions/purposes The purpose of this study is to provide an updated systematic review of available evidence regarding prognostic factors for radiographic knee OA progression.

Methods We searched for observational studies in Medline and Embase. Key words were: knee, osteoarthritis (or arthritis, or arthrosis, or degenerative joint disease), progression (or prognosis, or precipitate, or predictive), and case-control (or cohort, or longitudinal, or follow-up). Studies fulfilling the inclusion criteria were assessed for methodologic quality according to established criteria for reviews on prognostic factors in musculoskeletal disorders. Data were extracted and results were pooled if possible or summarized according to a best-evidence synthesis. A total of 1912 additional articles were identified; 43 met our inclusion criteria. The previous review contained 36 articles, thus providing a new total of 79 articles. Seventy-two of the included articles were scored high quality, the remaining seven were low quality.

Results The pooled odds ratio (OR) of two determinants showed associations with knee OA progression: baseline knee pain (OR, 2.38 [95% CI, 1.74-3.27) and Heberden nodes (OR, 2.66 [95% CI, 1.46-8.84]). Our best-evidence synthesis showed strong evidence that varus alignment, serum hyaluronic acid, and tumor necrosis factor-α are associated with knee OA progression. There is strong evidence that sex, former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not associated with knee OA progression. Evidence for the majority of determined associations, however, was limited, conflicting, or inconclusive.

Conclusions Baseline knee pain, presence of Heberden nodes, varus alignment, and high levels of serum markers hyaluronic acid and tumor necrosis factor-α predict knee OA progression. Sex, knee injury, and quadriceps strength, among others, did not predict knee OA progression. Large variation remains in definitions of knee OA and knee OA progression. Clinical studies should use more consistent definitions of these factors to facilitate data pooling by future meta-analyses.

INTRODUCTION

The prevalence of osteoarthritis of the knee (knee OA) is increasing worldwide and this burden will continue to increase owing to aging of the general population[95]. Consequent to an increase in incidence is the rise in the number of patients with knee OA who are prone to further deterioration of the knee. It therefore is important to better understand, control, and attempt to prevent further progression of disease in patients with knee OA.

In 2007, Belo et al.[4] published the first systematic review performed on prognostic factors for the progression of knee OA. They found that generalized OA and hyaluronic acid levels were associated with progression of knee OA. Knee pain, baseline radiographic severity, sex, quadriceps strength, knee injury, and regular sport activities were not associated. For the remaining factors the evidence was limited or conflicting. Their literature search had been performed up to December 2003; however, many articles studying radiographic progression of knee OA have been published in the decade since that review. Therefore, we performed an update of the systematic review of observational studies by Belo et al.[4] to determine the currently available evidence on prognostic factors for radiographic progression of knee OA.

SEARCH STRATEGY AND CRITERIA

Literature Search

In the review by Belo et al.[4], the search of the literature had been performed in Medline and Embase for all available observational studies up to December 2003. We searched in Medline and Embase from December 2003 up to February 2013. Key words were: knee, osteoarthritis (or arthritis, or arthrosis, or degenerative joint disease), progression (or prognosis, or precipitate, or predictive), and case-control (or cohort, or longitudinal, or followup). Articles were reviewed for inclusion independently by two authors (ANB and JNB or JR). The following inclusion criteria were used: 85% or more of participants in the analyses for OA progression had radiographic evidence of knee OA at baseline; the study investigated determinants associated with radiographic knee OA progression; radiographic progression was the outcome measure; the study had a case-control or cohort design with a minimal 1 year followup; full text of the article was available; the study was in English, Dutch, German, or French. Studies that observed the incidence of knee OA were excluded. A detailed description of our search strategy is available online (Appendix 1. Supplemental materials are available with the online version of CORR®). All articles were reviewed for inclusion independently by two authors (ANB and JNB or

JR). Studies that used MRI features to define OA progression were excluded. However, studies determining MRI features as prognostic factors were included.

Methodologic Quality

The same methodologic quality assessment criteria as in the original review by Belo et al.[4] were used for this review (Table 1). These criteria were based on established criteria used in systematic reviews of prognostic factors for patients with musculoskeletal disorders and were described by Lievense et al.[49], Scholten-Peeters et al. [69], and Altman[1]. The criteria cover the internal validity and the informativeness of the study. All included articles were scored independently by two authors (ANB and JNB or JR). Cohen's kappa coefficient (κ) was calculated to indicate the interrater agreement.

Table 1. Methodologic quality assessment criteria

Study population
Description of source population
Valid inclusion criteria
Sufficient description of inclusion criteria
Followup
Followup at least 1 year
Prospective or retrospective data collection
Loss to followup ≤ 20%
Information about loss to followup (selective for age, sex, or severity)
Exposure
Exposure assessment blinded for the outcome
Exposure measured identically in the studied population at baseline and followup
Outcome
Outcome assessment blinded for exposure
Outcome measured identically in the studied population at baseline and followup
Analysis
Measure of association or measures of variance given
Adjusted for age, sex, and severity

Data Extraction

Study population characteristics, observed risk factors, definitions of knee OA progression, and measures of association were extracted.

Evidence Synthesis

Odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) were pooled when there was consistency in definition of study population, measured determinants, and assessed outcome (using Review Manager [RevMan], Version 5.3; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We tested for heterogeneity with the Chi-square and I-square tests. If heterogeneity was absent, a fixed effects

model was applied to calculate pooled OR through the Mantel Haenszel test. In the absence of consistency among definitions for OA, a best-evidence synthesis was used to summarize the data. The level of evidence was based on the updated guidelines by Furlan et al.[34] and was divided into the following levels: (A) strong, ie, consistent (> 75%) findings among two or more high-quality studies; (B) moderate, ie, findings in one high-quality study and consistent findings in two or more low-quality studies; (C) limited, ie, findings in one high-quality study or consistent findings in three or more low-quality studies; and (D) conflicting or inconclusive evidence, ie, less than 75% of the studies reported consistent findings, or the results were based on only one study. High quality was defined as a quality score of 9 or greater (> 65% of the maximal attainable score). When performing the best evidence synthesis, we only differentiated between high- and low-quality studies.

Studies Included

Of the 1912 articles identified using our search strategy, 43 met the inclusion criteria[2, 5, 7, 11, 13, 19, 20, 25-28, 30, 35, 38-44, 46, 48, 50-52, 55, 57-62, 64-66, 73, 74, 78, 85, 88, 91-93]. Belo et al. reviewed 36 articles[3, 8, 12, 14-16, 18, 21-24, 29, 31, 32, 37, 45, 47, 53, 54, 56, 63, 70-72, 75-77, 79-83, 87, 89, 94, 96]; therefore the total number of included studies was 79, studying 59 different determinants for the progression of knee OA (Table 2). Three reviewers scored 559 items for the methodologic quality assessment of the 43 newly included articles and agreed on 519 items (93%; κ 0.79). The 53 disagreements were resolved in a single consensus meeting. Seventy-two of the 79 included articles were scored as high quality (score, 9-13), and only one article had the maximum attainable score. The remaining seven were scored as low quality, however no article was scored less than 6. Six different criteria were used for the inclusion of participants with OA and 13 definitions were applied to define radiographic OA progression. Furthermore, there were differences in how the determinants under study were measured, ie, continuous, dichotomous, or categorical with varying cut-off points.

Study Results

Because of the large number of studied determinants (n = 59), we pragmatically grouped our findings into five different categories: systemic factors (Table 3); disease characteristics (Table 4); intrinsic factors (Table 5); extrinsic factors (Table 6); and markers (Table 7). Some authors presented statistically significant associations to OA progression, but used p values or regression coefficients as measures of association[3, 5, 12, 14, 20, 21, 23, 31, 37, 41, 42, 44, 45, 47, 48, 52, 62, 63, 72, 74, 77, 80, 82, 85, 87, 93]. We chose to present only OR, RR, or HR as measures of associations; however, we have tabulated whether there was a significant association with OA progression in an article.

Table 2. Study characteristics of the reviewed manuscripts (n = 79)

First author, year	Number of participants	Followup (months)	Definition OA for inclusion	Mean age in years ± SD	Women (%)	Quality score
Sharma [78], 2010	950	30	K/L	63.6 ± 7.8	62	13
Brouwer [13], 2007	169	72	K/L	66.4 ± 6.7	59	12
Cerejo [16], 2002	230	18	K/L	64 ± 10.8	73	12
Dieppe [23], 1997	415	37.6 ∫	K/L	65.3	68	12
Felson [29], 2003	223	15 and 30	OARSI	66.2 ± 9.4	42	12
Madan-Sharma [50], 2008	186	24	ACR criteria	60.2	81	12
McAlindon [53], 1996	556	120	K/L	70.3	63	12
Sharma [79], 2001	230	18	K/L, JSW	64.0 ± 11.1	75	12
Spector [81], 1994	58	24	K/L	56.8 ± 5.9	100	12
Vilim [87], 2002	48	36	K/L, JSW	62.8 (48-74)	71	12
Bagge [3], 1992	74	48	K/L	-	57	11
Benichou [5], 2010	67	12	OARSI	60 ± 9	64	11
Botha-Scheepers [11], 2008	86	24	ACR criteria	61	80	11
Brandt [12], 1999	82	31.5∫	K/L	70.1	70	11
Denoble [20], 2011	69	36	K/L	64.5 ± 10.1	71	11
Dieppe [22], 1993	60	60	cOA and rOA	62.2 ± 1.5	65	11
Dieppe [21], 2000	349	96	K/L	65.3	68	11
Ledingham [48], 1995	188	24	K/L	71 (34-91)	63	11
Miyazaki [56], 2002	74	72	K/L, JSW	69.9 ± 7.8	81	11
Nevitt [59], 2010	1754	30	K/L	63 ± 8	63	11
Niu [61], 2009	2623	30	K/L	62.4 ± 8.0	59	11
Sharif [72], 1995	75	60	K/L	64.2 ± 11.6	69	11
Sharif [75], 1995	57	60	JSW	-	-	11
Sharif [76], 2000	40	60	K/L	65.2 ± 9.9	61	11
Sharif [74], 2004	115	60	K/L	63.6 ± 9.7	55	11
Sharif [73], 2007	115	60	K/L	63.6 ± 9.7	55	11
Zhang [96], 1998	551	96	K/L	71 (63-91)	100	11
Zhang [94], 2000	473	96	K/L	71 (63-91)	100	11
Bettica [8], 2002	216	48	Osteophytes, JSW	-	100	10
Cooper [18], 2000	354	61.2∫	K/L	71.3	72	10
Dam [19], 2009	138	21	ACR criteria	60	48	10
Doherty [24], 1996	134	30	K/L	71 (41-88)	56	10
Duncan [25], 2011	414	36	K/L	64.8 ± 8.1	51	10
Felson [31], 1995	869	97.2 ∫	K/L	70.8 ± 5.0	64	10
Felson [30], 2007	715 + 488	30 + 120	- , ACR criteria	53 + 66	53 + 40	10
Fraenkel [32], 1998	423	48	K/L	-	67	10
Hart [37], 2002	830	48	Osteophytes, JSW	54.1 ± 5.9	100	10
Kopec [43], 2012	259	72	K/L	-	65	10

Table 2. Study characteristics of the reviewed manuscripts (n = 79) (*continued*)

First author, year	Number of participants	Followup (months)	Definition OA for inclusion	Mean age in years ± SD	Women (%)	Quality score
Lane [45], 1998	55	108	Osteophytes, JSW	66	33	10
Larsson [46], 2012	74	90	OARSI	50 (32-73)	18	10
Mazzuca [51], 2006	319	30	K/L	60.0 ± 9.6	84	10
McAlindon [54], 1996	640	120	K/L	70.3	64	10
Miyazaki [55], 2012	84	96	K/L	72.3 ± 3.1	93	10
Muraki [57], 2012	1313	40	K/L	68.7 ± 11.3	75	10
Nelson [58], 2010	329	60	K/L	61.9 ± 9.7	61	10
Pavelka [63], 2000	139	60	K/L	59.1 ± 8.0	76	10
Reijman [66], 2007	532	72	K/L	68.6 ± 7.0	68	10
Schouten [70], 1992	239	146.4 ∫	K/L	57.2 ± 6.1	59	10
Sharma [77], 2003	171	18	K/L	64.0 ± 11.1	74	10
Spector [80], 1992	63	132	K/L	60 and 61	72	10
Spector [82], 1997	845	48	K/L	-	100	10
Sugiyama [83], 2003	110	48	JSW	50.2 ± 6.0	100	10
Wilder [88], 2009	217	67.2 ∫	K/L	65.9 ± 9.6	61	10
Yoshimura [91], 2012	1296	36	K/L	63	66	10
Zhai [93], 2007	618	84	-	56	-	10
Attur [2], 2011	98	24	K/L	60.7	56	9
Bergink [7], 2009	1248	72	K/L	66.2 ± 6.7	58	9
Bruyere [14], 2003	157	36	ACR criteria	66.0 ± 7.3	76	9
Bruyere [15], 2003	157	36	ACR criteria	66.0 ± 7.3	76	9
Felson [27], 2005	270	30	K/L	66.6 ± 9.2	40	9
Golightly [35], 2010	1583	72	K/L	60.9 ± 10.0	64	9
Harvey [38], 2010	2964	30	K/L	62 ± 8	58	9
Haugen [39], 2012	267	12	OARSI	61.0 ± 9.5	55	9
Kraus [44], 2009	138	36	K/L	-	74	9
Le Graverand [47], 2009	141	24	K/L	56	100	9
Mazzuca [52], 2004	73	30	K/L	55.2 ± 5.8	100	9
Nishimura [60], 2010	92	48	K/L	71 ± 4.7	61	9
Peregoy [64], 2011	157	72	K/L	66.5 ± 8.7	56	9
Reijman [65], 2004	237	72	K/L	69.1 ± 6.9	71	9
Schouten [71], 1993	239	146	K/L	57.4 ± 6.3	59	9
Wolfe [89], 2002	583	31 + 102	ACR criteria	63.4 ± 11.8	77	9
Yusuf [92], 2011	155	72	K/L	59.6 ± 7.5	85	9
Fayfman [26], 2009	490	120	K/L	60.5	62	8
Felson [28], 2004	227	30	K/L	66.4 ± 9.4	41	8
Hunter [40], 2007	595	36	Clinical symptoms	73.6 ± 2.9	60	8
Valdes [85], 2004	280	120	K/L	56.9	100	8

Table 2. Study characteristics of the reviewed manuscripts (n = 79) (*continued*)

First author, year	Number of participants	Followup (months)	Definition OA for inclusion	Mean age in years ± SD	Women (%)	Quality score
Kerkhof [41], 2010	835	72	K/L	67	64	6
Kerna [42], 2009	141	36	K/L	-	70	6
Pavelka [62], 2004	89	24	ACR criteria	56.7 ± 7.2	66	6

SD = Standard Deviation; OA = osteoarthritis; K/L = Kellgren and Lawrence score; OARSI = Osteoarthritis Research Society International atlas; ACR = American College of Rheumatology; JSW = joint space width, cOA = clinical OA; rOA = radiographic OA. ∫ indicates mean followup time in months.

Sensitivity Analysis

For factors in which we were forced to use a best-evidence synthesis, we conducted a sensitivity analysis to check whether differences in sample size could have altered our conclusions. Additionally we checked whether large variances in followup could have led to different conclusions.

RESULTS

Summaries of the results presented in the tables for systemic factors, disease characteristics, intrinsic factors, extrinsic factors, and markers are discussed below.

Systemic Factors (Table 3)

Three studies found positive associations between age and OA progression[56, 57, 70]. All other authors studying age reported no association with OA progression[3, 5, 22, 31, 51, 60, 89]. Only one study found an association for gender[48]. The remaining eight authors found no association[5, 22, 31, 56, 60, 70, 80, 89]. Kopec et al[43] found that blacks were more susceptible to radiographic OA progression compared with whites. Three studies were performed to determine an association for low bone density[37, 59, 94]. Only Zhang et al[94] found a protective effect of high versus low bone density (fourth, third, and second quartiles versus first all showed associations, not all presented in Table 3). Nishimura et al[60] found no association for osteoporosis. Fraenkel et al[32] found no association for insulin-like growth factor-1. Schouten et al[71] only found an association in their third versus first tertile analysis. Yoshimura et al[91] studied the association with metabolic syndrome (overweight, hypertension, dyslipidemia, impaired glucose tolerance). Having two or more of these components was associated with OA progression. Zhang et al[96] found no associations for women with past and current estrogen use and women who never used estrogen. Schouten et al[70] found no association for uric acid concentration. Fayfman et al[26] found no association for plasma homocysteine levels. Zhai et al[93] found a genetic influence on the progression of knee OA, mainly in the medial knee compartment, by calculating and comparing hereditary estimates between mono-

Table 3. Systemic factors discussed in the reviewed studies

Determinant	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Age	Bagge [3], 1992	Dichotomous	Increase K/L ≥ 1 (baseline K/L not provided)	Not provided	o
(N = 3690)	Benichou [5], 2010	< 60 versus ≥ 60 years	Change in JSW (mean difference)	Not provided	o
	Dieppe [22], 1993		JSN ≥ 2 mm	Not provided	o
	Felson [31], 1995		Increase K/L ≥ 1 (baseline K/L ≥ 2)	Not provided	o
	Mazzuca [51], 2006	Continuous (years)	Change in JSW (mean difference)	OR 1.13 (0.87-1.48)	o
	Miyazaki [56], 2002	Continuous (years)	JSN > 1 grade on a 4-grade scale	OR 1.22 (1.05-1.41)	+
	Muraki [57], 2012	Per 5-year increase	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.17 (1.05-1.30)	+
	Nishimura [60], 2010	Continuous (years)	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.93 (0.83-1.06)	o
	Schouten [70], 1992	Fourth quartile versus first	Change in JSW ≥ 1 on a 9-point scale	OR 3.84 (1.10-13.4)	+
	Wolfe [89], 2002	Continuous (years)	JSN score = 3 on a 4-point scale	HR 1.00 (0.98-1.02)	o
Female sex	Benichou [5], 2010		Change in JSW (mean difference)	Not provided	o
(N = 2235)	Dieppe [22], 1993		JSN ≥ 2 mm	Not provided	o
	Felson [31], 1995		Increase K/L ≥ 1 (baseline K/L ≥ 2)	RR 1.43 (0.80-2.58)	o
	Ledingham [48], 1995	Increase K/L or JSW (cutoff not provided) Change in cyst size/number		Not provided OR 2.17 (1.13-4.15)	o +
	Miyazaki [56], 2002		JSN > 1 grade on a 4-grade scale	OR 2.14 (0.34-13.5)	o
	Nishimura [60], 2010		Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.32 (0.22-7.75)	o
	Schouten [70], 1992		Change in JSW ≥ 1 on a 9-point scale	OR 0.50 (0.22-1.11)	o
	Spector [80], 1992		Change JSN ≥ 1 (4-grade scale), or ≥ 10% JSW reduction	Not provided	o
	Wolfe [89], 2002		JSN score = 3 on a 4-point scale	HR 0.73 (0.44-1.19)	o

Table 3. Systemic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Ethnicity (N = 1091)	Kopec [43], 2012	Black versus white	Increase K/L ≥ 1 (baseline K/L ≥ 2)	HR 1.67 (1.05-2.67)	+
Low bone density (N = 3057)	Hart [37], 2002	Low versus high	Change JSN ≥ 1 grade on a 4-grade scale	Not provided	o
	Nevitt [59], 2010	High versus low	Change JSN ≥ 0.5 grade or osteophytes ≥ 1	OR 1.3 (0.7-2.0)	o
	Zhang [94], 2000	Fourth quartile (high) versus first	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.1 (0.03-0.3)	-
Osteoporosis (N = 92)	Nishimura [60], 2010	Present versus absent	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.67 (0.44-6.28)	o
IGF-1 (N = 662)	Fraenkel [32], 1998	Third tertile versus first in women	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.9 (0.5-1.6)	o
		Third tertile versus first in men	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.9 (0.3-3.0)	o
	Schouten [71], 1993	Third tertile versus first	Change ≥ 2 on a 5-point scale for radiographic OA	OR 2.58 (1.01-6.60)	+
Metabolic syndrome (OW, HT, DL, IGT) (N = 1296)	Yoshimura [91], 2012	≥ 3 components versus none	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.80 (1.68-4.68)	+
		2 components versus none		OR 2.29 (1.49-3.54)	+
		1 component versus none		OR 1.38 (0.91-2.08)	o
Estrogen use (N = 551)	Zhang [96], 1998	Past use versus never used	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.9 (0.6-1.4)	o
		Current use versus never used	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.4 (0.1-1.5)	o

Table 3. Systemic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Uric acid concentration	Schouten [70], 1992	High tertile versus low	Change in JSW ≥ 1 on a 9-point scale	OR 1.36 (0.46-4.02)	o
		Middle versus low	Change in JSW ≥ 1 on a 9-point scale	OR 1.05 (0.36-3.00)	o
(N = 239)					
Plasma homocysteine	Fayfman [26], 2009	Third tertile versus first in men		OR 0.6 (0.1-1.1)	o
		Third tertile versus first in women		OR 1.7 (0.8-3.8)	o
(N = 490)					
Genetic components	Zhai [93], 2007		Change ≥ 1 in JSN or osteophyte score	Not provided	o
		Hereditability in MZ			
(N = 618)		Hereditability in DZ		Not provided	+
SNP	Kerna [42], 2009		Increase JSN ≥ 1 or osteophyte grade	OR 2.66 (1.19-5.98)	+
		rs3740199 in women			
(N = 421)			Increase JSN ≥ 1 or osteophyte grade	Not provided	o
		rs1871054			
	Valdes [85], 2004			Not provided	o
			Increase K/L ≥ 1 (baseline K/L not provided)		
		ADAM12_48			
		CILP_395		Not provided	+
		TNA_106		Not provided	o
Depression/anxiety	Wolfe [89], 2002	Depression, yes versus no	JSN score = 3	HR 1.09 (0.93-1.28)	o
(N = 583)		Anxiety, yes versus no		HR 0.95 (0.84-1.08)	o

*Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable); OA = osteoarthritis; CI = confidence interval; K/L = Kellgren and Lawrence score; JSW = joint space width; JSN = joint space narrowing; IGF-1 = insulin-like growth factor 1; OW = overweight; HT = hypertension; DL = dyslipidemia; IGT = impaired glucose tolerance; MZ = monozygotic; DZ = dizygotic; SNP = single nucleotide polymorphisms; OR = odds ratio; RR = relative risk; HR = hazard ratio; N = combined sample size.

zygotic and dizygotic twins. There was no association in the monozygotic but there was in the dizygotic twins. The associations between several single nucleotide polymorphisms (SNPs) and knee OA progression were studied by two authors[42, 85]. Kerna et al[42] found an association for an rs3740199 polymorphism in women but not in men. An rs1871054 polymorphism was not associated. Valdes et al[85] found several genes that appeared to influence OA progression. The polymorphisms at ADAM12, CILP, and TNA appeared to correlate; however, only CILP_395 was associated. Wolfe and Lane[89] found no associations for depression or anxiety.

Disease Characteristics (Table 4)

Six authors studied the association for baseline knee pain[18, 22, 56, 57, 80, 89]. Two authors[57, 89] found associations. Multiple studies were performed determining the association for baseline radiographic or clinical OA severity. Bruyere et al found no association for an initial high radiographic OA score[15]. Duncan et al[25] report a association for mild patellofemoral joint OA at baseline. Mazzuca et al[51] found that a larger joint space width (JSW) at baseline was associated with a decreased risk of mean change in JSW and the presence of patellofemoral OA at baseline was positively associated with change in mean JSW. They found no association for baseline clinical severity. Ledingham et al[48] found an association with baseline radiographic OA severity and change in attrition, but not with change in Kellgren-Lawrence score or JSN. Wolfe and Lane[89] determined an association for an initial high joint space narrowing (JSN) score and for global severity of symptoms. They found no association with an initial Health Assessment score. Miyazaki et al[56] and Pavelka et al[63] found no association for baseline radiographic severity. Dieppe et al[23] found no association for baseline clinical knee OA severity. An association for the presence of Heberden nodes was found by Schouten et al[70]. Cooper et al[18] and Nishimura et al[60] found no associations. Haugen et al[39] found no association for radiographic features of hand OA. Schouten et al[70] and Ledingham et al[48] reported positive associations for generalized osteoarthritis. Muraki et al[57] found no association for hand grip strength. Two studies determined the association between duration of symptoms and OA progression[22, 89]. Only Wolfe and Lane[89] found an association.

Intrinsic Factors (Table 5)

Eight authors studied the association for knee alignment, both varus and valgus[13, 16, 40, 56, 70, 78, 79, 92]. Most analyses showed associations; however, Brouwer et al[13] and Cerejo et al[16] found that valgus versus neutral-aligned knees had no association. Hunter et al[40] studied patella alignment on the progression of tibiofemoral (TF) OA. They found associations between the bisect offset of the patella and both medial and lateral TF OA progression. Also, the patellar tilt was associated with medial TF OA progression. Miyazaki et al[56] found an association in the univariate analysis for varus alignment. Miyazaki et

Table 4. Disease characteristics discussed in the reviewed studies

Determinant	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Knee pain	Cooper [18], 2000	Present versus absent	Increase K/L ≥ 1 (baseline K/L ≥ 1)	OR 0.8 (0.4-1.7)	o
(N = 2444)			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.4 (0.7-8.0)	o
	Dieppe [22], 1993	Present versus absent	JSN ≥ 2 mm	Not provided	o
	Miyazaki [56], 2002	Present versus absent	Change JSN ≥ 1 grade on a 4-grade scale	OR 0.93 (0.78-1.11)	o
	Muraki [57], 2012	Present versus absent	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.63 (1.81-3.81	+
	Spector [80], 1992	Present versus absent	Change JSN ≥ 1 grade on a 4-grade scale, or ≥ 10% JSN	Not provided	o
	Wolfe [89], 2002	Present versus absent	JSN score = 3 on a 4-point scale	HR 1.55 (1.07-2.24)	+
Severity					
Radiographic	Bruyere [15], 2003	Severity high versus low	JSN ≥ 0.5 mm	RR 2.39 (0.99-5.79)	o
(N = 1874)	Duncan [25], 2011	Mild PFJOA versus none†	Increase K/L ≥ 1 (baseline K/L ≥ 2) for TFJOA	OR 4.5 (1.8-11.2)	+
		Mild TFJOA versus none†	Increase K/L ≥ 1 (baseline K/L ≥ 2) for PFJOA	OR 1.7 (0.3-9.0)	o
	Ledingham [48], 1995	Change ≥ 1 radiographic OA feature versus no change	Change in attrition (cutoff not provided) Increase K/L or JSW (cutoff not provided)	OR 1.72 (1.36-2.19) Not provided	+ o
	Mazzuca [51], 2006	JSW high versus low‡	Change in JSW (mean difference)	OR 0.67 (0.49-0.91)	+
		Patellofemoral OA	Change in JSW (mean difference)	OR 3.01 (1.63-5.57)	+
	Miyazaki [56], 2002	JSW, > 3 versus < 3 mm	Change JSN ≥ 1 grade on a 4-grade scale	OR 0.74 (0.25-2.19)	o
	Pavelka [63], 2000	JSW (continuous)	Increase K/L ≥ 1 (baseline K/L not provided)	Not provided	o
	Wolfe [89], 2002	Initial JSN, high versus low	JSN score = 3 on a 4-point scale	HR 2.62 (2.03-3.40)	+
Clinical	Dieppe [23], 1997	Steinbrocker grade	JSN ≥ 2 mm, sclerosis, osteophytes	Not provided	o
(N = 1317)	Mazzuca [51], 2006	WOMAC-PF†	Change in JSW (mean difference)	OR 1.16 (0.92-1.47)	o
	Wolfe [89], 2002	Global severity (continuous)	JSN score = 3 on a 4-point scale	HR 1.02 (1.01-1.03)	+

Table 4. Disease characteristics discussed in the reviewed studies (*continued*)

Determinant	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
		HAQ, high versus low	JSN score = 3 on a 4-point scale	HR 1.34 (0.93-1.93)	o
Heberden nodes	Cooper [18], 2000		Increase K/L ≥ 1 (baseline K/L ≥ 1)	OR 0.7 (0.4-1.6)	o
(N = 685)			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.0 (0.7-5.7)	o
	Nishimura [60], 2010		Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.01 (0.60-6.76)	o
	Schouten [70], 1992		Change in JSW ≥ 1 on a 9-point scale	OR 5.97 (1.54-23.1)	+
Osteoarthritis	Haugen [39], 2012	Score hand JSN	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.00 (0.93-1.08)	o
(N = 694)		Score hand osteophytes		OR 0.96 (0.87-1.06)	o
	Ledingham [48], 1995	Multiple joints versus local joint OA	Increase K/L (cutoff not provided)	OR 2.39 (1.16-4.93)	+
			Change in attrition	OR 2.42 (1.02-5.77)	+
			Change in JSW or rOA (cutoff not provided)	Not provided	o
	Schouten [70], 1992	Generalized OA	Change in JSW ≥ 1 on a 9-point scale	OR 3.28 (1.30-8.27)	+
		Localized OA	Change in JSW ≥ 1 on a 9-point scale	OR 1.17 (0.51-2.72)	o
Hand grip strength (muscle strength)	Muraki [57], 2012	Per 1-kg strength increase	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.99 (0.96-1.01)	o
(N = 1313)					
Duration of symptoms	Dieppe [22], 1993	Continuous (years)	JSN ≥ 2 mm	Not provided	o
(N = 643)	Wolfe [89], 2002	Continuous (years)	JSN score = 3 on a 4-point scale	HR 1.03 (1.00-1.05)	+

*Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable); †at baseline; OA = osteoarthritis; CI = confidence interval; K/L = Kellgren and Lawrence score; JSN = joint space narrowing; TFJOA = tibiofemoral joint OA; PFJOA = patellofemoral joint OA; JSW = joint space width; WOMAC-PF = physical function scale of the WOMAC; VAS = visual analog scale; NRS = Numeric Rating Scale (0-10); HRS = hip replacement surgery; HAQ = Health Assessment Questionnaire; TWT = Timed Walking Test; OR = odds ratio; RR = relative risk; HR = hazard ratio; N = combined sample size.

al found an association for adduction moment. Two studies found no association for former knee injury[18, 70]. Madan-Sharma et al[50] found no associations for bone marrow lesions; MRI detected subchondral bone cysts, cartilage loss, and joint effusion. They did find an association for meniscal damage detected on MRI. Schouten et al[70] found no association for meniscectomy or chondrocalcinosis. The association for tibiofemoral osteophytes was studied by Felson et al[27]. They found a positive association for ipsilateral osteophytes and JSN. They found a negative association for contralateral osteophytes. Benichou et al[5] found no association for osteophytes. Nishimura et al[60] reported that a larger ROM of the knee was associated with less knee OA progression.

Extrinsic Factors (Table 6)

Fifteen authors performed a total of 24 analyses determining the association for body mass index (BMI) [5, 18, 22, 28, 47, 48, 56, 57, 60, 61, 66, 70, 81, 89, 92]. Twelve of these 24 analyses found positive associations[5, 18, 28, 48, 57, 66, 89, 92]. The remaining 12 analyses found no associations. Two authors found no association between quadriceps strength and OA progression[12, 77].

Golightly et al[35] found an association comparing leg length inequality (LLI) with no LLI in patients with baseline Kellgren-Lawrence score ≥ 2. Harvey et al[38] found an increased risk for the shorter leg in patients with LLI ≥ 1 cm compared with no LLI, but not when comparing LLI ≥ 2 cm compared with no LLI. Miyazaki et al[55] found that the degree of AP knee laxity was not associated with OA progression; however, the degree of enhanced laxity resulting from exercise was. Two studies found no association for running on the progression of OA[45, 70]. Cooper et al[18] found no association for regular sport activities. Schouten et al[70] analyzed different types of activities: physical activity in general; walking; and squatting/kneeling, but no associations were found. For duration of standing (hours), an association was found in the comparison of the medium duration versus the low duration groups. Two authors determined a protective effect of vitamin D dietary intake[7, 53]. McAlindon et al[53, 54] also found a protective effect for vitamin D serum levels, vitamin C dietary intake, and β-carotene dietary intake. Felson et al[30] found no associations for serum vitamin D levels in two cohorts. Peregoy and Wilder[64] found no relation with vitamin C dietary intake. Wilder et al[88] found a protective role for vitamin intake. Nishimura et al[60] and Schouten et al[70] found no associations for smoking.

Markers (Table 7)

Three authors studied the association for baseline serum C-reactive protein levels[41, 76, 82]. Only Spector et al[82] reported an association. Attur et al[2] found that serum levels of interleukin (IL)-1β proved to be a good predictor. Botha-Scheepers et al[11] however found no association. Neither did they find an association for IL-1Ra. They did find an association for serum levels of IL-10. Three studies found associations for tumor necrosis factor-α (TNFα) in patients with OA progression[2, 11, 20]. Nelson et al[58] found no association for serum levels

of transforming growth factor-β1. The predictive value of serum levels of hyaluronic acid on OA progression was determined in four studies[14, 62, 72, 76]. All studies reported associations. Bruyere et al[14] found an association for serum levels of keratan sulfate. Sharif et al[72] found no association. Five studies determined the predictive value of serum cartilage oligometric matrix protein levels[14, 62, 74, 75, 87]. Only the studies performed by Sharif et al[74, 75] and Vilim et al[87] found an association. Pavelka et al[62] studied the associations for multiple serum markers, namely serum cartilage oligometric matrix protein, pentosidine, YKL-40, MMP-9, and TIMP-9. They only found an association for serum pentosidine. Sharif et al[73] found an association for the serum marker N-propeptide of type II collagen . Two of three authors[19, 65, 73] found associations between urinary crosslinked C-telopeptide and knee OA progression. Larsson et al[46] found an association for synovial aggrecan neoepitope amino acid sequence levels. Denoble et al[20] found an association for synovium fluid level of IL-18. Kraus et al[44] found that fractal signature analysis of the medial tibial plateau was predictive for medial knee JSN, but not for osteophyte formation or JSN of the lateral compartment. Mazzuca et al[52] found no association for 99mTc-MDP uptake on bone scintigraphy.

Pooled Results

The presence of knee pain at baseline and Heberden nodes were associated with the progression of knee OA. The pooled ORs based on pools of studies with consistency among the definitions for OA inclusion, OA progression, and the determinant under study , were 2.38 for knee pain at baseline (95% CI,1.74-3.27; $I^2 = 52\%$)(Fig. 1) and 2.66 for the presence of Heberden nodes (95% CI, 1.46-8.84); $I^2 = 0\%$) (Fig. 2). Because of the large number of determinants with only a restricted number of studies per determinant and owing to lack of consistency between the reviewed studies regarding inclusion criteria, outcome measures, and measures of association, statistical pooling was not possible for the majority of the determinants.

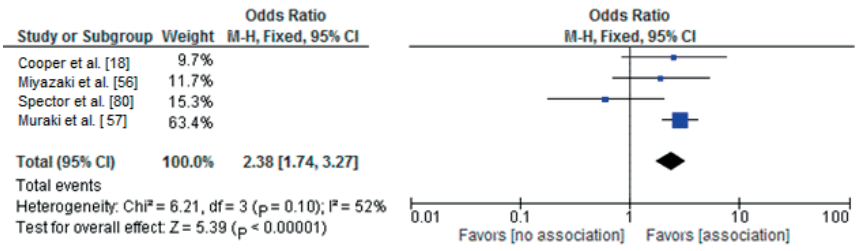

Figure 1. A forest plot for the pooled odds ratio (OR) shows the association between the presence of knee pain at baseline and radiographic progression of knee osteoarthritis (OA). The OR can deviate from the OR in Table 4 because pooled ORs were obtained through crude ORs, as opposed to the adjusted OR in Table 4. The results from Dieppe and for pooling were not available and were not included in this analysis. The results from the chi-square and I^2 tests indicate homogeneity between the studies. M-H = Mantel Haenszel test; Fixed = fixed effects model; df = degrees of freedom.

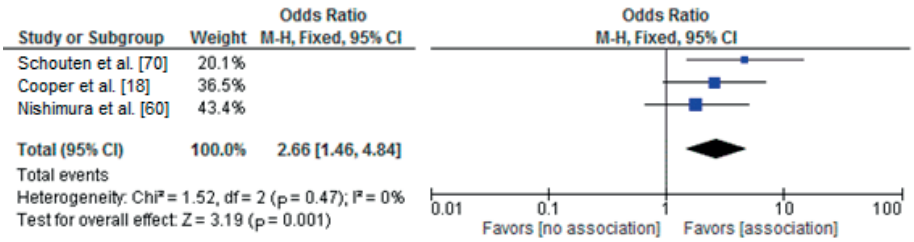

Figure 2. A forest plot for the pooled odds ratio (OR) shows the association between the presence of Heberden nodes at baseline and radiographic progression of knee osteoarthritis (OA). The OR can deviate from that in Table 4 because pooled ORs were obtained through crude ORs, as opposed to the adjusted OR in Table 4. The results from the chi-square and I^2 tests indicate homogeneity between the studies. M-H = Mantel Haenszel test; Fixed = fixed effects model; df = degrees of freedom.

Best-evidence Synthesis

For the remaining determinants, we applied a best-evidence synthesis, which showed that based on consistent findings in multiple high-quality studies, there seems to be strong evidence that varus alignment, serum TNFα level, and serum hyaluronic acid level are associated with radiographic progression of knee OA. There also is strong evidence that sex (female), former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not associated with progression of knee OA.

There was moderate evidence showing that a higher dietary intake of vitamin D is inversely associated with knee OA progression. Thus far, there is limited evidence that ethnicity, metabolic syndrome, genetic components adduction moment, meniscal damage, knee ROM, general vitamin and β-carotene intake, serum levels IL-10 and N-propeptide of type II collagen, synovial levels aggrecan neoepitope amino acid sequence and IL-18, and fractal dimension progression on radiographic fractal signature analysis are associated with progression of knee OA. There also is limited evidence that knee OA progression is not associated with osteoporosis; past or present estrogen use; uric acid concentrations; depression or anxiety; hand grip (muscle) strength; bone marrow lesions or edema; meniscectomy; chondrocalcinosis; MRI-detected subchondral bone cysts, cartilage loss, or joint effusion; AP knee laxity; vitamin E intake; serum levels IL-1Ra and transforming growth factor-β1; and ^{99m}Tc-MDP uptake on bone scintigraphy.

Conflicting evidence was found for the associations between knee OA progression and age; low bone density; serum insulin growth factor-1 level; baseline radiographic or clinical OA severity; generalized osteoarthritis; duration of symptoms; valgus alignment or malalignment in general; past knee injury; the presence of tibiofemoral osteophytes; BMI; leg length inequality; serum vitamin D level; dietary intake of vitamin C; serum C-reactive protein, IL-1β, keratan sulfate, and serum cartilage oligometric matrix protein levels, and urinary crosslinked C-telopeptide level. Inconclusive evidence was found for

Table 5. Intrinsic factors discussed in the reviewed studies

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Alignment	Brouwer [13], 2007	Varus versus neutral	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.90 (1.07-7.88)	+
(N = 2642)		Valgus versus neutral	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.39 (0.48-4.05)	o
	Cerejo [16], 2002	Varus versus nonvarus (K/L 0-1)	Change JSN > 1 grade on a 4-grade scale	OR 2.50 (0.67-9.39)	+
		Varus versus nonvarus (K/L 2)		OR 4.12 (1.92-8.82)	+
		Varus versus nonvarus (K/L 3)		OR 11.0 (3.10-37.8)	+
		Valgus versus nonvalgus (K/L 2)		OR 2.46 (0.95-6.34)	o
		Valgus versus nonvalgus (K/L 3)		OR 10.4 (2.76-39.5)	+
	Hunter [40], 2007	Patellar tilt, fourth versus first quartile	Medial patellofemoral change JSN ≥ 1 grade on a 4-grade scale	OR 0.19 (0.09-0.43)	-
		Sulcus angle, fourth versus first quart		OR 1.49 (0.60-3.73)	o
		Bisect offset, fourth versus first quart		OR 2.23 (1.10-4.50)	+
		Patellar tilt, fourth versus first quartile	Lateral patellofemoral change JSN ≥ 1 grade on a 4-grade scale	OR 1.13 (0.57-2.24)	o
		Sulcus angle, fourth versus first quart		OR 2.09 (0.99-4.41)	o
		Bisect offset, fourth versus first quart		OR 0.35 (0.15-0.83)	-
	Miyazaki [56], 2002	Varus versus nonvarus	Change JSN ≥ 1 grade on a 4-grade scale	OR 0.90 (0.66-1.23)	o
	Schouten [70], 1992	Malaligned, present versus absent	Change JSN ≥ 1 grade on a 4-grade scale	OR 5.13 (1.14-23.1)	+
	Sharma [79], 2001	Varus versus nonvarus	Change JSN ≥ 1 grade on a 4-grade scale	OR 4.09 (2.20-7.62)	+
		Varus versus mild valgus		OR 2.98 (1.51-5.89)	+
		Valgus versus nonvalgus		OR 4.89 (2.13-11.2)	+
		Valgus versus mild varus		OR 3.42 (1.31-8.96)	+
	Sharma [78], 2010	Valgus versus neutral	Change medial JSN ≥ 1 grade on a 4-grade scale	OR 0.34 (0.21-0.55)	-
		Varus versus neutral		OR 3.59 (2.62-4.92)	+
		Valgus versus neutral	Change lateral JSN ≥ 1 grade on a 4-grade scale	OR 4.85 (3.17-7.42)	+
		Varus versus neutral		OR 0.12 (0.07-0.21)	-
	Yusuf [92], 2011	Varus (< 182°) versus nonvarus	Change JSN ≥ 1 grade on a 6-grade scale	RR 2.3 (1.4-3.1)	+
		Valgus (> 184°) versus nonvalgus		RR 1.7 (0.97-2.6)	o
		Malaligned, BMI > 25 kg/m^2		RR 4.1 (1.8-6.1)	+

Table 5. Intrinsic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Adduction moment (N = 74)	Miyazaki [56], 2002	≥ 5 versus < 5 (% weight x height)	Change JSN ≥ 1 grade on a 4-grade scale	OR 6.46 (2.40-17.5)	+
Knee injury (N = 207)	Cooper [18], 2000	Yes versus no	Increase K/L ≥ 1 (baseline K/L ≥ 1)	OR 1.2 (0.5-3.0)	o
			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.1 (0.3-4.4)	o
	Schouten [70], 1992	Knee injury: yes versus no	Change JSN ≥ 1 grade on a 4-grade scale	OR 2.62 (0.93-7.36)	o
		Sport injury: yes versus no	Change JSN ≥ 1 grade on a 4-grade scale	OR 0.62 (0.17-2.19)	o
Bone marrow lesions/edema (BMLs/BME) (N = 186)	Madan-Sharma [50], 2008	Present versus absent	JSN > 1 grade on a 4-grade scale	RR 0.9 (0.18-3.0)	o
Subchondral bone cysts (MRI) (N = 186)	Madan-Sharma [50], 2008	Present versus absent	JSN > 1 grade on a 4-grade scale	RR 1.6 (0.5-4.0)	o
Cartilage loss (MRI) (N = 186)	Madan-Sharma [50], 2008	Present versus absent	JSN > 1 grade on a 4-grade scale	RR 3.0 (0.5-9.6)	o

Table 5. Intrinsic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Joint effusion (N = 186)	Madan-Sharma [50], 2008	Present on MRI	JSN > 1 grade on a 4-grade scale	RR 0.6 (0.6-1.8)	o
Meniscal damage (N = 186)	Madan-Sharma [50], 2008	Present versus absent on MRI	JSN > 1 grade on a 4-grade scale	RR 8.91 (1.1-22.8)	+
Meniscectomy (N = 239)	Schouten [70], 1992	Yes versus no	Change JSN ≥ 1 grade on a 4-grade scale	OR 2.28 (0.57-9.03)	o
Chondrocalcinosis (N = 239)	Schouten [70], 1992	Yes versus no	Change JSN ≥ 1 grade on a 4-grade scale	OR 2.01 (0.55-7.42)	o
Osteophytes tibiofemoral (N = 337)	Benichou [5], 2010	Definite versus not	Change in JSW (mean difference)	Not provided	o
	Felson [27], 2005	Ipsilateral score	Change JSN ≥ 1 grade on a 4-grade scale	OR 1.9 (1.5-2.5)	+
		Contralateral score		OR 0.6 (0.5-0.8)	-
Knee ROM (N = 92)	Nishimura [60], 2010	Mean ROM	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.94 (0.89-0.99)	-

*__Statistically significant__ association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable); OA = osteoarthritis; CI = confidence interval; K/L = Kellgren and Lawrence score; JSN = joint space narrowing; BMI = body mass index; (c)MFTC.ThC = (central) medial femorotibial compartment cartilage thickness (in mm); LFTC = lateral FTC; VAS = visual analog scale; WOMAC-PF = physical function scale of the WOMAC; US = ultrasonography; JSW = joint space width; TWT = Timed Walking Test; OR = odds ratio; RR = relative risk; HR = hazard ratio; N = combined sample size.

the determined associations between knee OA progression and the single nucleotide polymorphisms CILP_395 (cartilage intermediate-layer proteins) and rs3740199, patellofemoral alignment, and serum pentosidine levels. There also was inconclusive evidence for no associations found between knee OA progression and the single nucleotide polymorphisms rs1871054, ADAM12_48 (A disintegrin and matrix metalloproteinase domain 12), and TNA_106 (tetranectin plasminogen-binding protein), and serum levels of YKL-40 (chitinase-3-like protein 1), MMP-9 (matrix metalloproteinase-9); and TIMP-9 (tissue inhibitors of metalloproteinase).

Sensitivity Analysis

In this analysis, we tested whether conclusions from relatively small studies (less than 200) incorrectly influenced conclusions drawn from larger studies with more statistical power studying the same determinant, or that results from studies with a relatively short followup (cutoff 24 months) altered conclusions from studies with a longer followup. Our sensitivity analysis found that our conclusions did not change across the range of clinically plausible differences in followup duration or sample size regarding the strong, moderate, or conflicting evidence we found for the various presented determinants.

DISCUSSION

We performed an updated systematic review of available evidence regarding prognostic factors for radiographic knee OA progression. We found that there is strong evidence that baseline knee pain and Heberden nodes, varus alignment, and high baseline serum levels of hyaluronic acid and TNFα are predictive for knee OA progression. There also seems to be strong evidence that sex (female), former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not predictive for progression of knee OA. For all other studied factors in our review, the evidence is limited, conflicting, or inconclusive. In the best-evidence synthesis, we considered only significant associations as associated prognostic factors. However, several of the included articles had small sample sizes, which consequently can lead to lower statistical power and more often to failure to detect differences that might be present.

A possible limitation to our inclusion criteria was addressed by Zhang et al[97]. They reported that, unlike randomized trials, observational studies of patients with preexisting disease are subject to various biases that may account for discrepancies found between risk factors for disease incidence and progression. They hypothesized that risk factors actually might exist for progressive knee OA but that flaws in study design and the measure of disease progression may prevent us from detecting risk factors[97]. Having cited their article, it seems reasonable that there is the possibility that we have not

determined all risk factors for knee OA progression, because some factors may not have achieved significance in multivariable analyses in a study and thus were not included in our evidence synthesis. Nonetheless, we believe we have summarized all presently known risk factors of which a possible association with knee OA progression has been studied.

We acknowledge that when applying a best-evidence synthesis, one might unjustly conclude that there may be conflicting or strong evidence for or against an association of the determinant under study with knee OA. We would have preferred to pool the data of all included studies. However, because of large variation in criteria used in the articles for defining disease, or disease progression, pooling of the data generally was not possible. We encountered six different criteria that were used for the inclusion of OA (Table 2). Another approximately 13 different definitions were applied for OA progression (Tables 3-7). Furthermore, there were differences in how the determinants under study were measured, (continuous, dichotomous, or categorical), and varying cutoff points were used. As previously described, we pooled the results for "knee pain" and "Heberden nodes" for which both results showed associations with the progression of knee OA. This is different from the conclusions we would have drawn from a best-evidence synthesis, which would show conflicting evidence for both determinants. In our opinion, it is likely that more of the conflicting associations we presented are attributable to the differences in definitions of knee OA or knee OA progression. For example, the conflicting evidence for BMI probably would be altered if statistical pooling was feasible; given that all 11 significant risk estimates (OR/RR/HR) regarding BMI were positive associations and that six of the 12 nonsignificant associations also were positive associations, it seems likely that if pooled, the combined overall association between BMI and knee OA would be a positive, significant one. In addition, the conflicting evidence for age, seven of the 10 presented analyses (70%) showed no significant association, falling just short for the criteria for ascertaining strong evidence (> 75%) for no association between age and OA progression.

In the original review by Belo et al.[4] and in a review by van Dijk et al.[86], the evidence for association between varus alignment and OA progression was limited. However, a couple studies have been performed since these reviews were published that have determined significant associations with varus alignment, which enabled us to conclude that there is strong evidence for this finding. The latter is in accordance with results published in later systematic reviews by Tanamas et al.[84] and Chapple et al[17]. Except for the original review by Belo et al., there are to our knowledge no other reviews available that have determined the predictive value of serum hyaluronic acid levels and OA progression[9]. In addition, to our knowledge, no reviews have been published assessing the predictive value of serum level TNFα for knee OA progression.

Table 6. Extrinsic factors discussed in the reviewed studies

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Body mass index (BMI)	Benichou [5], 2010	< 30 versus ≥ 30 kg/m^2	Change in JSW (mean difference)	Not provided	+
	Cooper [18], 2000	Highest tertile versus lowest	Increase K/L ≥ 1 (baseline K/L ≥ 1)	OR 2.6 (1.0-6.8)	+
(N = 6791)			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.3 (0.3-5.0)	o
	Dieppe [22], 1993	Continuous	JSN ≥ 2 mm or knee surgery	Not provided	o
	Felson [28], 2004	Per 2-unit increase (1)	Change JSN ≥ 1 grade on a 4-grade scale	OR 0.98 (0.8-1.4)	o
		As 1, with 3°-6° malalignment		OR 1.23 (1.0-1.4)	+
		As 1, with ≥ 7° malalignment		OR 0.93 (0.7-1.2)	o
	Ledingham [48], 1995	Continuous	Change in JSW (cutoff not provided)	OR 1.07(1.02-1.14)	+
			Change in osteophytes (cutoff not provided)	OR 1.06 (1.00-1.12)	+
			Change in K/L (cutoff not provided)	Not provided	o
	Le Graverand [47], 2009	< 30 versus ≥ 30 kg/m^2	Change in JSW (mean difference)	Not provided	o
	Miyazaki [56], 2002	Continuous	JSN ≥ 1 grade on a 4-grade scale	OR 1.21 (0.91-1.61)	o
	Muraki [57], 2012	Per 5-unit increase	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 1.43 (1.16-1.77)	+
	Nishimura [60], 2010	Continuous	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.93 (0.78-1.11)	o
	Niu [61], 2009	< 25 versus ≥ 30 kg/m^2	Increase JSN ≥ 0.5 grade	RR 1.1 (0.9-1.4)	o
	Reijman [66], 2007	≤ 25 versus > 27.5 kg/m^2	Increase JSN ≥ 1 mm	OR 1.4 (0.8-2.6)	o
			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.1 (1.2-3.7)	+
	Schouten [70], 1992	Second quartile versus first	Change in JSW ≥ 1 on a 9-point scale	OR 1.77 (0.48-6.50)	o
		Third quartile versus first		OR 5.28 (1.54-18.1)	+
		Fourth quartile versus first		OR 11.1 (3.28-37.3)	+
	Spector [81], 1994	Third tertile versus first	Increase K/L or JSN (cutoff not provided)	RR 4.69 (0.63-34.8)	o
	Wolfe [89], 2002	Continuous	JSN score = 3	HR 1.03 (1.00-1.06)	+

Table 6. Extrinsic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
	Yusuf [92], 2011	BMI 25-30 versus < 25	Change JSN ≥ 1 grade on a 6-grade scale	RR 2.4 (1.3-3.6)	+
		BMI >30 versus < 25	Change JSN ≥ 1 grade on a 6-grade scale	RR 2.9 (1.7-4.1)	+
Quadriceps strength	Brandt [12], 1999	Progressive versus nonprogressive group†	Increase K/L ≥ 1 (baseline K/L not provided)	Not provided	o
	Sharma [77], 2003	High versus low strength‡	Increase JSN ≥ 1	Not provided	o
(N = 253)					
Leg length inequality (LLI)	Golighlty [35], 2010	LLI versus no LLI	Increase K/L ≥ 1 (baseline K/L ≥ 1)	HR 1.22 (0.82-1.80)	o
			Increase K/L ≥ 1 (baseline K/L ≥ 2)	HR 1.83 (1.10-3.05)	+
(N = 4547)	Harvey [38], 2010	≥ 1 cm versus no LLI, shorter leg	JSN ≥ 1 grade or knee surgery	OR 1.3 (1.0-1.7)	+
		≥ 2 cm versus no LLI, shorter leg		OR 1.4 (0.5-3.7)	o
Anteroposterior knee laxity	Miyazaki [55], 2012	Before exercise	Increase K/L ≥ 1 (baseline K/L ≥ 1) or radiographic cartilage loss > 0.2 mm annually	OR 1.29 (0.54-3.08)	o
		Enhanced laxity resulting from exercise		OR 4.15 (1.12-15.4)	+
(N = 84)					
Running	Lane [45], 1998	Dichotomous‡	Increase ≥ 1 on JSW and osteophyte score	Not provided	o
(N = 294)	Schouten [70], 1992	Dichotomous†	Change in JSW ≥ 1 on a 9-point scale	OR 0.53 (0.17-1.68)	o
Regular sports	Cooper [18], 2000	Dichotomous†	Increase K/L ≥ 1 (baseline K/L ≥ 1)	OR 0.7 (0.4-1.6)	o
(N = 593)			Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.9 (0.3-2.5)	o

Table 6. Extrinsic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
	Schouten [70], 1992	Physical activity‡	Change in JSW ≥ 1 on a 9-point scale	OR 0.43 (0.11-1.76)	o
		Walking‡		OR 1.47 (0.36-6.03)	o
		Standing (medium versus low)‡		OR 3.80 (1.03-14.0)	+
		Standing (high versus low)‡		OR 2.09 (0.43-10.3)	o
Nutritional variables	Bergink [7], 2009	Vitamin D intake (low versus high)	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 7.7 (1.3-43.5)	-
		Serum vitamin D (low versus high)	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 2.1 (0.6-7.4)	o
(N = 3381)	Felson [30], 2007	Vitamin D serum levels < 20 ng/mL	Change JSN ≥ 1 grade on a 4-grade scale, Framingham	OR 0.83 (0.54-1.27)	o
		Vitamin D serum levels < 20 ng/mL	Change JSN ≥ 1 grade on a 4-grade scale, BOKS study	OR 0.63 (0.35-1.14)	o
	McAlindon [53], 1996	Vitamin D intake (middle versus high)	Increase JSN ≥ 1	OR 2.99 (1.06-8.49)	-
		Serum vitamin D (middle versus high)	Increase JSN ≥ 1	OR 2.83 (1.02-7.85)	-
	McAlindon [54], 1996	Vitamin C intake (middle versus low)	Increase K/L ≥ 1	OR 0.32 (0.14-0.77)	-
		β-carotene intake (high versus low)		OR 0.42 (0.19-0.94)	-
		Vitamin E (high versus low)		OR 0.68 (0.28-1.64)	o
	Peregoy [64], 2011	Vitamin C intake	Increase K/L ≥ 1 (baseline K/L ≥ 2)	RR 0.94 (0.79-1.12)	o
	Wilder [88], 2009	Vitamin intake in general	Increase K/L ≥ 1 (baseline K/L ≥ 2)	RR 0.93 (0.87-0.99)	-

Table 6. Extrinsic factors discussed in the reviewed studies (*continued*)

Determinant	First author, year	Analysis of determinant	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Smoking	Nishimura [60], 2010	Yes versus no	Increase K/L ≥ 1 (baseline K/L ≥ 2)	OR 0.73 (0.09-6.15)	o
(N = 331)	Schouten [70], 1992	Past smoker versus never	Change in JSW ≥ 1 on a 9-point scale	OR 1.07 (0.38-3.04)	o
		Current smoker versus never	Change in JSW ≥ 1 on a 9-point scale	OR 0.96 (0.34-2.75)	o

*Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable); †assessed at baseline; ‡assessed at followup; OA = osteoarthritis; CI = confidence interval; JSW = joint space width; K/L = Kellgren and Lawrence score; JSN = joint space narrowing; WOMAC-PF = physical function scale of the WOMAC; VAS = visual analog scale; TWT = Timed Walking Test; OR = odds ratio; RR = relative risk; HR = hazard ratio; N = combined sample size.

Table 7. Markers discussed in the reviewed studies

Marker	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
CRP (serum)	Kerkhof [41], 2010	Continuous	Increase K/L ≥ 1 (baseline K/L ≥ 2) or surgery	Not provided	o
(N = 1720)	Sharif [76], 2000	Continuous	JSN ≥ 2 mm or knee surgery	OR 1.12 (0.81-1.55)	o
	Spector [82], 1997	Continuous	Increase K/L ≥ 1 (baseline K/L not provided)	Not provided	+
IL-1β (serum)	Attur [2], 2011	Increased versus normal	Increase K/L ≥ 1 or > 30% JSW reduction	OR 3.2 (1.2-8.7)	+
(N = 184)	Botha-Scheepers [11], 2008	Fourth quartile versus first	Change JSN ≥ 1 grade on a 4-grade scale	RR 1.3 (0.5-2.0)	o
IL-10 (serum)	Botha-Scheepers [11], 2008	Fourth quartile versus first	Change JSN ≥ 1 grade on a 4-grade scale	RR 4.3 (1.7-6.2)	+
(N = 86)					
IL-1Ra (serum)	Botha-Scheepers [11], 2008	Fourth quartile versus first	Change JSN ≥ 1 grade on a 4-grade scale	RR 2.1 (0.7-3.9)	o
(N = 86)					
TNFα (serum)	Attur [2], 2011	Increased versus normal	Increase K/L ≥ 1 or > 30% JSW reduction	OR 8.9 (2.6-30.8)	+
(N = 253)	Botha-Scheepers [11], 2008	Fourth quartile versus first	Change JSN ≥ 1 grade on a 4-grade scale	RR 6.1 (1.4-9.8)	+
	Denoble [20], 2011	Continuous	Change in osteophyte score	Not provided	+
TGF-β1 (serum)	Nelson [58], 2010	Continuous	Increase K/L ≥ 1 (baseline K/L ≥ 1)	HR 1.04 (0.41-2.65)	o
(N = 329)			Increase K/L ≥ 1 (baseline K/L ≥ 2)	HR 1.10 (0.46-2.63)	o
Hyaluronic acid (serum)	Bruyere [14], 2003	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	+
	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	+
(N = 361)	Sharif [72], 1995	High level versus low	JSN ≥ 2 mm or knee surgery	Not provided	+
	Sharif [76], 2000	High level versus low	JSN ≥ 2 mm or knee surgery	OR 2.32 (1.16-4.66)	+

Table 7. Markers discussed in the reviewed studies (*continued*)

Marker	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
Keratan sulfate (serum)	Bruyere [14], 2003	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	+
	Sharif [72], 1995	High level versus low	JSN ≥ 2 mm or knee surgery	Not provided	o
(N = 232)					
COMP (serum)	Bruyere [14], 2003	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	o
(N = 466)	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	o
	Sharif [75], 1995	High level versus low	JSN ≥ 2 mm or knee surgery	Not provided	+
	Sharif [74], 2004	OA progress versus non prog	JSN ≥ 2 mm or knee surgery	Not provided	+
	Vilim [87], 2002	High level versus low	JSN > 0.5 mm	Not provided	+
Pentosidine (serum)	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	+
(N = 89)					
YKL-40 (serum)	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	o
(N = 89)					
MMP-9 (serum)	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	o
(N = 89)					
TIMP-9 (serum)	Pavelka [62], 2004	High level versus low	Change in mean JSW (cutoff not provided)	Not provided	o
(N = 89)					
PIIANP (serum)	Sharif [73], 2007	Fourth quartile versus first	JSN ≥ 2 mm or knee surgery	RR 3.2 (1.1-9.0)	+
(N = 115)					

Table 7. Markers discussed in the reviewed studies (*continued*)

Marker	First author, year	Instrument of measurement	Definition of knee OA progression	OR/RR/HR (95% CI)	Association with OA progression*
CTX-II (urine)	Dam [19], 2009	Third tertile versus first	Increase K/L ≥ 1 (disregarding baseline K/L)	OR 2.3	o
(N = 490)		Third tertile versus first	JSN > mean JSN of non-OA control group (K/L ≤ 1)	OR 1.8	o
	Reijman [65], 2004	Fourth quartile versus first	JSN ≥ 2 mm	OR 6.0 (1.2-30.8)	+
		Fourth quartile versus first	JSN ≥ 1.5 mm	OR 1.8 (0.8-4.1)	o
		Fourth quartile versus first	JSN ≥ 1 mm	OR 1.1 (0.7-1.7)	o
	Sharif [73], 2007	> median versus ≤ median	JSN ≥ 2 mm or knee surgery	RR 3.4 (1.2-9.4)	+
ARGS (synovial)	Larsson [46], 2012	Baseline level ARGS > followup level ARGS	≥ 1-unit increase OARSI score	OR 6.77 (1.38-33.2)	+
(N = 74)					
IL-18 (synovial)	Denoble [20], 2011	Continuous	Change in osteophyte score	Not provided	+
(N = 69)					
FSA (radiographic)	Kraus [44], 2009	FD progress versus nonprogression	Medial JSN ≥ 1 or osteophyte formation	Not provided	+
(N = 138)					
Bone scintigraphy	Mazzuca [52], 2004	^{99m}Tc-MDP uptake	Change in JSW (mean difference)	Not provided	o
(N = 73)					

*Statistically significant association of the determinant with OA progression: + positive association, - negative association, o no association (adjusted for age and sex if applicable); OA = osteoarthritis; CI = confidence interval; K/L = Kellgren and Lawrence score; JSN = joint space narrowing; CRP = C-reactive protein; IL = interleukin; TNFα = tumor necrosis factor α; JSW = joint space width; TGF = transforming growth factor; C2C = collagen type II cleavage; COMP = cartilage oligomeric matrix protein; MMP = matrix metalloproteinase; TIMP = tissue inhibitors of metalloproteinase; PIIANP = N-propeptide of type IIA collagen; CTX-II = crosslinked C-telopeptide; ARGS = aggrecan neoepitope amino acid sequence; OARSI = Osteoarthritis Research Society International atlas; KOOS = Knee injury and Osteoarthritis Outcome Score; FSA = fractal signature analysis; FD = fractal dimension (horizontal and vertical); OR = odds ratio; RR = relative risk; HR = hazard ratio; N = combined sample size.

We found strong evidence that sex was not associated with knee OA progression, as did Belo et al.[4]. This is in contrast to the earlier reviews published by van Dijk et al.[86] and Chapple et al.[17]. Van Dijk et al. found limited evidence for the absence of an association with sex, but they included articles that used physical functioning as an outcome measure. Chapple et al. found conflicting evidence; however, their evidence was based on four analyses of three studies, which also are included in our review[21, 47, 70]. Three of the four analyses were consistent (no association); one was conflicting (significant association)[47]. Our evidence synthesis was based on 10 analyses, of which nine analyses were consistent (no association), consequently outweighing the one conflicting finding. van Dijk et al. and Chapple et al. reported limited evidence for the absence of an association between quadriceps strength and knee OA progression. This is consistent with our finding; however, our conclusion is based on more evidence. Consistent results also were found for regular performance of sports, in which van Dijk et al. reported limited and Chapple et al. reported strong evidence for absence of an association. However, in articles by Fransen and McConnell[33] and Bennell and Hinman[6] reviewing the effect of exercise therapy in patients with knee OA, the authors reported that exercise has a short-term benefit in patients with knee OA, although the magnitude of the reported benefit is small. This highlights the importance of the need to understand the working mechanism of exercise therapy.

A topic of considerable interest is the potential association between BMI and knee OA progression. Previous reviewers have established a positive association between BMI and incident knee OA[10, 95]. However, the evidence for an association between BMI and progression of knee OA remains conflicting in this review, which is consistent with the findings by Belo et al.[4] and Chapple et al[17].

Noteworthy is the lack of overlap in evidence for prognostic factors for hip and knee OA progression. In two large reviews studying prognostic factors for hip OA, Lievense et al.[49] provided strong evidence for an association between hip OA progression with type of hip migration and with atrophic bone response. They also presented strong evidence for the absence of an association with BMI. Wright et al.[90] reported strong evidence for association of hip OA progression with age, joint space width at entry, femoral head migration, femoral osteophytes, bony sclerosis, baseline hip pain, and certain hip OA severity indexes. They also provided strong evidence for the absence of an association with acetabular osteophytes. The discrepancy between the findings for hip and knee OA is unclear but could be attributable to the difference in the number of studies available determining risk factors for progression of hip or knee OA[9].

Future research on the true relationship between prognostic factors for radiographic progression of knee OA is needed, mainly on the factors where conflicting evidence was presented (eg, age, baseline OA severity, BMI). Furthermore, we presented limited, inconclusive, or conflicting evidence on many factors with potential associations with

OA progression. It would be important to investigate determinants that can be influenced or modified to reduce the risk of OA progression, perhaps including metabolic syndrome, bone marrow lesions, or osteoporosis. Moreover, there would be obvious advantages to testing the effect of new or existing disease-modifying pharmacologic or surgical interventions in patients with an established increased risk of OA progression.

We found strong evidence that baseline knee pain and Heberden nodes, varus alignment, and high baseline serum levels of hyaluronic acid and TNFα are predictive for knee OA progression. Sex (female), former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not predictive for progression of knee OA. Many studies have been performed and are being performed determining risk factors for knee OA progression, but the variability in how OA and OA progression are defined across the relevant studies remains an impediment to pooling the available evidence. We strongly recommend future researchers use uniform definitions of determinants, disease, and disease progression; it would enable a more precise determination of possible risk factors for knee OA progression through meta-analyses. The majority of the included studies used the Kellgren-Lawrence classification as definition of disease and disease progression. This classification has been criticized because the criteria have been described and interpreted differently in various studies[67]. However, the Kellgren-Lawrence criteria provide a reliable classification of knee OA and OA progression, given that the original description of the criteria are applied[67, 68]. We therefore recommend that future researchers use the Kellgren-Lawrence classification to define radiographic OA and OA progression. Furthermore, considering that some MRI scoring systems have been and currently are being developed to define knee OA progression[36], it seems preferable that the same MRI scoring system would be used universally in future studies on prognostic factors for knee OA progression. We would like to call on expert committees, such as the Osteoarthritis Research Society International (OARSI) for OA Imaging to announce their recommendations on this important topic.

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Chapter 4

Defining knee pain trajectories in early symptomatic knee osteoarthritis in primary care.

5-year results from a nationwide prospective cohort study (CHECK)

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ABSTRACT

Background General practitioners have high consultation rates for knee osteoarthritis (OA) related symptoms. Many risk factors for symptomatic knee OA progression remain unknown.

Aim To define distinct knee pain trajectories in individuals with early symptomatic knee OA and to determine risk factors for these pain trajectories.

Design and Setting Data were obtained from a multicenter prospective Cohort Hip and Cohort Knee study in The Netherlands. Participants with knee OA according to the clinical criteria of the American College of Rheumatology, and a completed 5-year follow-up were included.

Method Baseline demographic, anamnestic, physical examination characteristics were assessed. Outcome was annually assessed by the Numeric Rating Scale for pain. Pain trajectories were retrieved by latent class growth analysis. Multinomial logistic regression was used to calculate relative risk ratios.

Results In total, 705 participants were included. Six distinct pain trajectories were identified with favourable and unfavourable courses. We found significant differences in baseline characteristics, including body mass index (BMI); symptom severity; and pain coping strategies between the different trajectories. Higher BMI, lower education, more co morbidity, higher activity limitation scores and joint space tenderness were more often associated with trajectories characterized by more pain at first presentation and pain progression – compared with the reference group with a mild pain trajectory. No association was found for baseline radiographic features.

Conclusions These results can help differentiate those patients that require more specific monitoring in the management of early symptomatic knee OA from those for whom a 'wait-and-see' policy seems justifiable. Radiography provided no additional benefit over clinical diagnosis of early symptomatic knee OA in general practice.

INTRODUCTION

Osteoarthritis of the knee (knee OA) is a common disease with a relatively high prevalence and incidence amongst older patients in the general population.[1] Symptomatic knee OA, pain in particular, varies greatly in affected individuals and many patients encounter the disabling effect of pain.[1, 2] Consequently, general practitioners (GPs) have high consultation rates for OA related symptoms and see a large variability in the evolution of the disease.[3] As a result, they need to differentiate patients for whom a wait-and-see policy seems justifiable from the patients for whom a proactive management is necessary.

Many criteria have been developed to assess knee OA severity using clinical and radiographic features or MRI techniques to define disease progression.[4-6] Numerous studies have determined risk factors for incident and radiographic progression of knee OA, but only few studies have used symptomatic knee OA progression as an outcome measure.[7, 8]

Discordance remains in the apparent correlation between stages of knee OA assessed by clinical and radiographic criteria and pain severity. This seems to imply that there are differences in risk factors for (radiographic) disease progression and pain progression in knee OA. Although the exact aetiology remains unclear, pain due to knee OA is known to fluctuate and multiple assessments of pain over time could give a better indication of pain than one single assessment.[9, 10] This course of pain, or pain trajectory, could be a more accurate or more relevant representation of clinical disease progression. The ability to predict pain trajectories in an early stage of disease could help GPs and patients successfully to manage knee OA in a primary care setting. As such, this study aimed to: define distinct knee pain trajectories in individuals with early symptomatic knee OA; and determine patient- or disease characteristics associated with these pain trajectories.

PATIENTS AND METHODS

Study design and population

The data for the current study were acquired from the Cohort Hip and Cohort Knee (CHECK) study.[11] CHECK is a prospective, ten-year follow-up cohort of 1,002 participants with early symptomatic OA of the knee and/or hip in The Netherlands. Its inclusion period ran from October 2002 until September 2005. Inclusion criteria for the CHECK study were: pain and/or stiffness of the knee and/or hip; age between 45 and 65 years; and never, or less than six months prior to recruitment of the study, consulted a physician for these symptoms. Participants were excluded from the CHECK study if they had other pathological conditions that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis

dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus injury, plicasyndrome, Baker's cyst); co morbidity that would not allow physical evaluation during 10 years follow-up; malignancy in the past five years; and inability to understand the Dutch language. For the analyses of the current study we included participants whom at baseline reported knee pain and were considered to have knee OA according to the clinical criteria of the American College of Rheumatology (ACR) criteria.[4, 11] If a participant had two affected knees, we included the knee with the worst score based on pain, Kellgren and Lawrence (KL) score and physical examination findings. The latter included knee pain, range of motion, crepitus, joint space tenderness, palpable warmth and bony enlargement. If all findings were identical in both knees, we arbitrarily included the right knee.

Baseline characteristics

The study included a baseline medical history, physical examination and radiographs of the knee and hip to create variables that are available to the GP. The medical history was taken through questionnaires in which self-reported data were assessed. The following diseases were assessed as relevant co morbidity: asthma, chronic sinusitis, cardio-vascular disease, high blood pressure, gastric ulcer, gallstones, liver disease, renal disease, diabetes, thyroid gland disease, epilepsy, cancer (during follow-up), severe skin disease, and other chronic musculoskeletal diseases. Furthermore, the Western Ontario and McMaster osteoarthritis index (WOMAC) subscores were used to measure pain, stiffness and physical functioning with a higher score indicating worse health (range 0-100). To assess pain-coping behaviour a six scale Pain-Coping Inventory (PCI) was used that represents active and passive pain coping dimensions.[12] Active pain coping strategies are: pain transformation (i.e. to reinterpret and transform pain); distraction (i.e. to distract oneself from pain); and reducing demands (i.e. to function in spite of pain). Passive pain coping strategies are: retreating (i.e. to avoid environmental stimuli); worrying (i.e. to catastrophize pain); and resting (i.e. to restrict functioning).[11, 13] All six items are scored according to a four-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which strategies are applied. Standardized radiographs of the tibiofemoral joint were made by a weight-bearing posteroanterior view, semi-flexed (7-10°) according to Buckland-Wright.[14, 15] For the hip, standardized weight-bearing anteroposterior radiographs of the pelvis were made. Radiographs were read with the observers blinded to all patient characteristics. Scoring of radiographs was performed according to KL.[16] We used these two sets of radiographs, because these radiographs are available to the GP.

Outcome variable

Pain was assessed annually through questionnaires using the Numeric Rating Scale (NRS) for pain ranging from 0-10, a higher score indicating more pain. The participants were asked to score the pain they experienced in their most painful joint over the last week. Using latent class growth analysis (LCGA) the annually assessed NRS for pain were plotted longitudinally, blinded to all other characteristics, creating various pain trajectory groups, which formed our outcome variable. Pain scores of participants who underwent knee replacement surgery were scored as missing from the moment of surgery. If participants missed more than two pain assessments they were excluded from analyses.

Statistical analysis

Latent class growth analysis (LCGA) was used to identify the different pain trajectories. LCGA is a technique that uncovers heterogeneity in a population and makes it possible to distinguish groups of people who are similar in their growth trajectories longitudinally. This technique has been previously described by Verkleij and was applied to our study population.[10] In short, it was 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, clinical relevancy and the interpretability of the model. The indices of fit used were: Bayesian Information Criterion (BIC); Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRT) and the bootstrap LRT; and entropy indices.

Baseline characteristics were calculated per pain trajectory group using descriptive statistics. After checking for collinearity setting the cut-off value for Pearson's correlation coefficient (R) at 0.70, we performed multinomial logistic regression analyses per variable to test whether differences were statistically different, obtaining a cut-off point P <0,10. All variables with P<0,10 were later included in a final multivariable multinomial logistic regression model (P-removal P<0,05) to obtain relative risk ratios (RR) and 95% confidence intervals (CI) for belonging in each trajectory. The final model was adjusted for age and sex to make the results more generalizable to the general population with knee OA related symptoms.

The LCGA was performed using *Mplus 6.1 ed 1998-2010*. All other analyses were performed using *SPSS Statistical Package PASW 20.0*.

RESULTS

Baseline characteristics

In total, 743 of the 1,002 participants met the inclusion criteria at baseline. Of these, 38 (5%) participants missed more than two annual pain assessments or were lost to follow-up and were excluded from the analyses. The baseline values of BMI, NRS, age,

sex and KL of the 38 excluded participants did not differ significantly from the study population. The total study population after 5 years consisted of 705 participants (=705 knees), mean age 56.0 ± 5.1 years and 81% was female, see **Tables 1** and **2** for a further description. The baseline variables 'NRS of the past week' and 'NRS at the moment of the questionnaire' were strongly correlated (Pearson's R=0.83), as were each of the WOMAC subscales (pain, joint stiffness and physical function) with 'NRS of the past week' (Pearson's R is 0.68, 0.51 and 0.63 respectively). The baseline 'NRS at the moment of the questionnaire' was excluded due to strong collinearity. Although Pearson's R was <0.70 for all WOMAC subscales, only the WOMAC physical function subscale was included in the final model; this was to avoid overfitting the model and because this WOMAC subscale is most frequently used for assessing limitations due to knee OA.

Table 1. Baseline characteristics of the study population.

Baseline characteristic / factor	**Total population (N=705)**	**Lost to follow-up (N=38)**	P-value
Demographics block			
Age (years)	56.0 ± 5.1	56.0 ± 5.6	0.97
Sex (% female)	81 %	89 %	0.19
Body Mass Index (kg/m^2)	26.5 ± 4.3	27.0 ± 3.3	0.43
Baseline NRS in the past week	3.7 ± 2.1	3.6 ± 2.0	0.23
WOMAC subscales score			
Physical function	24.8 ± 17.0	28.2 ± 20.8	0.25
Kellgren & Lawrence grade			
Distribution, % knees with grade 0/1	58/42	60/40	0.92
TKA after 5 years follow-up (total no.)	14	-	

Values are: mean values ± the standard deviation or percentages %
NRS: Numeric Rating Scale for pain, WOMAC: Western Ontario and McMaster osteoarthritis index, TKA: Total Knee Arthroplasty.
Differences in distribution between groups assessed with ANOVA or Pearson's χ^2 test when appropriate

Outcome variable

The most optimal and clinically relevant model retrieved by LCGA was a quadratic 6-group model (low BIC 18210 with best entropy indices 0.78, P-value 0.53). The quadratic 5-group model had BIC 18237, entropy 0.75 and LRT P-value <0.05; the 7-group model BIC 18205, entropy 0.76 and LRT P-value >0.05. Although the P-value from the 6-group LRT was >0,05, the model uncovered and distinguished sufficiently large groups of participants with distinct trajectories, which is highly informative and clinically relevant to both GPs and patients. **Figure 1** shows detailed depictions of the individual trajectories, with average fitted lines of these 6 pain trajectories shown in **Figure 2**. The figures show groups with different types of pain trajectories: constant mild pain (group

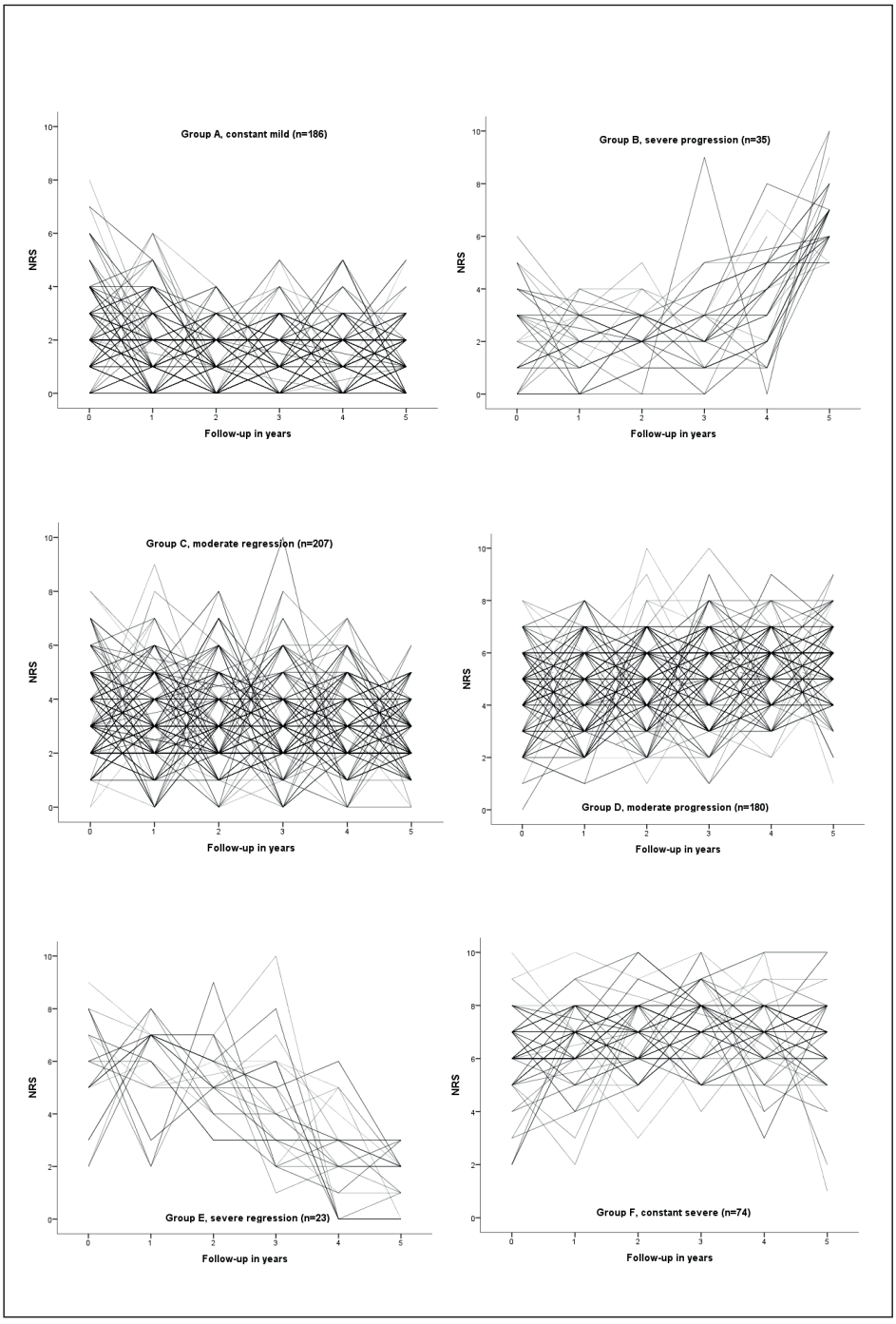

Figure 1. Detailed depictions of the pain trajectories per individual obtained by LCGA.

A, N=186), moderate pain regression (group C, N=207), major pain regression (group E, N=23), severe pain progression (group B, N=35), moderate pain progression (group D, N=180) and constant severe pain (group F, N=74).

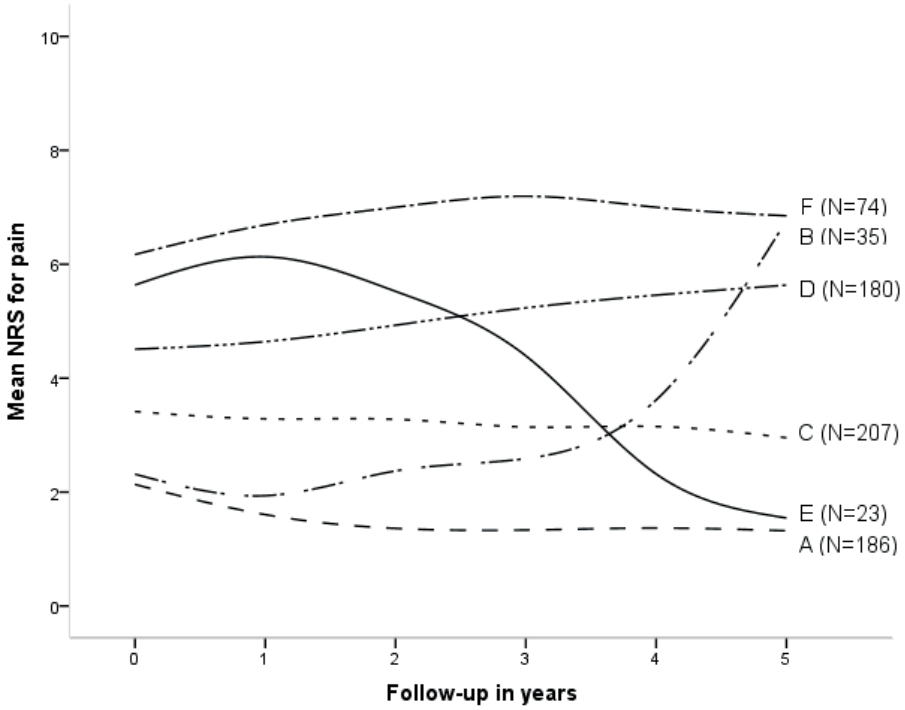

Figure 2. Average fitted lines of the pain trajectories retrieved by LCGA.

Multinomial logistic regression analyses

The mean of all characteristics per pain trajectory group are presented in **Table 2**. Variables with P-value <0.10 from the univariate analyses have been made bold. Statistically significant differences were found for various demographic and anamnestic features, including baseline pain and use of pain coping strategies. There were no significant differences in baseline radiographic severity scores.

The results from the final multivariable model are shown in **Table 3** (Nagelkerke R^2 = 0.42). The mildest trajectory group (group A) was set as the reference group. Compared to this group, participants with a higher BMI, lower education, more co morbidity, higher WOMAC physical function score and knee joint space tenderness had increased risks for pain trajectories characterized by greater pain.

Table 2. Characteristics of the 6 pain trajectories retrieved by LCGA depicted in Figure 1.

Pain trajectory groups	**A (constant mild pain)**	**C (moderate regression)**	**E (major regression)**	**B (severe progression)**	**D (moderate progression)**	**F (constant severe)**
	n=186	**n=207**	**n=23**	**n=35**	**n=180**	**n=74**
Baseline characteristic / factor						
Age (years)	56 ± 0.4	56 ± 0.4	57 ± 1.1	55 ± 0.9	56 ± 0.4	56 ± 0.5
Sex (% female)	80 %	79 %	83 %	80 %	83 %	85 %
Body Mass Index (kg/m^2) §	25 ± 0.3	26 ± 0.3	25 ± 0.8	26 ± 0.8	27 ± 0.3	28 ± 0.6
Highest achieved education level §						
Primary or secondary school	62 %	77 %	68 %	83 %	83 %	83 %
University / college	38 %	23 %	32 %	17 %	17 %	17 %
Ethnicity (% Caucasian versus other)	99 %	98 %	100 %	97 %	97 %	92 %
Participants with > 1 co morbidities §	32 %	48 %	59 %	57 %	49 %	69 %
NRS in the past week §	2.1 (1.0-3.0)	3.4 (2.0-4.0)	5.6 (5.0-7.0)	2.3 (1.0-3.0)	4.5 (4.0-6.0)	6.2 (5.0-7.0)
NRS at moment of questionnaire §	1.7 (1.0-2.0)	2.9 (2.0-4.0)	4.5 (3.0-6.0)	2.1 (1.0-3.0)	4.0 (3.0-5.0)	5.9 (5.0-7.0)
Pain-coping inventory subscales score						
Pain transformation §	2.0 (1.5-2.5)	2.1 (1.8-2.5)	2.4 (1.9-3.0)	2.2 (1.5-2.8)	2.3 (1.8-2.8)	2.4 (2.0-2.8)
Distraction §	2.1 (1.6-2.6)	2.2 (1.8-2.6)	2.2 (1.8-2.7)	2.3 (1.6-3.0)	2.3 (1.8-2.6)	2.5 (2.2-2.8)
Reducing demands §	1.9 (1.7-2.3)	2.0 (1.7-2.7)	2.3 (2.0-2.8)	1.9 (1.7-2.0)	2.0 (1.7-2.7)	2.3 (2.0-2.7)
Retreating §	1.5 (1.1-1.9)	1.6 (1.1-1.9)	1.7 (1.1-2.0)	1.5 (1.1-1.9)	1.5 (1.1-1.7)	1.7 (1.3-2.0)
Worrying §	1.4 (1.2-1.7)	1.5 (1.2-1.8)	1.7 (1.4-1.9)	1.6 (1.3-1.9)	1.6 (1.3-1.9)	1.8 (1.4-2.1)
Resting §	1.7 (1.4-2.0)	1.8 (1.4-2.0)	2.0 (1.6-2.3)	1.7 (1.4-1.8)	1.9 (1.6-2.2)	2.1 (1.6-2.6)
WOMAC subscales score						
Pain §	15 (5-20)	24 (10-33)	39 (25-55)	19 (10-30)	33 (25-40)	46 (25-60)
Joint stiffness §	24 (13-38)	34 (25-50)	48 (38-63)	24 (13-38)	42 (25-50)	53 (38-63)

Table 2. Characteristics of the 6 pain trajectories retrieved by LCGA depicted in Figure 1. (*continued*)

Pain trajectory groups	A (constant mild pain)	C (moderate regression)	E (major regression)	B (severe progression)	D (moderate progression)	F (constant severe)
Physical function §	14 (6-21)	23 (11-31)	37 (26-49)	16 (6-21)	31 (19-41)	45 (33-58)
Use of pain medication (% yes)	36 %	38 %	26 %	35 %	39 %	44 %
Do you drink alcohol (% yes)	78 %	78 %	91 %	74 %	76 %	63 %
Smoker or previous smoker (% yes)	11 %	12 %	18 %	14 %	16 %	18 %
Additional supplements or vitamin intake (% yes)	54 %	52 %	46 %	51 %	52 %	57 %
Pain in the ipsilateral hip §	28 %	42 %	74 %	31 %	49 %	51 %
Morning stiffness knees < 30 min §	64 %	67 %	61 %	59 %	76 %	80 %
Palpable warmth knee	6 %	6 %	9 %	0 %	6 %	4 %
Joint space tenderness knee §	36 %	51 %	52 %	61 %	70 %	68 %
Bony enlargement knee	4 %	4 %	0 %	9 %	6 %	4 %
Crepitus during flexion knee	53 %	56 %	43 %	51 %	50 %	57 %
Positive re-fill test knee	10 %	9 %	9 %	3 %	9 %	6 %
ROM flexion knee (°)	135 ± 1	134 ± 1	134 ± 2	132 ± 2	134 ± 1	131 ± 2
ROM extension knee (°)	3 ± 0	3 ± 0	3 ± 0	3 ± 0	3 ± 0	3 ± 0
Pain during active flexion knee §	32 %	33 %	13 %	32 %	39 %	46 %
Pain during active extension knee	12 %	21 %	18 %	12 %	24 %	29 %
Pain during active internal rotation ipsilateral hip §	20 %	28 %	55 %	25 %	39 %	46 %
Bouchard swelling digit. 2-5 left or right	18 %	19 %	17 %	20 %	19 %	24 %
Heberden node digit. 2-5 left or right	48 %	50 %	44 %	31 %	47 %	58 %
Erythrocyte sedimentation rate (mm/hr)	9.7 ± 0.6	9.4 ± 0.5	12.5 ± 2.3	9.9 ± 1.3	10.9 ± 0.6	12.3 ± 1.1
Kellgren & Lawrence grade						
Distribution, % knees with grade 0/1	57/43	63/37	70/30	56/44	55/45	49/51
Kellgren & Lawrence score ipsilateral hip						

Table 2. Characteristics of the 6 pain trajectories retrieved by LCGA depicted in Figure 1. (*continued*)

Pain trajectory groups	A (constant mild pain)	C (moderate regression)	E (major regression)	B (severe progression)	D (moderate progression)	F (constant severe)
Distribution, % hips with grade 0/1	81/19	75/25	70/30	85/15	80/20	79/21
TKA after 5 years follow-up (total no.)	1	2	0	0	8	3

Values are: mean values ± the standard deviation; mean (interquartile range); or percentages %

NRS: Numeric Rating Scale, WOMAC: Western Ontario and McMaster osteoarthritis index, ROM: Range Of Motion, TKA: Total Knee Arthroplasty.

Bold indicates P-value < 0.10 from the univariate multinomial regression analyses.

§ P-value <0.05 from the univariate multinomial regression analyses.

Table 3. Multivariable model. Relative risk ratios for belonging in each trajectory relative to reference trajectory (constant mild, group A) (n=186).

Pain trajectory groups	**C (moderate regression)**	**E (major regression)**	**B (severe progression)**	**D (moderate progression)**	**F (constant severe)**
	n=207	**n=23**	**n=35**	**n=180**	**n=74**
Baseline characteristic / factor					
Body mass index (kg/m^2)	1.06 (1.00-1.13)	0.96 (0.85-1.10)	1.07 (0.96-1.19)	**1.09 (1.02-1.16)**	**1.10 (1.01-1.20)**
Highest achieved education level					
Primary or secondary school	ref.	ref.	ref.	ref.	ref.
University / college	**0.53 (0.32-0.87)**	0.83 (0.27-2.51)	**0.33 (0.16-0.95)**	**0.44 (0.24-0.80)**	0.55 (023.-1.31)
> 1 co morbidities	**1.75 (1.10-2.77)**	1.37 (0.48-3.85)	**2.87 (1.23-6.67)**	1.23 (0.74-2.08)	**2.65 (1.25-6.99)**
WOMAC Physical Function subscale §	**1.04 (1.02-1.06)**	**1.13 (1.09-1.17)**	1.01 (0.98-1.05)	**1.09 (1.07-1.12)**	**1.14 (1.11-1.18)**
Joint space tenderness knee	**1.70 (1.07-2.69)**	2.13 (0.76-6.02)	**2.84 (1.21-6.67)**	**3.86 (2.28-6.62)**	2.03 (0.96-4.33)
Painful flexion knee	0.91 (0.56-1.49)	**0.14 (0.03-0.69)**	0.90 (0.37-2.19)	0.77 (0.44-1.33)	1.08 (0.51-2.29)

WOMAC: Western Ontario and McMaster osteoarthritis index.
Numbers indicate relative risk ratios (RR) with corresponding 95% confidence intervals in brackets.
Relative risk ratios obtained by multinomial logistic regression, adjusted for age and sex.
§ RR per unit increase. A higher WOMAC score indicates more limitations due to physical health.
Nagelkerke $R^2 = 0.42$ for the model.
Bold indicates $P<0.05$.

DISCUSSION

Summary

In this study six pain trajectories were uncovered over 5 years' follow-up in individuals with early symptomatic knee OA in a primary care setting. A substantial group (group A) of 186 participants (26% of the study population) that had a mild pain trajectory was identified. The largest group (group C) comprised of 207 participants (29% of the study population) and showed a similar trajectory, however they experienced moderate pain. Nonetheless, 56% of the study population showed a constant mild, or moderate pain trajectory during 5 years. The results from the multivariate analyses indicate that, when compared to the mild pain trajectory group, participants in group B, D and F had a higher BMI, suffered more co morbidity, had lower levels of education, and had joint space tenderness of the knee more often (which was borderline significant in group F).

Noteworthy are the results from group E. Participants from this group reported severe knee pain at baseline; however, joint space tenderness was not statistically significant in multivariate analysis. This group also had the highest percentage of pain in the ipsilateral hip.

Strengths and limitations

The fact that patients in group E had the highest percentage of pain in the ipsilateral hip may suggest that they do not actually have clinical knee OA; instead, they may have referred pain in the knee due to hip OA. The results from group E should therefore be interpreted with caution. The trajectory groups B and E are both relatively small and, as a result, although the findings are informative and noteworthy, they should be interpreted carefully.

A limitation of this study is that, although participants were asked where pain was located, the NRS and WOMAC scales were assessed on the joint with the most severe pain – hence, an individual with both hip and knee symptoms could consequently have a high NRS relating to pain in the hip. It is possible that the NRS, therefore, does not fully correspond with the pain the individual experiences in the knee. Another limitation is that the NRS was only undertaken once annually, whereas an even more frequent NRS assessment would lead to an even more precise estimation of the pain trajectories. A large number of variables in the analyses which could have led to bias were tested in the analyses. To deal with this, however, data reduction methods were used by testing for collinearity and by entering variables based on univariate p-values. Moreover, most included variables in the analyses are part of clinical examination and are assumed to relate to disease severity or overall health.

Comparison with existing literature

Overweight has often been recognized as potent risk factor for incident knee OA.[20] In a recent systematic review, strong evidence for the associations between BMI and clinical progression of knee OA was reported by the authors, which is consistent with the findings presented here.[7] The authors also found strong evidence for the association with co morbidity count,[7] and moderate evidence was found for the association between education level and symptomatic knee OA.[7] In this study a strong association for joint space tenderness, for which the evidence was limited in a systematic review, was found.[7] The findings related to joint space tenderness is consistent with earlier findings described by Altman and colleagues, and underlines the importance of physical examination.[4, 21] What is not included in the criteria by Altman and colleagues is painful knee flexion. Lastly, there were no significant differences in distribution of baseline radiographic knee OA severity which underlines current OA guideline recommendations to refrain from radiography in the early stages of disease.[17-19]

Using LCGA to define pain trajectories in knee OA is a relatively new technique and has only been applied by few authors to date.[22-24] Holla and colleagues applied this technique on the same study population (CHECK), but used WOMAC physical function as outcome variable.[23] They identified a three group model and found similar associations to our study results. Collins and colleagues applied LCGA on a study population from the Osteoarthritis Initiative (OAI) and used WOMAC pain, identifying 5 trajectories.[22] They suggest knee OA is characterized by persistent, rather than severe inevitable progression, which is in contrast to our findings. However, in a previous study comparing CHECK to OAI, the authors conclude that CHECK expectedly represents participants in an earlier stage of OA compared to OAI.[11] Nicholls and colleagues applied LCGA on a study population from the Knee Clinical Assessment Study and matched their model with a population drawn from the OAI.[24] They also used WOMAC pain as outcome variable and identified 5 trajectories. They conclude that various types of symptom progression in knee OA exist, varying from severe progression to regression, which is in accordance to our findings, which is in accordance with the findings presented here.

Implications for research and practice

The six distinct pain trajectories presented here can help GPs to differentiate those patients for whom, in accordance to the current guideline recommendations,[17-19] a 'wait-and-see policy' seems justifiable (that is, groups A, C, and E) from those participants who require more specific monitoring in the management of early symptomatic knee OA (that is, groups B, D, and F). For patients with moderate, severe, or progressing pain, it seems justifiable to maintain a pro-active management plan and offer re-assessments of pain and function limitations after at least 1 year. In that way, GPs can better assess which pain trajectory the patient is most likely to follow and can act accordingly – by promoting weight loss, prescribing pain medication, or referring patients for specialist treatment.

The results also show that proper physical examination of the knee is essential in the management of symptomatic knee OA. Those individuals with knee pain who have a higher BMI, are less educated, experience more co morbidity, have a higher WOMAC physical function score and show joint space tenderness should be proactively monitored during the first year of management, as opposed to a 'wait-and-see' approach. Baseline radiographic severity was not associated with the pain trajectories. As a result of these findings, the authors would recommend that GPs who are consulted by patients with early symptomatic knee OA should: assess pain severity, limitations in daily activities and presence of comorbidity; should properly examine the knee (focusing on joint space tenderness); and should refrain from radiographic examination. Future research should be aimed at measuring symptomatic progression of knee OA with even more

frequent symptom assessment to further identify those patients in whom an active monitoring policy from general practice is required.

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Chapter 5

Defining hip pain trajectories in early symptomatic hip osteoarthritis.

Five year results from a nationwide prospective cohort study (CHECK)

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ABSTRACT

Objective To define distinct hip pain trajectories in individuals with early symptomatic hip osteoarthritis (OA) and to determine risk factors for these pain trajectories.

Method Data were obtained from the nationwide prospective Cohort Hip and Cohort Knee (CHECK) study. Participants with hip pain or stiffness and a completed 5-year follow-up were included. Baseline demographic, anamnestic, physical examination characteristics were assessed. Outcome was annually assessed by the Numeric Rating Scale (NRS) for pain. Pain trajectories were retrieved by latent class growth analysis (LCGA). Multinomial logistic regression was used to calculate risk ratios.

Results 545 participants were included. Four distinct pain trajectories were uncovered by LCGA. We found significant differences in baseline characteristics, including body mass index (BMI); symptom severity; pain coping strategies and in criteria for clinical hip OA (American College of Rheumatology (ACR)). Lower education, higher activity limitation scores, frequent use of pain transformation as coping strategy and painful internal hip rotation were more often associated with trajectories characterized by more severe pain. No association was found for baseline radiographic features.

Conclusion We defined four distinct pain trajectories over 5 years follow-up in individuals with early symptomatic hip OA, suggesting there are differences in symptomatic progression of hip OA. Baseline radiographic severity was not associated with the pain trajectories. Future research should be aimed at measuring symptomatic progression of hip OA with even more frequent symptom assessment.

INTRODUCTION

Osteoarthritis (OA) of the hip is a painful and disabling condition. The prevalence and incidence of hip OA are increasing and will continue to increase due to the current aging of the general population[1]. Several studies have been performed to determine predictors for hip OA progression, however only few studies have used pain as a definition of progression[2-4]. Furthermore, consensus is not yet met on the apparent correlation between severity of radiographic hip OA and severity of perceived pain[5]. The latter could imply that there may be differences in risk factors or patient characteristics for both radiographic hip OA progression and pain progression in hip OA. In addition, pain due to hip OA is known to fluctuate and consequently multiple assessments of pain over a longer time period would provide a better indication of the course of pain than one single assessment[4]. This course of pain, or pain trajectory, would consequently be a more accurate representation of clinical disease progression. Physicians, mainly general practitioners (GP), are frequently consulted by patients with suspected hip OA. In most cases, they present themselves in the beginning stages of the disease. Hence the ability to predict pain trajectories in an early stage of the disease could guide the clinician in choosing preventive activities for further pain progression. Therefore, the objective of our study was to define distinct hip pain trajectories in individuals with early symptomatic hip OA and to determine which baseline characteristics are associated with these trajectories. To our knowledge, only one study has previously been published defining pain trajectories in patients with hip OA.[4].

METHOD

Study design and population

The data for the current study were acquired from the Cohort Hip and Cohort Knee (CHECK) study[6]. CHECK is a prospective, 10-year follow-up cohort of 1,002 participants with assumed early symptomatic OA of the knee and/or hip in The Netherlands. The CHECK inclusion period ran from October 2002 until September 2005. Inclusion criteria for the CHECK study were: pain and/or stiffness of the knee and/or hip; age between 45 and 65 years; and never, or less than 6 months prior to recruitment of the study, consulted a physician for these symptoms. Participants were excluded from CHECK if they had other pathological conditions that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome, Baker's cyst); co morbidity that would not allow physical evaluation during 10 years follow-up; malignancy in the past 5 years; and

inability to understand the Dutch language. For the analyses of the current study we included all participants from CHECK who reported hip pain and/or stiffness at baseline. If a participant had two affected hips, we included the hip with the worst score based on pain, Kellgren and Lawrence (KL) score and physical examination findings. The latter included hip pain during internal and external rotation and flexion, and internal and external range of motion (ROM). If all findings were identical in both hips, we arbitrarily included the right hip.

Baseline characteristics

The study included a baseline medical history assessment, physical examination and radiographs of the hip and knee. The medical history was taken through questionnaires in which self-reported data were assessed. The following diseases were assessed as co morbidity: asthma, chronic sinusitis, cardio-vascular disease, high blood pressure, gastric ulcer, gallstones, liver disease, renal disease, diabetes, thyroid gland disease, epilepsy, cancer (during follow-up), severe skin disease, and other chronic musculoskeletal diseases. The Western Ontario and McMaster osteoarthritis index (WOMAC) was used to measure pain, stiffness and physical functioning with a higher score indicating worse health (range 0-100). Pain-coping behavior was assessed with a six scale Pain-Coping Inventory (PCI): pain transformation (i.e. reinterpreting pain); distraction; reducing demands; retreating; worrying; and resting.[6, 7] All six items are scored according to a four-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which strategies are applied when dealing with pain. Clinical hip OA was determined according to the American College of Rheumatology (ACR) criteria, which are: hip pain and all of the following criteria under (1) or (2): (1) hip internal rotation greater than or equal to 15 degrees, pain present on internal rotation of the hip, morning stiffness of the hip for less than or equal to 60 min and age greater than 50 years; (2) hip internal rotation less than 15° and hip flexion less than or equal to 115° .[8]

Radiographs

Standardized weight-bearing anteroposterior (AP) radiographs of the pelvis were made along with a weight-bearing single faux profile (FP) radiograph of the hip.[9] Radiographs were scored for individual OA features according to criteria described by Altman.[10] Radiographic OA severity was defined by the Kellgren & Lawrence (K/L) classification.[11] Superior or medial hip joint space narrowing (JSN), superior or inferior acetabular osteophytes (OP), superior or inferior femoral OP, inferior acetabular OP and femoral subchondral sclerosis were scored as absent or present. On the FP radiographs, superior or posterior JSN was scored as absent (i.e., normal) or present.

Outcome variable

Pain was assessed annually through questionnaires during the 5 years of follow-up using the Numeric Rating Scale (NRS) for pain ranging from 0 to 10, with a higher score indicating more pain. The participants were asked to score the pain they experienced in their most painful joint over the last week. Using latent class growth analysis (LCGA) pain trajectories based on the annually assessed NRS were identified (see Statistical analysis), blinded to all other characteristics. If participants underwent hip replacement surgery (HRS) during follow-up, their pain scores were scored as missing from the moment of surgery. If a participant missed more than two pain assessments, he or she was excluded from the analyses.

Statistical analysis

LCGA was used to identify the different pain trajectory groups. LCGA is a technique that uncovers heterogeneity in a population and makes it possible to distinguish groups of people who are similar in their growth trajectories longitudinally. It was 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 clinical relevance (i.e. are the mean pain scores of the trajectories clinically distinguishable), indices of fit and the interpretability of the model (i.e. are the uncovered groups each sufficiently large for further statistical analyses). The following indices of fit used were: Bayesian Information Criterion (BIC); Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRT) and the bootstrap LRT; and entropy indices.

Baseline characteristics were calculated per obtained pain trajectory group using descriptive statistics. After checking for collinearity setting the cut-off value for Pearson's correlation coefficient (R) at 0.70, we performed univariable multinomial logistic regression analyses to test whether differences were statistically different and to obtain crude risk estimates, setting the group with the mildest pain trajectory as the reference group. All variables from the univariable analyses with $p<0.10$ were ultimately included in a final multivariable multinomial logistic regression model (p-removal $p<0.05$), again setting the group with the mildest pain trajectory as the reference group. Risk ratios (RR) and 95% confidence intervals (CI) were obtained for belonging to a trajectory characterized by greater pain compared to the reference group.

The LCGA was performed using *Mplus 6.1 ed 1998-2010*. All other analyses were performed using *SPSS Statistical Package PASW 20.0*.

RESULTS

Baseline characteristics

At baseline, 588 of the 1002 participants reported hip pain and therefore fulfilled our inclusion criteria. 43 (7%) participants missed more than two annual pain assessments or were lost to follow-up. The baseline values of body mass index (BMI), NRS, age, sex and KL of the 43 lost to follow-up did not differ significantly from the study population. The total study population after 5 years therefore consisted of 545 participants The mean age was 55.7 ± 5.2 years and 81% was female. 140 participants (26%) fulfilled the ACR criteria for clinical hip OA. See **Tables 1** and **2** for a detailed description of the study population. The variables 'NRS at the moment of questionnaire' and the 'WOMAC pain subscale' were positively correlated (R>0.70) and were excluded from the multivariable analyses. There were no other strong correlations. After 5 years follow-up 38 study participants (7%) had undergone HRS.

Table 1. Baseline characteristics of the study population.

Baseline characteristic / factor	Total population (N=545)	Lost to follow-up (N=43)	*p-value*
Demographics block			
Age (years)	55.7 ± 5.2	56.6 ± 6.4	0.29
Sex (% female)	81 %	81 %	0.92
Body Mass Index (kg/m^2)	26.2 ± 4.2	25.4 ± 3.6	0.24
Baseline NRS in the past week	3.7 ± 2.1	3.7 ± 2.0	0.99
WOMAC subscales score			
Pain	27.2 ± 17.0	27.4 ± 17.9	0.93
Joint stiffness	34.7 ± 20.8	36.6 ± 25.8	0.56
Physical function	25.3 ± 17.5	25.5 ± 19.7	0.96
Clinical hip OA §	26 %	23 %	0.73
Kellgren & Lawrence grade			
Distribution, % hips with grade 0/1	67/33	100/0	0.06
THA after 5 years follow-up (total no.)	38 (7%)	-	-

Values are: mean values ± the standard deviation or percentages %
NRS: Numeric Rating Scale for pain, THA: Total Hip Arthroplasty.
Differences in distribution between groups assessed with ANOVA or Pearson's χ^2 test when appropriate.
§ According to the ACR criteria for clinical hip OA.[8]

Table 2. Baseline characteristics of the four pain trajectory groups retrieved by LCGA.

Pain trajectory groups	A (mild pain)	B (moderate decrease)	C (moderate progression)	D (severe pain)
	N=231	N=94	N=132	N=88
Baseline characteristic / factor				
Age (years)	56 ± 5	56 ± 6	55 ± 6	56 ± 5
Sex (% female)	77 %	86 %	81 %	84 %
Body Mass Index (kg/m^2)	25 ± 4	26 ± 4	27 ± 5	27 ± 5
Highest achieved education level				
Primary or secondary school	67 %	79 %	82 %	78 %
University / college	33 %	21 %	18 %	22 %
Ethnicity (% Caucasian versus other)	100 %	98 %	98 %	97 %
Participants with > 1 co morbidity	38 %	54 %	59 %	66 %
Baseline NRS at moment of questionnaire	1.9 (1.0-3.0)	4.3 (3.0-5.0)	3.1 (2.0-4.0)	5.7 (5.0-7.0)
Baseline NRS in the past week	2.2 (1.0-3.0)	5.5 (4.0-7.0)	3.4 (2.0-5.0)	6.1 (5.0-7.0)
Pain-coping inventory subscales score				
Pain transformation	2.0 (1.5-2.5)	2.3 (1.8-2.8)	2.3 (1.8-2.8)	2.5 (2.0-3.0)
Distraction	2.1 (1.6-2.6)	2.3 (1.8-2.6)	2.3 (1.8-2.6)	2.5 (2.2-2.9)
Reducing demands	1.9 (1.7-2.0)	2.1 (1.7-2.7)	2.0 (1.7-2.3)	2.2 (1.7-2.7)
Retreating	1.5 (1.1-1.9)	1.5 (1.1-1.9)	1.5 (1.1-1.7)	1.6 (1.3-1.9)
Worrying	1.5 (1.2-1.7)	1.6 (1.3-1.9)	1.5 (1.2-1.8)	1.8 (1.4-2.1)
Resting	1.7 (1.4-2.0)	1.9 (1.6-2.4)	1.9 (1.6-2.6)	2.1 (1.6-2.6)
WOMAC subscales score				
Pain	17 (8.8-25)	40 (25-45)	37 (20-40)	51 (30-55)
Joint stiffness	25 (13-38)	44 (25-50)	51 (25-50)	54 (38-63)
Physical function	15 (5.9-21)	30 (19-40)	27 (15-37)	44 (31-56)
Use of pain medication (% yes)	41 %	40 %	34 %	40 %
≤ 2 times/week physical activity ≥ 0.5 hrs/day	61 %	54 %	56 %	44 %
Do you drink alcohol (% yes)	82 %	77 %	76 %	73 %
Smoker, or previous smoker (% yes)	12 %	15 %	12 %	22 %
Additional supplements or vitamins (% yes)	58 %	51 %	53 %	55 %
Knee pain ipsilateral knee	52 %	64 %	68 %	68 %
Morning stiffness of the hips < 60 min	48 %	50 %	65 %	66 %
Pain internal hip rotation	44 %	50 %	59 %	69 %
Pain external hip rotation	22 %	23 %	42 %	43 %
Pain flexion hip	42 %	48 %	58 %	64 %
Pain adduction hip	25 %	34 %	43 %	58 %
Pain abduction hip	34 %	31 %	49 %	64 %
ROM internal hip rotation hip (°)	30 ± 9	30 ± 10	28 ± 9	27 ± 9
ROM external hip rotation (°)	28 ± 8	27 ± 9	27 ± 9	27 ± 10
ROM flexion hip (°)	120 ± 11	117 ± 11	114 ± 11	113 ± 12

Table 2. Baseline characteristics of the four pain trajectory groups retrieved by LCGA. (*continued*)

Pain trajectory groups	A (mild pain)	B (moderate decrease)	C (moderate progression)	D (severe pain)
Pain flexion ipsilateral knee	15 %	12 %	27 %	28 %
Bouchard swelling digitorum 2-5 left/right	19 %	28 %	19 %	28 %
Heberden node digitorum 2-5 left/right	49 %	53 %	50 %	53 %
Clinical hip OA §	21 %	21 %	29 %	38 %
Kellgren & Lawrence grade hip				
% hips with grade 0/1	65/35	76/27	64/36	63/37
JSN score > 0 (AP) hip	38 %	25 %	38%	45 %
JSN score > 0 (FP) hip	20 %	11 %	14 %	22 %
Osteophyte score > 0 hip	41 %	33 %	48 %	38 %
THA after 5 years follow-up (absolute no.)	9	10	4	15

Values are: mean values ± the standard deviation; mean (interquartile range); or percentages %.
NRS: Numeric Rating Scale, WOMAC: Western Ontario and McMaster osteoarthritis index, ROM: Range Of Motion, JSN: Joint Space Narrowing, AP: Anterior Posterior view; FP: Faux Profile; THA: Total Hip Arthroplasty.
Differences in distribution between groups assessed with multinomial logistic regression analysis setting the group with mildest pain trajectory as the reference group.
Bold indicates p-value <0.10 from the univariable multinomial logistic regression analyses. All variables made bold also had p-value <0.05.
§ According to the ACR criteria for clinical hip OA.[8]

Outcome variable

The most optimal and clinically relevant model retrieved by LCGA was a quadratic four-group model (lower BIC 12360 with best entropy indices 0.74 and LRT p-value <0.05). The quadratic three-group model had BIC 12412, entropy 0.75 but LRT p-value >0.05; the five-group model BIC 12340, entropy 0.70 and LRT p-value >0.05. The model uncovered sufficiently large groups of participants with extreme trajectories, which were considered highly informative and clinically relevant: group A (n=231) showed a constant mild pain trajectory during follow-up; group B (n=94) showed moderate pain and moderate pain regression during follow-up; group C (n=132) also showed moderate pain, but showed pain progression; and group D (n=88) showed a constant severe pain trajectory. Detailed depictions of the individual trajectories are presented in **Figure 1**. Average fitted lines of these four pain trajectories are depicted in **Figure 2**.

Multinomial logistic regression analyses

The means of all baseline characteristics per pain trajectory group are presented in **Table 2**. Variables with p-value <0.10 from the univariable analyses have been made bold, however all of these variables also had p-value <0.05. Statistically significant differences were found for various demographic and anamnestic features, including baseline pain and function severity scores, use of pain coping strategies, clinical findings for the hip and in fulfilling criteria for clinical hip OA. Distribution of JSN on the AP view

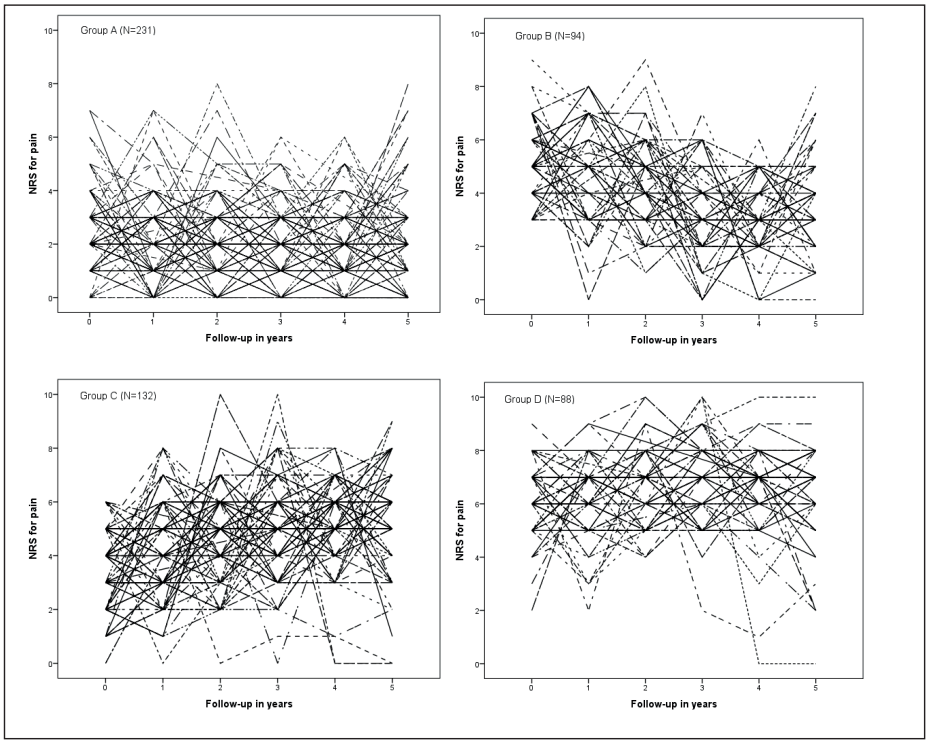

Figure 1. Detailed depictions of the pain trajectories of the four group model obtained by LCGA.

differed significantly amongst the groups. No other significant differences in baseline radiographic severity scores were found. The crude risk estimates from the univariable multinomial regression analyses are presented in **Table 3**.

The results from the final multivariable model are shown in **Table 4** (Nagelkerke R^2 = 0.41). The trajectory group with the mildest trajectory (group A) was set as the reference group. Baseline education level, WOMAC physical function, frequent use of coping strategy pain transformation and painful internal hip rotation showed significant associations.

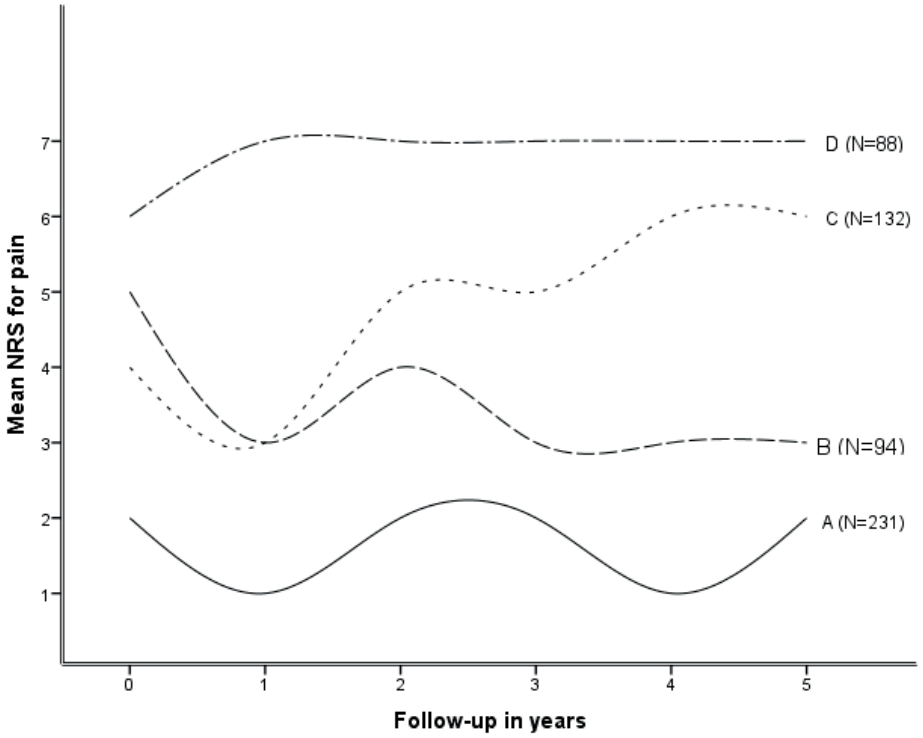

Figure 2. Average fitted lines of the pain trajectories obtained by LCGA as depicted in figure 1.

Table 3. Univariable crude risk estimates. Risk ratios for belonging in each trajectory relative to reference trajectory (mild, group A) (N=231).

Pain trajectory groups	B (moderate decrease) N=94	C (moderate progression) N=132	D (severe pain) N=88
Baseline characteristic / factor			
Age (years) ∫	1.02 (0.97-1.04)	1.00 (0.95-1.04)	1.04 (0.99-1.09)
Sex (% female)	1.86 (0.96-3.60)	1.27 (0.74-2.17)	1.57 (0.82-3.01)
Body Mass Index (kg/m^2) ∫	**1.07 (1.00-1.14)**	**1.10 (1.04-1.16)**	**1.12 (1.05-1.19)**
Highest achieved education level			
University / college	ref.	ref.	ref.
Primary or secondary school	**2.07 (1.17-3.64)**	**2.03 (1.24-3.32)**	**4.42 (2.17-9.02)**
Ethnicity (% Caucasian versus other)	5.00 (0.45-55.6)	5.38 (0.55-52.6)	8.13 (0.83-76.9)
Participants with > 1 co morbidity	**3.16 (1.89-5.32)**	**2.42 (1.56-3.77)**	**1.94 (1.19-3.16)**
Baseline NRS at moment of questionnaire ∫	**2.57 (2.13-3.10)**	**1.66 (1.43-1.93)**	**4.45 (3.47-5.72)**
Pain-coping inventory subscales score ∫			
Pain transformation	**1.65 (1.07-2.54)**	**1.84 (1.25-2.70)**	**2.23 (1.38-3.59)**

Table 3. Univariable crude risk estimates. Risk ratios for belonging in each trajectory relative to reference trajectory (mild, group A) (N=231). (*continued*)

Pain trajectory groups	B (moderate decrease)	C (moderate progression)	D (severe pain)
Distraction	**1.51 (1.02-2.23)**	**1.42 (1.00-2.01)**	**2.18 (1.44-3.31)**
Reducing demands	**1.58 (1.05-2.37)**	1.36 (0.94-1.96)	**2.08 (1.37-3.14)**
Retreating	0.59 (0.30-1.13)	**0.42 (0.23-0.77)**	**0.36 (0.18-0.74)**
Worrying	**2.62 (1.24-5.54)**	1.68 (0.83-3.40)	**7.17 (3.28-15.7)**
Resting	1.87 (0.97-3.63)	**2.59 (1.42-4.72)**	**3.36 (1.67-6.76)**
WOMAC subscales score ∫			
Pain	**1.09 (1.07-1.11)**	**1.07 (1.05-1.09)**	**1.14 (1.11-1.17)**
Joint stiffness	**1.04 (1.03-1.06)**	**1.04 (1.02-1.05)**	**1.07 (1.06-1.09)**
Physical function	**1.08 (1.06-1.11)**	**1.07 (1.05-1.09)**	**1.15 (1.12-1.17)**
Use of pain medication (% yes)	1.04 (0.64-1.71)	1.35 (0.86-2.12)	1.02 (0.62-1.70)
≤ 2 times/week physical activity ≥ 0.5 hrs/day	1.28 (0.79-2.10)	1.19 (0.77-1.85)	**1.98 (1.20-3.29)**
Do you drink alcohol (% yes)	1.38 (0.76-2.51)	1.46 (0.86-2.49)	1.70 (0.95-3.07)
Smoker, or previous smoker (% yes)	1.31 (0.65-2.63)	1.02 (0.53-1.98)	**2.07 (1.08-3.95)**
Additional supplements or vitamins (% yes)	0.74 (0.45-1.20)	0.82 (0.53-1.26)	0.89 (0.54-1.47)
Knee pain ipsilateral knee	1.65 (1.00-2.72)	**1.96 (1.24-3.09)**	**1.98 (1.16-3.39)**
Morning stiffness of the hips < 60 min	1.10 (0.68-1.79)	**2.08 (1.33-3.25)**	**2.16 (1.29-3.62)**
Pain internal hip rotation	1.18 (0.74-1.88)	**1.88 (1.22-2.92)**	**2.69 (1.60-4.50)**
Pain external hip rotation	1.27 (0.66-2.43)	**2.87 (1.69-4.85)**	**2.72 (1.49-4.98)**
Pain flexion hip	1.30 (0.80-4.01)	**1.90 (1.23-2.93)**	**2.40 (1.44-4.02)**
Pain adduction hip	1.63 (0.90-2.96)	**2.20 (1.31-3.70)**	**4.39 (2.42-7.94)**
Pain abduction hip	0.88 (0.49-1.57)	**1.91 (1.18-3.11)**	**3.37 (1.89-6.02)**
ROM internal hip rotation hip (°)	1.01 (0.98-1.03)	**0.98 (0.95-1.00)**	**0.97 (0.95-1.00)**
ROM external hip rotation (°)	1.00 (0.97-1.04)	0.99 (0.96-1.03)	0.99 (0.95-1.02)
ROM flexion hip (°)	0.97 (0.95-0.99)	0.95 (0.93-0.97)	0.95 (0.93-0.97)
Pain flexion ipsilateral knee	0.72 (0.35-1.49)	**2.02 (1.20-3.40)**	**2.18 (1.20-3.94)**
Bouchard swelling digitorum 2-5 left/right	0.64 (0.36-1.12)	1.04 (0.60-1.81)	0.62 (0.35-1.1)
Heberden node digitorum 2-5 left/right	0.86 (0.53-1.39)	0.97 (0.63-1.50)	0.84 (0.51-1.37)
Clinical hip OA §	1.00 (0.56-1.81)	1.50 (0.92-2.46)	**2.23 (1.31-3.80)**
Kellgren & Lawrence grade hip			
% hips with grade 0/1	0.61 (0.36-1.07)	1.09 (0.68-1.75)	1.10 (0.63-1.92)
JSN score > 0 (AP) hip	**1.78 (1.02-3.11)**	0.99 (0.62-1.57)	0.70 (0.41-1.21)
JSN score > 0 (FP) hip	2.14 (0.99-4.62)	1.54 (0.83-2.89)	0.91 (0.48-1.74)
Osteophyte score > 0 hip	1.39 (0.82-2.36)	0.76 (0.48-1.20)	1.13 (0.65-1.98)

NRS: Numeric Rating Scale, WOMAC: Western Ontario and McMaster osteoarthritis index, ROM: Range Of Motion, JSN: Joint Space Narrowing, AP: Anterior Posterior view; FP: Faux Profile; THA: Total Hip Arthroplasty.
Numbers indicate risk ratios with corresponding 95% confidence intervals in brackets.
Risk ratios obtained by multinomial logistic regression.
§ According to the ACR criteria for clinical hip OA.[8]
∫ RR per unit increase.
Bold indicates p<0.05.

Table 4. Multivariable model. Risk ratios for belonging in each trajectory relative to reference trajectory (mild, group A) (N=231).

Pain trajectory groups	B (moderate decrease) N=94	C (moderate progression) N=132	D (severe) N=88
Baseline characteristic / factor			
Highest achieved education level			
University / college	ref.	ref.	ref.
Primary or secondary school	1.59 (0.86-2.95)	**1.75 (1.00-3.06)**	**3.35 (1.37-8.20)**
PCI subscale pain transformation ∫	1.51 (0.99-2.30)	**1.47 (1.00-2.16)**	**1.89 (1.13-3.17)**
WOMAC Physical Function subscale †	**1.07 (1.06-1.10)**	**1.06 (1.04-1.08)**	**1.14 (1.11-1.17)**
Painful internal rotation hip	1.16 (0.67-2.00)	**1.78 (1.08-2.92)**	**2.57 (1.29-5.13)**

PCI: Pain-Coping Inventory, WOMAC: Western Ontario and McMaster osteoarthritis index.
Numbers indicate risk ratios with corresponding 95% confidence intervals in brackets.
Risk ratios obtained by multinomial logistic regression.
∫ RR per unit increase. A higher score indicates more frequent usage of pain transformation.
† RR per unit increase. A higher WOMAC score indicates more limitations due to physical health.
Nagelkerke $R^2 = 0.41$ for the model.
Bold indicates $p<0.05$.

DISCUSSION

This study is one of the first to uncover distinct pain trajectories over 5 years follow-up in individuals with early symptomatic hip OA. We identified a substantial group (group A) of 231 participants (42% of the study population) with a constant mild pain trajectory. Another group (group B) comprised of 94 participants (17% of the study population) and showed a moderate pain trajectory. Thus, 60% of our study population showed a constant mild, or moderate pain trajectory during 5 years follow-up. It therefore seems justifiable to maintain a wait-and-see policy for participants from these trajectory groups in managing their disease. It seems more important to identify participants with pain trajectories characterized by greater pain and/or pain progression, i.e. groups C and D. The results from the multivariable analyses indicate that these participants had a lower education, higher activity limitation scores, frequent use of the pain coping strategy pain transformation and painful internal hip rotation more often were associated with trajectories characterized by greater pain compared to the mild pain trajectory group. No association was found for baseline radiographic features in multivariable analyses. Noteworthy is group B with a moderate decrease pain trajectory. At baseline, these participants had higher pain scores, however no other variables, including painful internal hip rotation, from the multivariable analyses showed associations. This implies that clinicians should re-assess patients within the first year of follow-up whom initially have hip pain, but have no painful internal hip rotation during physical examination, to better establish which pain trajectory the patient is likely to be in. Baseline differences were

also found between the trajectory groups in BMI, co morbidity count, symptom severity, use of pain coping strategies, morning stiffness of the hip <60 min, painful movement of the hip during examination, fulfilling the ACR criteria for clinical hip OA and JSN on the AP radiograph.

Previous studies have not found strong, significant associations between BMI and clinical or radiographic hip OA progression.[12, 13] Frequent usage of the pain coping strategy pain transformation, an active pain coping strategy which reflects a patient's effort to reinterpret and transform the pain, had a significant association with the pain trajectories.[7] It is important for patients to have proper knowledge of their condition and its prognosis. Only then will they be able to learn to optimally manage and cope with their conditions.[14] The ACR, the Osteoarthritis Research Society International (OARSI) and the National Institute for Health and Clinical Excellence (NICE) all recommend patient education interventions for the treatment of hip OA.[15-17]

In the trajectory groups with greater pain, individuals had significantly more hip pain during active movements of the hip joint. Pain during internal hip rotation proved to have a strong association with these pain trajectories. These findings indicate strong similarities between criteria for symptomatic hip OA progression and diagnostic ACR criteria for hip OA described by Altman et al.[8] In a previous article by Lievense et al, the authors longitudinally studied the prognosis of hip pain in a population similar to ours.[3] They found that baseline painful internal hip rotation significantly contributed to the prediction of HRS after 3 years (OR 3.5), adjusted for factors assessed during history taking and regardless of radiographic hip OA severity. Moreover, their univariable analysis showed a significant association between painful hip adduction and HRS after six years (OR 3.6). They also presented significant associations between hip ROM in all directions and HRS after 3 and 6 years. In our study population, the baseline means of the ROM differed significantly between the trajectory groups. Birrell et al previously reported similar findings.[18] They found that a lower range of internal rotation and range of flexion were significantly associated with an increased hazard of HRS.

To our knowledge, only one other study by Verkleij et al has been published determining pain trajectories in hip OA.[4] The authors defined five distinct pain trajectories in a study population (n=222) with clinically and radiographically defined hip OA according to ACR criteria over a 2 year follow-up period. Main baseline risk factors (in univariable analyses) for trajectories characterized by greater pain compared to the mild pain group were BMI, education level, radiographic severity, morning stiffness and decreased ROM. These findings are very similar to our results, however we found no association for radiographic severity. The latter is likely to be caused by the fact that their study population was in a more advanced stage of the disease at baseline compared to our study population.

One of the limitations to our study is that although patients were asked where the pain was located (knee and/or hip; left and/or right), the NRS and WOMAC scales were assessed on the joint with the most severe pain. Hence, an individual with both hip and knee or bilateral symptoms could have more pain in his or her knee, or contralateral hip and consequently have a high NRS. It is possible that the NRS therefore would not fully correspond with the pain the individual experiences in the included hip. On the other hand, it might be difficult for an individual to score his or her NRS separately for affected joints. Nevertheless, the abovementioned could have led to misclassification bias in our outcome measure. Also for this reason, we decided to apply a person-specific approach in our analyses as opposed to a hip-specific approach. A second limitation to our study is that we used the NRS that was assessed annually during the follow-up period to create the different pain trajectories; however an even more frequent NRS assessment would lead to an even more precise estimation of the pain trajectories. Thirdly, we excluded participants from the analyses if they missed more than two pain assessments, which could have led informative censoring. Fourthly, we included all participants with hip pain due to early symptomatic hip OA at baseline, however only 26% of these individuals actually fulfilled the ACR criteria for hip OA at baseline. Performing our analyses only on participants fulfilling the ACR criteria would have made our study population too small. Nevertheless, an important part of the participants in our study suffered from an aggravation of hip pain symptoms making them a clinically relevant group for follow-up. Lastly, we tested a relatively large number of variables in the analysis which could have lead to a type I error. Most variables in the analysis however are all part of the standard clinical examination and are assumed to relate to disease severity or overall health. In addition we used data reduction methods, testing for co-linearity, and by entering variables based on univariable p-values.

In conclusion, we defined four distinct pain trajectories over 5 years follow-up in individuals with early symptomatic hip OA. Individuals whom are less educated, have higher activity limitation scores, use the pain coping strategy pain transformation frequently and have painful internal hip rotation have an increased risk for being in a trajectory with more severe pain. Moreover, individuals whom were at risk for pain progression showed differences in pain coping strategies, more often had morning stiffness of the hip at baseline, and fulfilled existing criteria for clinical hip OA during physical examination. Baseline radiographic severity was not associated with the pain trajectories. We would like to emphasize that radiography does not provide benefit over clinical diagnosis of early symptomatic hip OA. Also, the majority of the study population (58%, groups A and B combined) had a relatively mild pain trajectory throughout the entire follow-up period, which endorses current recommendations in OA guidelines for conservative treatment in the early stages of the disease. Re-assessment of clinical symptoms due to hip OA should take place within the first year of follow-up. Future research should

be aimed at measuring symptomatic progression of hip OA with even more frequent symptom assessment.

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Chapter 6

Characteristics associated with joint replacement in early symptomatic knee or hip osteoarthritis

Six year results from a nationwide prospective cohort study (CHECK)

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ABSTRACT

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

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

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

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

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

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

INTRODUCTION

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

METHOD

Study design and population

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

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

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

Baseline characteristics

The CHECK study included a baseline medical history, physical examination and radiographs of the knees and hips, which formed the different variables.[6] The medical history was taken through questionnaires with which participant specific self-reported data were assessed. The following diseases were considered as co morbidities: asthma, chronic sinusitis, cardio-vascular disease, high blood pressure, gastric ulcer, gallstones, liver disease, renal disease, diabetes, thyroid gland disease, epilepsy, cancer, severe skin disease, and other chronic musculoskeletal diseases. Symptom severity was assessed by the Numeric Rating Scale (NRS, range 0-10) and the Western Ontario and McMaster osteoarthritis index (WOMAC) for pain, stiffness and physical functioning (range 0-100, with a higher score indicating worse health).[6] To assess pain-coping behaviour, a six scale Pain-Coping Inventory (PCI) was used: pain transformation; distraction; reducing demands; retreating; worrying; and resting. All six scales (33 items) were scored according to a four-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which strategies are applied when dealing with pain.[7] Physical examination of the joints was based on the clinical criteria for knee and hip OA.[8, 9] Regarding the knee this encompassed range of motion (ROM) of knee flexion and extension measured in degrees with a goniometer, palpable warmth, crepitus, joint space tenderness, bony enlargements, effusion and painful ROM. The hip examination included ROM of hip internal and external rotation, measured in degrees with a goniometer and painful ROM.

Radiographs

Radiographs were read paired and in sequence, but with the observers blinded to all other patient characteristics.[10] Standardized radiographs of the tibiofemoral joints were made by a weight-bearing posteroanterior (PA) view, semi-flexed (7-10°) according to Buckland-Wright[6, 11] and standardized weight-bearing anteroposterior (AP) radiographs of the pelvis were made along with a weight-bearing single faux profile (FP) radiograph of the hip.[6, 12] Radiographs were scored for individual OA features according to criteria described by Altman.[13] Radiographic OA severity was defined by the Kellgren & Lawrence (K/L) classification.[14] With regards to the knee, baseline medial or lateral joint

space narrowing (JSN), femoral medial or lateral osteophytes (OP), and tibial medial or lateral OP were initially scored on a 4 point scale (0 = normal; 1 = mild; 2 = moderate; and 3 = severe). However, in the present study we have dichotomized these variables into absent (score 0) and present (score 1-3). In addition, medial or lateral tibial bone attrition, and medial or lateral tibial or femoral sclerosis were scored as absent or present. Presence of spiking of the tibial spines was scored according to the atlas by Burnett.[15] The hip radiographs were scored in a similar manner as the knees: superior or medial hip JSN, superior or inferior acetabular OP, superior or inferior femoral OP, inferior acetabular OP and femoral subchondral sclerosis were scored as absent or present.[15] The α angles on AP pelvic view hip radiographs were measured to determine whether a cam-type deformity was present at baseline.[16] The α angle measures the deviation of the femoral head from a normal spherical-shaped femoral head. Cam-type deformity is one of two types of femoroacetabular impingement, which is associated with the development of hip OA. For this analysis, an α angle >60° was defined as a cam-type deformity.[16-18] In addition, the Wiberg angles on AP pelvic view radiographs were measured to determine the degree of dysplasia.[19] The center-edge angle of Wiberg is formed by a vertical line through the center of the femoral head, perpendicular to the transverse axis of the pelvis (radiographic 'teardrop' landmark),[20] and a line joining the head center with the lateral rim of the acetabulum.[21] Hips with Wiberg angle <25° were considered dysplastic.[22] On the FP radiographs, superior or posterior JSN was scored as absent (i.e. normal) or present.

Statistical analysis

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

Lastly, to assess possible more rapid clinical OA progression in patients from the TJR groups, we calculated the mean change in WOMAC pain and physical functioning scores

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

RESULTS

Baseline characteristics

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

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

	Total cohort	*Knee pain subgroup*			*Hip pain subgroup*		
Baseline characteristics	*N=908*	*TKA- n=732*	*TKA+ n=19*	*p value*	*THA- n=485*	*THA+ n=53*	*p value*
Age in years ± sd	55.8 ± 0.2	55.8 ± 0.2	58.0 ± 1.1	0.07	**55.4 ± 0.2**	**58.0 ± 0.6**	**<0.01**
Gender (% female)	79 %	79 %	95 %	0.10	**82 %**	**68 %**	**0.01**
Body mass index (kg/m^2) ± sd	26.2 ± 0.1	**26.3 ± 0.2**	**29.1 ± 1.0**	**<0.01**	26.3 ± 0.2	25.9 ± 0.5	0.60
Ethnicity (% Caucasian vs other)	98 %	97 %	100 %	0.47	98 %	100 %	0.32
Education level							
% ≤ high school graduate	73 %	73 %	84 %	0.29	73 %	77 %	0.55
% college or university degree	27 %	27 %	16 %		27 %	23 %	
Subjects (%) with > 1 co morbidity	45 %	46 %	47 %	0.91	52 %	40 %	0.13
NRS of the past week (iqr)	3.5 (2.0-5.0)	**3.5 (2.0-5.0)**	**4.5 (3.0-6.0)**	**0.04**	**3.6 (2.0-5.0)**	**4.3 (2.0-6.0)**	**0.03**
WOMAC pain (iqr)	25 (10-35)	**25 (10-35)**	**35 (20-40)**	**0.02**	27 (15-40)	31 (15-45)	0.07
WOMAC physical function (iqr)	23 (10-34)	**24 (10-34)**	**34 (20-44)**	**<0.01**	**25 (10-35)**	**31 (18-40)**	**0.02**
WOMAC joint stiffness (iqr)	33 (25-50)	**33 (25-50)**	**47 (38-63)**	**<0.01**	34 (25-50)	38 (25-50)	0.30
Pain coping strategies (iqr)							
Pain transformation	2.1 (1.8-2.5)	2.2 (1.8-2.8)	2.2 (1.8-2.5)	0.67	2.2 (1.8-2.8)	2.2 (1.8-2.7)	0.67
Distracting	2.2 (1.8-2.6)	2.2 (1.8-2.6)	2.3 (1.8-2.8)	0.69	2.2 (1.8-2.6)	2.2 (1.8-2.8)	0.55
Reducing demands	2.0 (1.7-2.3)	2.0 (1.7-2.3)	2.0 (1.3-2.7)	0.83	2.0 (1.7-2.3)	1.9 (1.7-2.3)	0.16
Resting / avoidance	1.8 (1.4-2.2)	1.8 (1.4-2.2)	2.0 (1.6-2.4)	0.09	1.8 (1.4-2.2)	1.8 (1.5-2.0)	0.93
Worrying	1.6 (1.2-1.8)	1.6 (1.2-1.8)	1.6 (1.2-2.0)	0.87	1.6 (1.2-1.8)	1.6 (1.2-1.9)	0.79
Retreating	1.5 (1.1-1.9)	1.6 (1.1-1.9)	1.5 (1.1-1.7)	0.56	1.5 (1.1-1.9)	1.5 (1.0-1.7	0.34
Smoker or previous smoker	14 %	15 %	0 %	0.07	15 %	6 %	0.07
Alcohol consumption	78 %	77 %	65 %	0.23	79 %	71 %	0.18
Use of pain medication	38 %	38 %	21 %	0.13	39 %	34 %	0.45
Morning stiffness knees < 30 min	53 %	62 %	83 %	0.06	-	-	-

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

	Total cohort	*Knee pain subgroup*			*Hip pain subgroup*		
Morning stiffness hips < 60 min	36 %	-	-	-	55 %	64 %	0.20
Heberden nodes hands	48 %	48 %	56 %	0.53	50 %	59 %	0.22
Bouchard swellings hands	19 %	19 %	21 %	0.81	22 %	17 %	0.42
ESR (mm/hr) ± sd	9.8 ± 0.3	10.1 ± 0.3	10.7 ± 1.7	0.77	9.9 ± 0.4	12.9 ± 1.4	0.05
		TKA- 1,480 knees	*TKA+ 22 knees*	*p*[1] *value*	*THA- 1,014 hips*	*THA+ 62 hips*	*p*[1] *value*
Palpable warmth of the knee joint		**3 %**	**18 %**	**<0.01**	-	-	-
Joint space tenderness of the knee		12 %	18 %	0.59	-	-	-
Bony enlargements of the knee		2 %	0 %	0.51	-	-	-
Crepitus during knee flexion		**10 %**	**23 %**	**<0.01**	-	-	-
Positive knee re-fill test (effusion)		**4 %**	**14 %**	**0.02**	-	-	-
Painful active knee flexion		**13 %**	**36 %**	**<0.01**	-	-	-
Painful active knee extension		**8 %**	**23 %**	**0.04**	-	-	-
ROM knee flexion ± sd		**135° ± 0.2°**	**127° ± 2.6°**	**<0.01**	-	-	-
ROM knee extension ± sd		3° ± 0.1°	3° ± 0.8°	0.94	-	-	-
JSN knee score >0		**55 %**	**86 %**	**0.03**	-	-	-
Femoral or tibial OP score >0		**45 %**	**91 %**	**<0.01**	-	-	-
Tibial attrition		**0 %**	**10 %**	**<0.01**	-	-	-
Femoral or tibial sclerosis		**1 %**	**10 %**	**<0.01**	-	-	-
Tibial spiking		**32 %**	**63 %**	**0.03**	-	-	-
K/L score 1 (versus K/L score 0)		**39 %**	**86 %**	**<0.01**	**26 %**	**72 %**	**<0.01**
ROM hip flexion ≤ 115°		-	-	-	**41 %**	**68 %**	**<0.01**
ROM hip internal rotation ≤ 15°		-	-	-	**4 %**	**26 %**	**<0.01**
Painful active hip flexion		-	-	-	**17 %**	**48 %**	**<0.01**

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

	Total cohort	*Knee pain subgroup*			*Hip pain subgroup*		
Painful active hip internal rotation		-	-	-	**16 %**	**46 %**	**<0.01**
JSN hip score >0 (AP)		-	-	-	**31 %**	**79 %**	**<0.01**
JSN hip score >0 (FP)		-	-	-	**11 %**	**60 %**	**<0.01**
Acetabular or femoral OP score >0		-	-	-	**35 %**	**78 %**	**<0.01**
Femoral subchondral sclerosis		-	-	-	**1 %**	**26 %**	**<0.01**
Cam-type deformity(α angle>60°)‡		-	-	-	**11 %**	**38 %**	**<0.01**
Dyspalsia (Wiberg angle<25°)‡		-	-	-	**5 %**	**17 %**	**<0.01**

Subgroups are participants who did (+) or did not (-) undergo arthroplasty during the 6 years follow-up.
TKA: total knee arthroplasty, THA: total hip arthroplasty.
Values are: mean ± standard deviation/sd, mean (interquartile range/iqr), or percentages %.
p-values obtained with Student's *t*-test or Pearson's χ^2 when appropriate.
p^1-values obtained with generalized estimating equations (GEE).
NRS: Numeric Rating Scale, WOMAC: Western Ontario and McMaster osteoarthritis index, ESR: erythrocyte sedimentation rate, ROM: range of motion, JSN: joint space narrowing, OP: osteophyte, K/L: Kellgren & Lawrence, AP: anteroposterior pelvic view radiograph, FP: faux profile radiograph.
‡ Due to lower quality radiographs, these angles were determined in fewer hips (THA+: 781 hips, THA-: 45 hips).
Bold indicates *p*-value < 0.05.

Knee subgroup (Table 2)

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

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

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

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

Hip subgroup (Table 3)

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

WOMAC change between baseline and T2

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

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

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

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

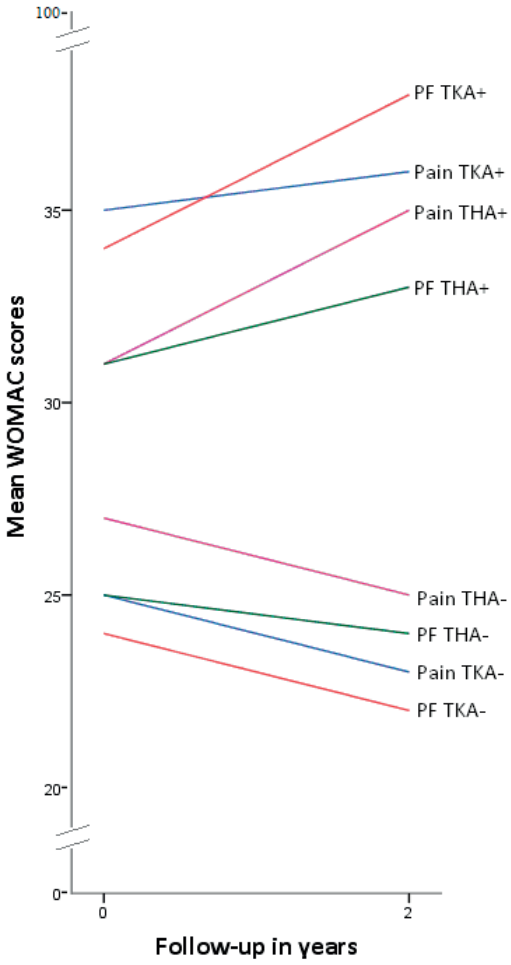

Figure 1. Depiction of the mean change in WOMAC scores from baseline to 2-year follow-up (T2). PF = physical functioning. THA= total hip arthroplasty. TKA= total knee arthroplasty. WOMAC = Western Ontario and McMaster osteoarthritis index .

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

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

Values are: mean change between T0 and T2 (standard error), or percentages %.
WOMAC: Western Ontario and McMaster osteoarthritis index, K/L: Kellgren & Lawrence, T0: baseline, T2: two year follow-up.
p-values obtained with * with Student's *t*-test or [‡]generalized estimating equations (GEE) and indicate whether the change in mean values (Δ) or in distribution of K/L score differ significantly. Progression of K/L score adjusted for baseline K/L score.

DISCUSSION

Summary

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

In participants with recent onset knee OA, significant differences in baseline BMI, symptom severity (NRS and all three WOMAC subscales), clinical findings and radiographic OA severity were seen between participants who underwent TKA during follow-up and those who did not.

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

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

Strengths and limitations

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

Comparison with existing literature

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

Baseline symptoms (NRS and WOMAC subscales) were significantly more severe in both TJR groups. This is in line with previous longitudinal studies showing that patients with higher pain or disability scores at baseline are more likely to undergo TJR.[28-30] The mean age of these study populations (72, 65 and 67 years respectively) however were higher than in our TJR groups (58 years). Unfortunately, symptom severity remains subjective and subsequently does not always form a clear indication for the GP to distinguish which patients are eligible for referral for TJR.

The participants from both our TJR groups significantly more often had typical OA symptoms during physical examination of the knee or hip, which are consistent with the criteria for clinical knee and hip OA.[8, 9] In longitudinal studies by Birrell[31] and Lievense,[32] the authors found associations for hip ROM and painful hip movements with hip replacement surgery in similar study populations. This is in line with our findings, but again the mean age of our THA group was relatively low (58 years compared to 63 and 66 years respectively).

Participants that underwent TKA significantly more often showed radiographic knee OA features.[9] The corresponding radiographs also had worse JSN, sclerosis, tibial attrition and tibial spiking. Participants that underwent THA significantly showed more radiographic features of hip OA.[8] They also more often showed JSN on the faux profile, dysplasia and femoral subchondral sclerosis. Furthermore, the radiographs from the TJR groups more frequently showed cam-type deformity (α angle >60°) and hip dysplasia

(Wiberg angle <25°), of which the associations with hip OA have previously been established.[16, 18, 24, 33, 34] Additionally, we found that participants from both the TJR groups showed earlier, more rapid radiographic progression of OA. All these abovementioned findings suggest that subjects who underwent TJR were in a more advanced stage of the disease at baseline. On the other hand, these findings could also suggest that participants from the TJR groups had a different underlying pathophysiology or phenotype of OA and therefore were prone to more rapid deterioration of the joint.[4, 5]

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

Implications for research and/or practice

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

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Chapter 7

Role limitations due to physical health in patients with recent onset osteoarthritis of the lower limbs

Five year results from a nationwide prospective cohort study (CHECK)

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ABSTRACT

Objective To test if pain coping strategies act as mediating factors between pain severity and role limitations in individuals with early symptomatic lower limb osteoarthritis (OA) and to determine these possible effects longitudinally.

Methods Data were acquired from a prospective cohort study of participants with early symptomatic hip and/or knee OA (CHECK study). WOMAC pain and role limitations due to physical health were measured repeatedly during 5 years follow-up. Role limitations were assessed by the SF-36 subscale. Structural equation models (SEM) were used to cross-sectionally determine the direct association between pain and role limitations, and the mediating effects of 6 types of pain coping strategies. Additionally, the mediating effects of coping strategies were tested in a longitudinal SEM model.

Results 920 participants were included (mean age 55.9 ± 5.1 years; 79% female). 705 participants reported knee pain; 545 participants reported hip pain at baseline. The univariate associations between WOMAC pain and role limitations remained statistically significant during follow-up, indicating that a higher WOMAC pain score is associated with more limitations. All six coping strategies showed significant mediating effects in the associations between WOMAC pain and role limitations cross-sectionally. Longitudinally, the mediating effects were small and only 'worrying' remained statistically significant.

Conclusions Pain coping strategies, worrying in particular, play an essential role on the causal pathway between pain severity and role limitations in individuals with (chronic) pain due to lower limb OA. Our results underline the potential importance of assessing pain coping behavior already in the early stage of OA.

INTRODUCTION

Osteoarthritis (OA) of the lower limbs is frequently diagnosed in general practice [1], with pain being the most common symptom in individuals with OA [2]. Pain experience is subjective and has many dimensions in individuals with OA, such as psychological stress or reduced independence [2, 3]. Individuals with OA use various strategies to cope with pain. These strategies play an essential part in pain experience and some cross-sectional studies indicate that coping strategies can significantly influence self-assessment of pain and function [4-7]. Moreover, patients with more severe pain are more likely to have problems managing their OA: they are limited from participating in daily activities or role functioning, which has been reported as one of the most severe consequences of OA [8, 9]. It therefore is important to focus on role limitations as an outcome measure in individuals with symptomatic OA [10]. It is essential to better understand the effect of pain coping strategies on role limitations. Focusing on training individuals with OA to better cope with their disabilities and pain, preferably already in a primary care setting, could be the first step in preventing role limitations. The aim of our study is to test the hypothesis that pain coping strategies play a role in the causal pathway, i.e. act as mediating factors [11], between pain severity and role limitations in individuals with early symptomatic lower limb OA (see **Figure 1)**. Additionally, we aimed to test the mediating effect of pain coping strategies on role limitations longitudinally.

METHODS

Study design and population

The data for our study were acquired from the Cohort Hip and Cohort Knee (CHECK) study [12]. CHECK is a nationwide prospective, ten-year follow-up cohort of 1,002 participants with early symptomatic hip and/or knee OA, who were recruited by their general practitioner if they were eligible for inclusion, or via advertisements in the lay press. The inclusion period ran from October 2002 until September 2005. Inclusion criteria for the CHECK study were: pain and/or stiffness of the hip and/or knee; age between 45 and 65 years; and never, or less than six months prior to entry of the study, consulted a physician for these symptoms. Participants were excluded if they had any other pathological condition that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plicasyndrome, Baker's cyst); co morbidity that did not allow physical evaluation and/or follow-up of at least ten years; malignancy in the past five years; and inability to un-

derstand the Dutch language [12]. For the present analyses, we only included participants who completed the three visits during five years follow-up.

Baseline characteristics

At baseline, a medical history was taken, including the Short Form 36-item Health Survey (SF-36) [13], and a physical examination at the research centre. The medical history was taken through questionnaires. Self-reported data on age, co morbidities, pain, physical limitations and pain coping strategies were assessed (see below). The following diseases were assessed as co morbidity: asthma, chronic sinusitis, cardio-vascular disease, high blood pressure, gastric ulcer, gallstones, liver disease, renal disease, diabetes, thyroid gland disease, epilepsy, cancer (during follow-up), severe skin disease, and other chronic musculoskeletal diseases.

Pain and pain-coping assessment

The Western Ontario and McMaster Universities osteoarthritis index pain subscore (WOMAC pain) was used to measure pain severity, with a higher score indicating more pain (range 0-100). To assess pain-coping behaviour a six scale Pain-Coping Inventory (PCI) was used that represents active and passive pain coping dimensions [14]. Active pain coping strategies are: pain transformation (i.e. to reinterpret and transform pain); distraction (i.e. to distract oneself from pain); and reducing demands (i.e. to function in spite of pain). Passive pain coping strategies are: retreating (i.e. to avoid environmental stimuli); worrying (i.e. to catastrophize pain); and resting (i.e. to restrict functioning). All six items are scored according to a four-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which the strategies are applied when coping with pain. WOMAC pain was assessed at baseline, after two (T2) and after five (T5) years follow-up.

Role limitation

Role limitation was determined using the SF-36 subscale *Role limitations due to physical health* (SF-36 RLP). This score ranges from 0 to 100, with a higher score indicating better health, i.e. less limitations [13]. The SF-36 was assessed at baseline, T2 and T5.

Statistical analysis

In order to perform our analyses, we firstly tested whether our variables met the assumptions for linear regression. We checked the distribution of continuous variables and we checked for collinearity, maintaining a cut-off point of Pearson's $R < 0.7$. Secondly, we checked whether a direct association between WOMAC pain and SF-36 RLP existed, using Structural Equation Modeling (SEM), adjusting for the following confounders: age, gender, comorbidity count (less than 2 versus 2 or more), body mass index (BMI), educa-

tion level and race. The mediating effect of all six pain coping strategies on the causal pathway between WOMAC pain severity and the SF-36 RLP score were independently tested cross-sectionally at baseline, T2 and T5. If the direct association between WOMAC pain and SF-36 RLP decreased by adding coping strategies to the model, then mediation was present. This has also been depicted in **Figure 1**. Lastly, we built a final model using SEM testing the mediating effect of the 6 pain coping strategies independently over 5 years of follow-up. All analyses were performed using *SPSS Statistical Package PASW 20.0* and *IBM SPSS Amos 23.0.0*.

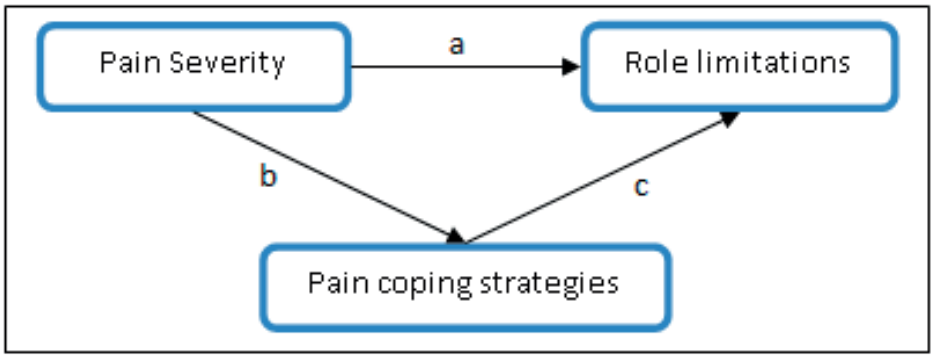

Figure 1. Hypothesis that pain coping strategies act as mediators in the causal pathway between pain severity and role limitations due to physical health in individuals with OA. If either of the regression coefficients 'b' or 'c' are non-significant, then there is no mediation. If regression coefficient 'a' remains significant after adding the mediator 'Pain Coping Strategy' to the model, then there is partial mediation. If regression coefficient 'a' is non-significant, but 'b' and 'c' are, then there is complete mediation.

RESULTS

Baseline characteristics

Of the 1,002 participants included at baseline, 82 were lost to follow-up after five years (8%), resulting in a total study population of 920 participants included in our analyses. An overview of their baseline characteristics is presented in **Table 1**. There was no strong collinearity between any of the baseline values. The 82 participants lost to follow-up did not differ significantly from our study population at baseline with regards to age, gender, BMI, WOMAC pain score and SF-36 RLP score.

The mean WOMAC-pain score at baseline was 25 (standard deviation (sd) 17), at T2 23 (sd 18) and at T5 24 (sd 19). The mean SF-36 RLP score at baseline was 69 (sd 40), at T2 72 (sd 39) and at T5 73 (sd 39).

Table 1. Baseline characteristics of the total population (n=920)

Characteristic	*Value*
Age (years), mean ± SD	55.9 ± 5.1
Gender (female), %	79 %
Body mass index (kg/m^2), mean ± SD	26.2 ± 4.1
Co morbidities ≥ 2, %	44 %
Highest education level (university/college), %	26 %
Race (Caucasian), %	98 %
WOMAC subscales	
Pain (range 0-100), mean ± SD	25 ± 17
Physical function (range 0-100), mean ± SD	23 ± 17
Joint stiffness (range 0-100), mean ± SD	33 ± 21
Pain coping inventories (PCI)	
Pain transformation (range 1-4), mean ± SD	2.15 ± 0.68
Distracting (range 1-4), mean ± SD	2.19 ± 0.63
Reducing demands (range 1-4), mean ± SD	2.00 ± 0.61
Retreating (range 1-4), mean ± SD	1.55 ± 0.49
Worrying (range 1-4), mean ± SD	1.56 ± 0.40
Resting (avoidance) (range 1-4), mean ± SD	1.83 ± 0.50
Knee pain and/or stiffness	705 (77 %)
Clinical knee OA in ≥ 1 knee (ACR criteria) [26], %	67 %
Hip pain and/or stiffness	545 (59 %)
Clinical hip OA in ≥ 1 hip (ACR criteria) [27], %	16 %
SF-36 role limitations, physical (range 0-100), mean ± SD	69 ± 40

SD: standard deviation; WOMAC: Western Ontario and McMaster Universities osteoarthritis index; OA: osteoarthritis; ACR: American College of Rheumatology; SF-36: Short Form 36-item Health Survey.

Structural Equation Modeling

The model used in SEM for testing the direct association between WOMAC pain and SF-36 RLP is depicted in **Figure 2**. The confounding variable 'age' did not contribute significantly to any of the analyses, hence was left out. The baseline univariate association between WOMAC pain and SF-36 RLP was statistically significant (standardized β = -0.313, $p < 0.01$), indicating that a higher WOMAC pain score is associated with a lower SF-36 RLP score, i.e. more limitations. Similar direct associations were found at T2 and T5, as presented in **Table 2**. All six coping strategies showed significant, positive effects with WOMAC pain at baseline, T2 and T5, indicating that more severe pain is associated with more usage of pain coping strategies. The model used in SEM for testing the mediating effect of coping strategies on the direct association between WOMAC pain and SF-36 RLP is depicted in **Figure 3**. All six coping strategies showed mediating effects cross-sectionally at baseline and T2, with the exception of the coping strategy distracting at

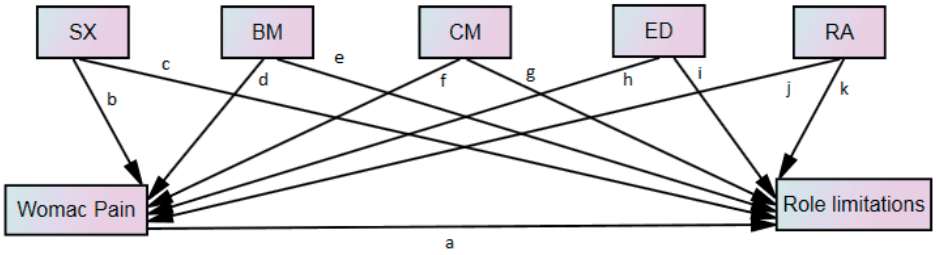

Figure 2. Direct association between WOMAC pain and SF-36 RLP, adjusted for confounders. This model was applied to the data at baseline, T2 and T5.
SX = gender, BM = body mass index, CM = 2 or more co morbidities, ED = highest achieved education level, RA = Caucasian versus non-Caucasian.

Table 2. Results from the model depicted in Figure 2 (the direct association between WOMAC pain and SF-36 RLP).

Model	a	χ^2	df	*p*	RMSEA	CFI	Hoelter
Baseline	-0,313*	33,7	10	<0,01	0,049	0,92	691
T2	-0,358*	33,7	10	<0,01	0,049	0,93	691
T5	-0,425*	33,7	10	<0,01	0,049	0,94	691

a: standardized regression coefficient
*p<0,01
RMSEA: Root Mean Square Error of Approximation, CFI: Comparative Fit Index
Coefficients b – k are available in an online supplement.

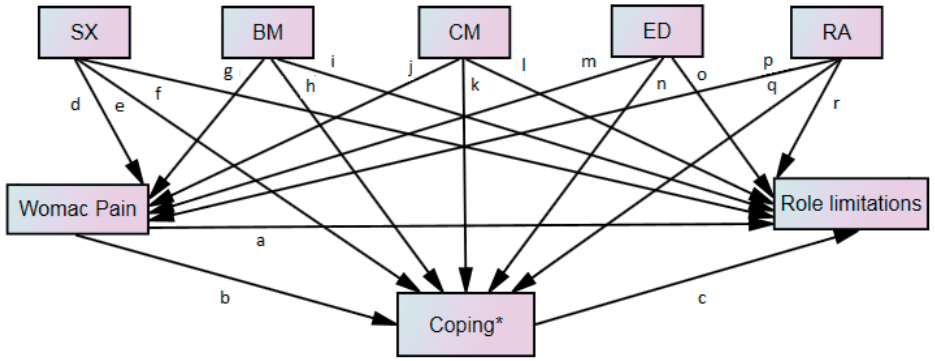

Figure 3. Testing for the mediating effect of coping strategies on the association between WOMAC pain and SF-36 RLP, adjusted for confounders. This model was applied to the data at baseline, T2 and T5.
SX = gender, BM = body mass index, CM = 2 or more co morbidities, ED = highest achieved education level, RA = Caucasian versus non-Caucasian.
Coping*: the mediating effect was tested for each PCI subscale separately, i.e.: pain transformation, distracting, reducing demands, retreating, worrying, resting.

T2, as the regression coefficient 'c' for distracting at T2 was non-significant. At T5, three out of the six coping strategies showed mediating effects, namely reducing demands, worrying and resting. The association between WOMAC pain and role limitations at baseline decreased by the mediating effects of all coping strategies, but remained significant, indicating partial mediation. Again, similar results were seen at T2 and T5. The passive coping strategies worrying, retreating and resting had the largest effect on the association between pain and role limitations at baseline, T2 and T5 (with the exception of retreating at T5). All results from the cross-sectional SEM are presented in **Table 3.**

Table 3. Results from the model depicted in Figure 3 (testing for the mediating effect of coping strategies on the association between WOMAC pain and SF-36 RLP).

Model/ *coping*	a	b	c	χ^2	df	p	RMSEA	CFI	Hoelter
Baseline									
PT	-0,296*	0,213*	-0,078*	33,7	10	<0,01	0,049	0,94	691
DI	-0,297*	0,198*	-0,081*	33,7	10	<0,01	0,049	0,94	691
RD	-0,285*	0,202*	-0,139*	33,7	10	<0,01	0,049	0,94	691
WY	-0,248*	0,245*	-0,263*	33,7	10	<0,01	0,049	0,96	691
RT	-0,294*	0,128*	-0,147*	33,7	10	<0,01	0,049	0,94	691
RS	-0,254*	0,244*	-0,241*	33,7	10	<0,01	0,049	0,96	691
T2									
PT	-0,345*	0,180*	-0,070†	33,7	10	<0,01	0,049	0,95	691
DI	-0,352*	0,132*	-0,043	33,7	10	<0,01	0,049	0,95	691
RD	-0,345*	0,132*	-0,094*	33,7	10	<0,01	0,049	0,94	691
WY	-0,338*	0,158*	-0,125*	33,7	10	<0,01	0,049	0,95	691
RT	-0,346*	0,094*	-0,128*	33,7	10	<0,01	0,049	0,95	691
RS	-0,332*	0,160*	-0,160*	33,7	10	<0,01	0,049	0,95	691
T5									
PT	-0,423*	0,151*	-0,017	33,7	10	<0,01	0,049	0,95	691
DI	-0,420*	0,122*	-0,040	33,7	10	<0,01	0,049	0,95	691
RD	-0,413*	0,104*	-0,114*	33,7	10	<0,01	0,049	0,95	691
WY	-0,404*	0,165*	-0,128*	33,7	10	<0,01	0,049	0,96	691
RT	-0,419*	0,052	-0,117*	33,7	10	<0,01	0,049	0,95	691
RS	-0,405*	0,116*	-0,173*	33,7	10	<0,01	0,049	0,96	691

For all models counts: $\chi^2 = 33,7$, degrees of freedom = 10 and $p < 0,01$.
PT: pain transformation, DI: distracting, RD: reducing demands, WY: worrying, RT: retreating, RS: resting.
a, b, c: standardized regression coefficients
*p<0,01 † p<0,05
RMSEA: Root Mean Square Error of Approximation, CFI: Comparative Fit Index
Coefficients d – r are available in an online supplement.

The model used for longitudinal analyses, or final model, is depicted in **Figure 4**. In this model, the regression coefficient between WOMAC pain at T5 and role limitations at T5 decreases only to some extent compared to cross-sectional analyses. There is no mediating effect for five out of six pain coping strategies. Only the strategy worrying in longitudinal analyses showed a mediating effect, albeit only slightly. The strategy worrying had the strongest effect in longitudinal analyses. The results from the final model are presented in **Table 4**.

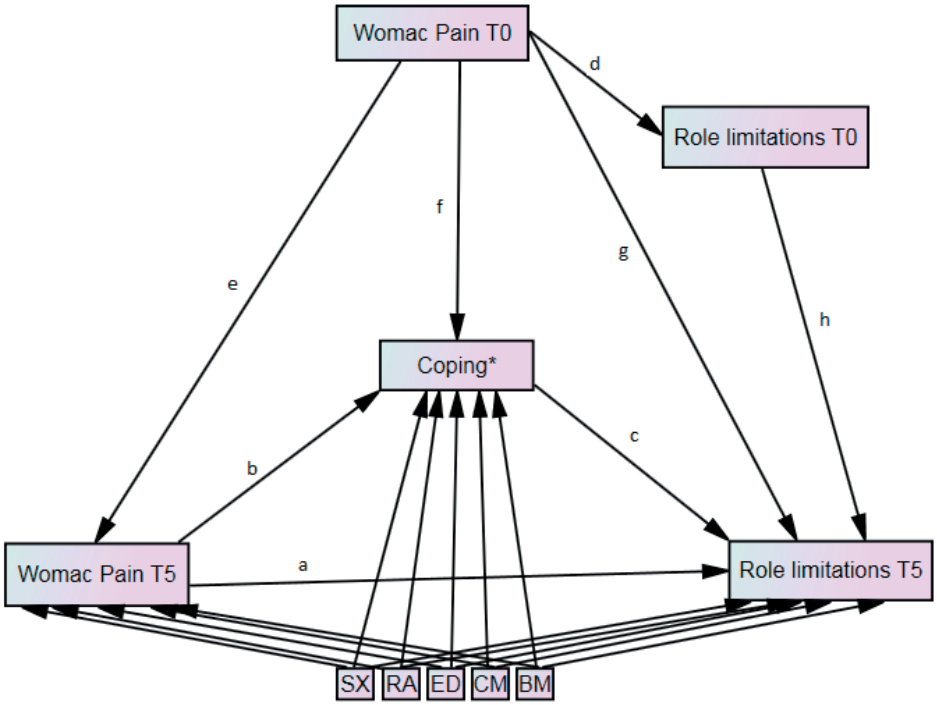

Figure 4. Final model. Longitudinal mediating effect of pain coping strategies. The standardized estimates are presented for the main associations.
SX = gender, BM = body mass index, CM = 2 or more co morbidities, ED = highest achieved education level, RA = Caucasian versus non-Caucasian.
Coping*: the mediating effect was tested for each PCI subscale separately measured at T5, i.e.: pain transformation, distracting, reducing demands, retreating, worrying, resting.
Womac Pain T0/T5 = WOMAC pain at baseline and T5 respectively, Role limitations T0/T5 = role limitations at baseline and T5 respectively.

Table 4. Results from the model depicted in Figure 4 (final model; longitudinal mediating effect of pain coping strategies).

Model	a	b	c	d	e	f	g	h	χ^2	df	*p*	RMSEA	CFI	Hoelter
PT	-0,39*	0,07†	0,00	-0,36*	0,42*	0,19*	0,01	0,20*	197	22	<0,01	0,089	0,83	205
DI	-0,39*	0,05	-0,02	-0,36*	0,42*	0,18*	0,01	0,20*	197	22	<0,01	0,089	0,83	204
RD	-0,39*	0,02	-0,09*	-0,36*	0,42*	0,19*	0,02	0,19*	197	22	<0,01	0,093	0,81	190
WY	-0,38*	0,07†	-0,08*	-0,36*	0,42*	0,22*	0,02	0,18*	197	22	<0,01	0,105	0,80	154
RT	-0,39*	-0,00	-0,09*	-0,36*	0,42*	0,13*	0,02	0,18*	197	22	<0,01	0,094	0,81	187
RS	-0,39*	0,02	-0,13*	-0,36*	0,42*	0,24*	0,03	0,17*	197	22	<0,01	0,102	0.80	160

For all six models counts: $\chi^2 = 197$, degrees of freedom = 22 and $p < 0,01$.
PT: pain transformation, DI: distracting, RD: reducing demands, WY: worrying, RT: retreating, RS: resting.
a – h: standardized regression coefficients
*p<0,01 † p<0,05
RMSEA: Root Mean Square Error of Approximation, CFI: Comparative Fit Index
The additional coefficients regarding the confounders are available an online supplement.

DISCUSSION

In this article we hypothesized that pain coping strategies play a role in the causal pathway, i.e. act as mediating factors between pain severity and role limitations in individuals with early symptomatic lower limb OA. We used advanced statistical methods to establish mediating effects for six pain coping strategies in the association between WOMAC pain severity and role limitations due to physical health in cross-sectional analyses, adjusted for confounders, in subjects with early stage lower limb OA. In longitudinal analyses, the mediating effects of coping strategies were small and only the strategy worrying remained statistically significant. The association between pain, avoidance of activities and activity limitations in patients with early symptomatic knee or hip OA (the avoidance model) has previously been described [15, 16]. In a systematic review, only weak evidence based on cross-sectional analyses is available to support this association [15]. Holla et al have published similar results from the CHECK cohort, but the study determinant and outcome variable differed from the current study. They presented an association between pain-related avoidance of activities (measured by the PCI subscale resting) and limitations in activities (measured by the WOMAC physical function scale) longitudinally in patients with knee OA [17]. Moreover, in a study by Hermsen et al, the authors report an association between avoidance of activities and physical limitations and/or participation restrictions (cross-sectional data) [18].

Our results support the theory that pain coping strategies, worrying in particular, play a crucial part in pain experience and the subsequent role limitations in individuals with lower limb OA. The position of psychological and social factors in the assessment and management of OA is internationally becoming more prominent [9]. In accordance

with the currently available OA guidelines [19-21], physicians generally assess pain severity in patients with OA and the disabilities these patients encounter due to OA. However, the way an individual copes with his or her pain is not commonly assessed and limited research has been performed determining the implications and/or added value of measuring pain coping behavior [9, 22]. Previous studies have shown that pain coping strategies can easily and reliably be assessed through questionnaires in general practice [6, 22]. The association between poorer outcomes in patients with (chronic) pain and passive coping strategies, such as withdrawal, resting, worrying or catastrophizing has previously been established in patients with rheumatoid arthritis (RA) [23]. It makes sense that similar results are found in patients with chronic pain due to OA. These results indicate that potential benefit for individuals with early stage lower limb OA can be achieved in primary care settings by proper patient education and further incorporating and integrating the existing psychosocial training programs into the general management of OA [24, 25].

In conclusion, we determined that pain coping strategies play an essential part in the association between pain severity and role limitations in individuals with (chronic) pain due to lower limb OA. Our results underline the potential importance of assessing pain coping behavior in the management of OA already in the early stage of the disease. Future research should be aimed at the benefit of applying psychosocial intervention techniques in primary care settings to further optimize management of pain in patients with OA.

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Chapter 8

General discussion

The aim of this thesis was to determine risk factors for the progression of knee and hip osteoarthritis (OA). Firstly, we systematically reviewed previously identified risk factors for progression of radiographic and clinical knee OA. Secondly, we studied risk factors for pain progression and joint replacement surgery in a large study cohort of individuals with early symptomatic knee and/or hip OA. Lastly, we studied how pain coping strategies can influence pain severity and subsequent physical disabilities. In this chapter we will further discuss our findings, the strengths and limitations of our research and the implications of our findings as a whole for future research and clinical practice.

MAIN FINDINGS OF THIS THESIS

Knee OA

In Chapter 2 we studied prognostic factors for the clinical progression of knee OA. We found that 7 out of 38 investigated prognostic factors had strong evidence for the association with symptomatic OA progression. These were: higher age, non-Western ethnicity, higher body mass index (BMI), higher co-morbidity count, presence of MRI-detected knee synovitis, presence of knee joint effusion and greater baseline OA severity. Additionally we saw a large variety in definitions of clinical OA and OA progression, which complicates a proper summarization of the available evidence through meta-analyses. More research on prognostic factors for knee OA is needed using symptom progression as an outcome measure.

In Chapter 3 we reviewed the evidence for prognostic factors for radiographic progression of knee OA. We found that 5 out of 59 prognostic factors showed strong evidence for the association with radiographic OA progression. These were: greater baseline knee pain, stronger varus knee alignment, high serum TNF-α or hyaluronic acid levels and the presence of Heberden nodes. Another 6 prognostic factors were strongly not associated with radiographic knee OA progression. These factors were: female sex, former knee injury, greater quadriceps strength, being a (former) smoker, frequent running activity and the regular performance of sports. The evidence for the majority of the determined associations however was conflicting or inconclusive. Again, we saw large variation in definitions of radiographic knee OA and OA progression. Clinical studies should use more consistent definitions to facilitate data pooling by meta-analyses.

In Chapter 4 we defined 6 distinct pain trajectories with favourable or unfavourable courses using Latent Class Growth Analyses (LCGA), in individuals with early symptomatic knee OA. 56% of the study population showed a mild or moderate pain trajectory, for which a 'wait-and-see' policy seems justifiable in accordance with OA guideline recommendations. We found that a higher BMI, lower level of education, greater co-morbidity, higher activity limitation scores and joint space tenderness were more often associated

with trajectories characterized by more pain. Radiographic characteristics for knee OA were not associated with the knee pain trajectories. These results can help differentiate those patients who require more specific monitoring in the management of early symptomatic knee OA from those whom are likely to suffice with a 'wait-and-see' policy.

Hip OA

In Chapter 5 we identified 4 distinct pain trajectories using LCGA in individuals with early symptomatic hip OA, also with favorable and unfavorable pain courses. 60% of the study population showed a mild or moderate pain trajectory. Lower education level, higher activity limitation scores, frequent use of pain transformation as coping strategy and painful internal hip rotation were associated with trajectories characterized by greater pain. Again, radiographic OA severity was not associated with the pain trajectories. These results suggest there are differences in symptomatic progression of hip OA.

Knee and Hip OA

In Chapter 6 we presented risk factors for undergoing total joint replacement surgery of the knee and/or hip within six years after first presentation of symptoms to a physician. Participants with higher BMI, painful knee flexion and radiographic knee OA scores were more likely to undergo knee replacement surgery. Participants who underwent hip replacement surgery had painful internal hip rotation and showed more severe radiographic OA features. We saw a trend in rapid progression of radiographic and symptomatic OA severity amongst subjects whom underwent joint replacement surgery.

In Chapter 7 we used advanced statistical methods (*Structural Equation Modeling*) to establish that six coping strategies play an essential part in the cross-sectional association between pain severity and role limitations in individuals with (chronic) pain due to lower limb OA. Longitudinally, the mediating effects of these six strategies were (too) small, but the passive coping strategy 'worrying' remained statistically significant. These results underline the potential importance of assessing pain coping behavior in the management of OA already in the early stages of disease.

STRENGTHS AND LIMITATIONS OF OUR RESEARCH

As mentioned, the Cohort Hip & Cohort Knee (CHECK) study is a prospective, multi-centre, ten-year follow-up cohort initiated and funded by the Dutch Arthritis Foundation in The Netherlands. As a result of the conceived inclusion criteria, primarily the early onset of joint pain and/or stiffness, the CHECK study population is highly representative for patients in general practice with alleged early symptomatic knee and/or hip OA. It is the first of its kind, with 1,002 relatively young participants for an OA cohort (mean age at

baseline was 56 years), hence very informative for researchers and physicians in primary care. It has achieved international recognition for its originality and vastness of studied characteristics.[1, 2] We were fortunate to use data from the CHECK study in Chapters 4-7 and consequently provided original, strong and relevant evidence for the GP regarding early knee and hip OA.

In Chapters 2 and 3 we systematically reviewed the available evidence for progression of clinical and radiographic knee OA. The reviews included 109 research articles combined, consequently giving high power to the presented evidence of the reviews. These results are very informative for physicians and researchers in the field of knee OA. But are these results also that useful to the GP? Unfortunately, these results might lack clinical relevance for primary care. Firstly, 66 out of the 109 articles used radiographic criteria to define whether a participant had knee OA. Although many patients in general practice have knee X-rays taken prior to referral, current GP guidelines for OA do not recommend the use of radiography in general practice in early OA. [3, 4] Secondly, inclusion criteria were a radiographic Kellgren and Lawrence score of 2 or higher, or an equivalent of this classification. These criteria represent subjects with more progressed knee OA, which is not a good representation of early onset knee OA patients in general population.[5] Lastly, approximately 45 possible risk factors for knee OA progression, i.e. determinants, were examined in the two reviews, but over a quarter of the determinants cannot (easily) be assessed by the GP without the use of X-rays, MRI's or specific laboratory testing.

THE CHALLENGES OF MANAGING KNEE AND HIP OSTEOARTHRITIS

In previous chapters of this thesis it has been stated that OA is one of the most common chronic diseases and is one of the leading causes of pain and disability worldwide.[6] OA occurs in many joints in the body, but patient consultation rates due to knee and hip OA are the highest in primary care.[7] As a result, GP's are frequently consulted with knee and/or hip OA related symptoms, but criteria for early recognition of OA and treatment options so far are limited. In general, preventing further disease progression is a primary goal in the management of any chronic condition. However, only relatively few prognostic factors for knee OA (Chapters 2 and 3) and hip OA[8, 9] have been determined and the majority of these factors cannot (easily) be modified. Moreover, the results from this thesis indicate that we should not focus on prevention of disease progression in all patients with early symptomatic lower limb OA. In chapters 4 and 5, we have seen that 56% of the knee OA study population and 60% of the hip OA study population showed a constant mild or moderate course of pain throughout the first 5 years after onset of their symptoms. Similar findings are presented in Chapter 6 where pain and physical function scores of participants whom ultimately did not undergo joint replacement surgery,

which was the majority of the population, remained stable or even decreased during follow-up. In Chapter 7 we saw that the influence of coping strategies on limitations of daily activities was minimal in longitudinal analysis. Hence, so far the evidence is limited that the implementation of time-consuming or perhaps costly preventive strategies on all individuals with early onset lower limb OA in a primary care setting would lead to significant benefit of their prognosis, at least in the first five years of the disease. It would seem preferable in general practice to focus on detecting the slight minority of all patients with early OA who do have a higher chance of progression of the disease (in the first years after onset of symptoms). Perhaps the effects of preventive strategies and/or pain coping training programs would be substantial in these individuals. As seen in this thesis regarding knee OA, these are patients who consult their GP because of their knee pain and a have high BMI, lower education, more activity limitations, greater co-morbidity, knee joint space tenderness and painful knee flexion. Regarding hip OA, these are patients with who consult their GP because of their hip pain and have lower education, more activity limitations, usage of pain transformation coping strategy and painful internal hip rotation.

RADIOGRAPHIC OR (EARLY) CLINICAL OSTEOARTHRITIS

Throughout this thesis I have encountered and studied two main definitions of OA: clinical and radiographic OA. Multiple definitions for describing one condition or disease, often depending on the setting in which the definition is used, is not desirable; it can confuse physicians and patients when discussing the patient's condition and it complicates proper comparisons of disease severity between patients in a research environment. But, clinical OA and radiographic OA are not the same condition. It is important to appreciate which patients one refers to when speaking of 'patients with OA' and to consider the principal purpose for maintaining a certain type of disease classification. A patient will most often only be concerned about the clinical severity of his or her OA regardless of the radiographic severity, whereas an orthopedic surgeon will also be keen on the radiographic stage of disease in deciding eligibility for joint replacement.[10, 11] There is a well-known discordance in the apparent correlation between clinical and radiographic OA severity.[12, 13] A remarkable finding in this thesis, is that baseline radiographic features of neither the hip or knee showed an association with symptom progression (Chapters 4 and 5), but were associated with undergoing joint replacement surgery within the same study population (Chapter 6). This underlines the suggestion that radiographic OA severity strongly influences the surgeon's decision to operate. It would help the GP if clear criteria were developed as to when a patient is eligible for

joint replacement surgery. To date these criteria are not available, but I will elaborate on this topic further on in this chapter.

The criteria for diagnosing knee and hip OA were first described in 1986.[14, 15] The authors developed multiple sets of criteria for diagnosing OA, allowing for variations in available characteristics, using either clinical criteria or radiographic features. This has never altered over the years, but the definition 'OA' has been interpreted in various ways for both the knee and hip. In Chapters 2 and 3 we have seen that within the 109 articles included in the reviews, 6 different sets of OA criteria were used to define knee OA, either clinical, radiographic or a combination of the two. Moreover, 22 different sets of criteria were used to assess disease progression. Making it even more complicated, the interpretation of one single radiographic OA definition can vary between studies.[16] It is important that criteria for OA are accurately and uniformly applied for either radiographic or clinical OA when diagnosing the disease.

I feel that there is a distinction between clinical and radiographic OA and acknowledge the usefulness of this distinction in different care or research settings. I also feel that there yet is insufficient evidence for clinical criteria for diagnosing knee and/or hip OA accurately in an early stage of disease in general practice. Primary care physicians should be enabled to use easy to establish clinical OA criteria to diagnose early symptomatic knee or hip OA, and preferably to immediately distinguish the OA patients at high risk for progression. The existing ACR criteria for clinical knee and hip OA however, seem to define more progressed OA.[14, 15] For example, bony enlargement in knee OA, or hip internal rotation $< 15^0$ in hip OA are seen in more severe stages of disease.[5] In various GP guidelines, similar brief criteria are presented to diagnose clinical OA, but there still is diversity in these criteria which is undesirable.[3, 4] The criteria: age >45 years, activity related joint pain and morning stiffness < 30 minutes do not sufficiently constitute the diagnoses early OA. Additional criteria, including physical examination characteristics should be included, such as joint space tenderness regarding knee OA or painful internal hip rotation regarding hip OA. The CHECK study population is an excellent representation of individuals with alleged early symptomatic knee or hip OA. At present, Dutch researchers are using data from CHECK to develop and validate diagnostic criteria for early hip and knee osteoarthritis (the CREDO study, funded by the Dutch Arthritis Foundation).[17]

RECOMMENDATIONS FOR FUTURE RESEARCH

It is important for future researchers to clearly define the type of OA under study, i.e. clinical or radiographic OA and the aim of the study (e.g. diagnosis or prognosis). In addition, the clinical setting of the study (primary, secondary or tertiary care) and stage of

disease should properly be taken into account. It is essential that OA criteria are strictly defined and accurately applied.[16] Considering that some MRI scoring systems have been and currently are being developed to define knee OA progression, it is desirable, albeit challenging, that the same MRI scoring system would be used universally in future studies on prognostic factors for knee OA progression.[18]

In the previous paragraph, it was already explained that having various types of OA classifications for describing the same (stage of) disease is inconvenient for clinicians, patients and researchers, because it complicates achieving universal consensus on diagnosis, progression and management of disease. The development of clinical criteria for early knee and hip OA however would help in distinguishing patients with different stages of clinical OA (i.e. early OA compared to progressed OA).

Secondly, it is recommended that more studies are performed investigating progression of clinical OA. As seen in Chapter 2, there is a lack of studies investigating risk factors for pain progression in knee OA. One definition used to define clinical OA progression is joint surgery, but this definition is debatable because of contraindications for surgery, patient preference, and a large doctor and hospital variation. Moreover, joint surgery only describes the end-stage of progression, when symptoms (pain, disability) will have increasingly progressed from previous stages of OA. Studies have shown that key indicators for surgeons to perform joint replacement surgery on patients with OA are pain, disability and/or radiographic progression.[11, 19, 20] So far, clear criteria for clinical use as for when joint replacement surgery should be performed, thus when a patient should be referred by their GP have yet to be developed.[21] For research purposes criteria were defined by the Osteoarthritis Research Society International (OARSI) to determine patients in need of joint replacement surgery. Based on a sum-score of the Intermittent and Constant Osteoarthritis Pain (ICOAP) score for pain and Knee injury and Osteoarthritis Outcome Physical function Short form (KOOS-PS) score for physical function, they introduced a discriminatory cut-off point to define an indication for joint replacement.[22] However, none of the studies included in our review on prognostic factors used such an outcome.

Thirdly, it is important that pain due to OA is assessed properly, especially in research settings. If more studies are being performed investigating pain or symptom progression in patients with OA, then we would like to emphasize that pain due to OA is known to fluctuate (Chapters 4 and 5). This underlines the importance of frequent pain or symptom assessments by patient and physician during a longer follow-up time to assess a more accurate estimation of symptomatic progression over time.

Fourthly, we repeatedly found associations for joint space tenderness or painful joint movements with OA progression (Chapters 4, 5 and 6). These findings suggest active joint inflammation in patients with OA, possibly leading to further destruction of the knee or hip joint. Precisely understanding the underlying cascade of joint inflamma-

tion and the progression of joint pain should be the aim of future studies and might be crucial in better treatment of patients at risk of fast progression.

Fifthly, we found small, but significant effects of coping strategies on the association between pain and activity limitations (Chapter 7). Future research should focus on the implications of these findings. Previous studies have shown that pain coping strategies can easily and reliably be assessed through questionnaires in general practice.[23] However, the way an individual copes with his or her pain is not commonly assessed in general practice and thus far limited research has been performed determining the benefit of measuring pain coping behavior, and acting accordingly.[24, 25] Future research should be aimed at determining effects of preventive strategies and/or pain coping training programs in individuals with early lower limb OA (at high risk for progression).

Lastly, previous studies indicate high rates of patient dissatisfaction following joint replacement surgery for the knee and hip (20% and 7-15% respectively) and that GP perceptions of efficacy of joint surgery are overestimated.[26-28] If the abovementioned recommendations are taken into account, ultimately leading to a more accurate selection of patients eligible for joint replacement surgery, perhaps patient satisfactory rates following joint surgery would improve.

IMPLICATIONS FOR CLINICAL PRACTICE

The exact pathogeneses of knee and hip OA progression are not fully understood and many risk factors for disease progression have yet to be uncovered. Efficacious preventive or intervention strategies therefore are challenging to develop and apply. We repeatedly have seen that the small majority of participants from our study population (CHECK) showed a relatively mild course of symptom progression throughout the follow-up period. This endorses current recommendations in OA guidelines for a wait-and-see policy in the early stages of the disease for the majority of the patients. It could be beneficial in general practice to identify patients in whom a more rapid disease progression can be expected and in whom preventive measures should be advised to attempt delaying disease progression.

To achieve this goal, re-assessment of symptoms (i.e. pain and joint stiffness), limitations in daily activities, weight change, joint space tenderness and knee alignment should take place by the GP within the first years of follow-up in participants who initially showed severe symptoms (Chapters 4, 5 and 6). The GP has a responsibility in explaining to patients that a higher BMI is associated with more rapid symptom progression. The results from this thesis can help the GP in identifying patients whom require more specific monitoring so that, in accordance with current OA guidelines, exercise programmes should be applied; pain could be managed by (prescription of) pain medication, i.e.

paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs); intra-articular corticosteroid injections, although debatable, could be given[29-31]; or ultimately the patient could be referred for specialist treatment.[3, 4] The current GP guidelines contain recommendations for referral, stating that if joint pain, stiffness and reduced function have a substantial impact on quality of life and are refractory to non-surgical treatment, joint surgery could be considered. These recommendations unfortunately remain subjective and the implementation of clear criteria for referral would be a major improvement. Our results from Chapter 6 for example suggest that it could be beneficial to also consider ascertaining radiographic OA severity prior to referral to better assess if a patient would at least be eligible for surgery. Also, GPs should consider and discuss the expectations of referral for specialist treatment. Is it to get reassurance from the specialist of the current diagnosis and treatment strategy? Or to discuss joint surgery? GPs should be well aware of the limitations of joint surgery and should invest in explaining benefits and harms to the patient prior to referral. So called GPwSIs (GPs with special interest) can play an essential role in advising and training GPs on this topic. They can also be consulted in optimizing treatment options by the GP, such as teaching intra-articular corticosteroid injections for the knee (and perhaps even the hip).[29]

We have also seen that pain coping plays an important role in patients with knee or hip OA. It seems likely that patients with non-optimal coping would benefit from proper patient education and from further incorporating and integrating existing psychosocial training programs into the general management of OA.[32, 33] However, there is low to moderate quality evidence stating that self-management education programmes (SMEP), which include coping skills training, are not efficacious in patients with knee or hip OA. (Kroon et al, PEARL) This evidence is based on results from mostly secondary care settings. At this time, we do not recommend SMEP in primary care until more and stronger evidence is available on the efficacy of SMEP in patients with OA in general practice.

Throughout this thesis, we recurrently have seen that physical examination characteristics (such as joint space tenderness in knee OA) are important predictors for the progression of early symptomatic OA. The majority of radiographic features were not (strong) predictors for OA progression, with the exception of hip radiographic features for undergoing total hip arthroplasty. I would like to strongly underline the importance of performing proper physical examination on patients with suspected knee and/or hip OA in general practice. Additionally, I emphasize that knee and hip OA are clinical diagnoses in primary care and that the GP should restrain from unnecessary X-rays when diagnosing the disease. As mentioned, X-rays of the knee and/or hip could prove to have added value when deciding when to refer for specialist treatment (eligibility for total joint arthroplasty, Chapter 6).

In conclusion: how does this thesis help physicians in managing patients with (early) OA? Or more specifically, what does it tell me as a GP? Knee and hip OA are very common and chronic diseases in general practice. They can lead to severe pain and serious disability and the need for surgical intervention. General practitioners should diagnose knee and hip OA by anamnestic but also physical examination features, without the use of X-rays. Pain due to OA fluctuates and so the GP should monitor the patient with severe symptoms to properly assess the impact of disease. Many (alleged) risk factors for knee OA progression have been examined, but many risk factors have yet to be studied. Following a wait-and-see policy in the management of early symptomatic lower limb OA seems justifiable for the small majority of OA patients. Identification of patients with a fast disease progression is a challenge. Pain coping plays an important role in pain experience, but the significance for clinical practice remains unclear and deserves more attention in future study designs.

Finally, I would like to emphasize that the GP plays an essential role in diagnosing and managing early symptomatic knee and/or hip OA.

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Summary

Osteoarthritis (OA) is one of the most common chronic diseases and is one of the leading causes of pain and disability worldwide. OA can occur in many joints in the body, but patient consultation rates due to knee and hip OA are the highest in primary care. The main symptoms of both knee and hip OA are joint pain and stiffness, varying from mild to severe or disabling symptoms. Consequently, patients are restricted in their daily activities which has an impact on an individual's quality of life.

KNEE OA

Only relatively few prognostic factors for knee (and hip) OA are known, and the evidence for the majority of these factors is nearly a decade old and is often not based on primary care patients with OA or those in an early symptomatic phase of the disease.

Prognostic Factors

In **Chapter 2**, we therefore performed a systematic review of prognostic factors for the progression of symptomatic knee OA, defined as increase in pain, decline in physical function or total joint replacement. For that, we searched for all available observational studies to a specified search strategy. In total, 30 out of 1,392 identified articles articles met the inclusion criteria and 38 determinants were investigated. The best evidence synthesis showed strong evidence that age, ethnicity, body mass index (BMI), co morbidity count, magnetic resonance imaging (MRI)-detected infrapatellar synovitis, joint effusion and baseline OA severity (both radiographic and clinical) are associated with clinical knee OA progression. There was moderate evidence showing that education level, vitality, pain-coping subscale resting, MRI-detected medial femorotibial cartilage loss and general bone marrow lesions are associated with clinical knee OA progression. However, evidence for the majority of determinants was limited (including knee range of motion or markers) or conflicting (including age, gender and joint line tenderness). A large variety in definitions of clinical knee OA (progression) remains. The pathophysiology of radiographic factors and their relation with symptoms needs to be further explored. In **Chapter 3**, we updated a systematic review of available evidence regarding prognostic factors for radiographic knee OA progression. The original review contained 36 articles and additionally 43 out of 1,912 articles were included, resulting in a total of 79 articles in the updated review. The pooled odds ratio (OR) of two determinants showed associations with knee OA progression: baseline knee pain (OR, 2.38 [95% CI, 1.74-3.27) and Heberden nodes (OR, 2.66 [95% CI, 1.46-8.84]). Our best-evidence synthesis showed strong evidence that varus alignment, serum hyaluronic acid, and tumor necrosis factor-α are associated with knee OA progression. There is strong evidence that sex, former knee injury, quadriceps strength, smoking, running, and regular performance of sports are

not associated with knee OA progression. Evidence for the majority of determined associations, however, was limited, conflicting, or inconclusive. Again, large variation remains in definitions of knee OA and knee OA progression. Clinical studies should use definitions more consistently to facilitate data pooling by future meta-analyses.

Pain progression

Pain is the primary symptom in individuals with OA. But pain due to knee or hip OA is known to fluctuate, characterized by periods of severe joint pain and periods with less or even no pain in the affected joint. Assessing the average pain severity in an individual with OA can be challenging, because it is so time dependent. Multiple assessments of pain over time therefore could provide a better indication of an individual's course of pain throughout the disease as opposed to one single pain assessment during the course of follow up. This course of pain, or pain trajectory, might be a more accurate representation of clinical disease severity or clinical disease progression.

In **Chapter 4**, we define distinct pain trajectories in individuals with early symptomatic knee OA and determine risk factors for these pain trajectories. We used 5-year follow-up data from a multicenter prospective Cohort Hip and Cohort Knee study (CHECK) in The Netherlands. The outcome was annually assessed by the Numeric Rating Scale (NRS) for pain. Pain trajectories were retrieved by using latent class growth analysis. In total, 705 participants were included. Six distinct pain trajectories were identified with favourable and unfavourable pain trajectory courses. We found significant differences in baseline characteristics, including body mass index (BMI); symptom severity; and pain coping strategies between the different trajectories. Higher BMI, lower education, more co morbidity, higher activity limitation scores and joint space tenderness were more often associated with trajectories characterized by more pain at first presentation and pain progression – compared with the reference group with a mild pain trajectory. No association was found for baseline radiographic features. These results can help differentiate those patients that require more specific monitoring in the management of early symptomatic knee OA from those for whom a 'wait-and-see' policy seems justifiable.

HIP OA

In **Chapter 5**, we performed similar analyses for hip pain as in the previous chapter. In this chapter, we define distinct hip pain trajectories in individuals with early symptomatic hip OA and determine risk factors for these pain trajectories. Again data were obtained from the CHECK study. Participants with hip pain or stiffness and a completed 5-year follow-up were included. Outcome again was annually assessed by the NRS for pain. Pain trajectories were retrieved by latent class growth analysis. As a result, 545

participants were included. Four distinct pain trajectories were uncovered by LCGA. We found significant differences in baseline characteristics, including BMI; symptom severity; pain coping strategies and in criteria for clinical hip OA. Lower education, higher activity limitation scores, frequent use of pain transformation as coping strategy and painful internal hip rotation were more often associated with trajectories characterized by more severe pain. Similar to the results from the previous chapter, no association was found for baseline radiographic features. Defining four distinct pain trajectories suggests that there are differences in symptomatic progression of hip OA.

KNEE & HIP OA

As previously mentioned, an increasing number of patients are at risk for progression of knee and hip OA, which can ultimately lead to total joint replacement (TJR) surgery if symptoms progress severly. However, not all patients with lower joint OA undergo surgery, suggesting that OA progression is dependent on patient characteristics; or varies between so called phenotypes of OA; or there is variability between surgeons in when to offer surgery. In **Chapter 6**, we determine patient- and disease characteristics associated with undergoing TJR within six years follow-up in participants from CHECK with recent onset knee and/or hip OA. Joint dependent characteristics were compared using generalized estimating equations (GEE). Differences in symptomatic and radiographic progression were determined between baseline and two years follow-up (T2). In total, 751 participants (1,502 knees) were included in the knee subgroup; 538 participants in the hip subgroup (1,076 hips). 19 participants (22 knees) underwent Total Knee Arthroplasty (TKA) and 53 participants (62 hips) Total Hip Arthroplasty (THA). Participants who underwent TKA had higher baseline BMI, painful knee flexion and higher K/L scores. Participants who underwent THA had painful internal hip rotation and showed more severe radiographic OA features. Participants who underwent TKA or THA showed more rapid symptomatic and radiographic OA progression at T2. In all subjects with recent onset knee or hip pain, radiographic OA features already exist and a substantial number of subjects fulfil existing criteria for knee and hip OA.

Pain is the most common symptom in individuals with OA. Pain experience is subjective and has many dimensions, such as psychological stress or reduced independence. Individuals with knee and hip OA use various strategies to cope with their pain. These strategies play an essential part in pain experience. In **Chapter 7**, we test if pain coping strategies act as mediating factors between pain severity and role limitations in individuals with early symptomatic lower limb OA. These are participants from CHECK with either knee and/or hip pain. We also determine the possible mediating effect lon-

gitudinally. WOMAC pain and role limitations due to physical health were measured repeatedly during 5 years follow-up. Role limitations were assessed by the SF-36 subscale. Structural equation models (SEM) were used to cross-sectionally determine the direct association between pain and role limitations, and the mediating effects of 6 types of pain coping strategies. Additionally, the mediating effects of coping strategies were tested in a longitudinal SEM model. A total of 920 participants were included (mean age 55.9 ± 5.1 years; 79% female). 705 participants reported knee pain; 545 participants reported hip pain at baseline. The univariate associations between WOMAC pain and role limitations remained statistically significant during follow-up, indicating that a higher WOMAC pain score is associated with more limitations. All six coping strategies showed significant mediating effects in the associations between WOMAC pain and role limitations cross-sectionally. Longitudinally, the mediating effects were small and only 'worrying' remained statistically significant. This concludes that pain coping strategies play an essential role on the causal pathway between pain severity and role limitations in individuals with (chronic) pain due to lower limb OA. These results underline the potential importance of assessing pain coping behavior already in the early stage of OA.

Finally, in **Chapter 8**, we reflected on the main findings in this thesis and elaborate on their implications for clinical practice and research.

Nederlandse samenvatting

Artrose is een van de meest voorkomende chronische aandoeningen en is wereldwijd een van de belangrijkste oorzaken van pijn en functiebeperkingen. Artrose kan in vele gewrichten van het lichaam voorkomen, maar in de huisartsenpraktijk komen knie- en heupartrose het vaakst voor. De belangrijkste symptomen van zowel knie- als heupartrose zijn gewrichtspijn en stijfheid, variërend van milde tot ernstige en zelfs invaliderende symptomen. Als gevolg hiervan worden patiënten beperkt in hun dagelijkse activiteiten, wat de kwaliteit van leven van een individu kan beïnvloeden.

KNIEARTROSE

Er zijn slechts relatief weinig prognostische factoren voor knie(en heup-)artrose bekend. Het is belangrijk om prognostische factoren van een aandoening te kennen, met name om progressie van een aandoening of ziekte te proberen te voorkomen en om personen met een hoge(re) kans op snelle progressie meer intensief te monitoren en te behandelen. Het bewijs voor de meeste van de prognostische factoren voor knieartrose is bijna een decennium oud en is vaak niet gebaseerd op een patiëntenpopulatie met artrose uit de eerstelijn, of op patiënten in een vroeg-symptomatische stadium van de aandoening.

Prognostische factoren

In **Hoofdstuk 2** hebben we een systematische review over prognostische factoren voor progressie van knieartrose uitgevoerd. Progressie werd gedefinieerd als toename van pijn, fysieke beperkingen of het verkrijgen van een gewrichtsprothese. We hebben gezocht naar alle beschikbare observationele studies volgens een specifieke zoekstrategie. In totaal voldeden 30 van de 1.392 gevonden artikelen aan de inclusie criteria en werden 38 determinanten onderzocht. Een 'best evidence synthesis' toonde sterk bewijs dat leeftijd, etniciteit, body mass index (BMI), co-morbiditeit, infrapatellaire synovitis op 'Magnetic Resonance Imaging'(MRI), vocht in het gewricht, en ernst van artrose klachten op baseline (zowel radiografisch als klinisch) geassocieerd zijn met progressie van klinische knieartrose. Er was matig bewijs dat opleidingsniveau, vitaliteit, een strategie om met pijn om te gaan, ofwel 'pain-coping' strategie 'rusten', mediale femorotibiaal kraakbeenverlies aantoonbaar op een MRI en beenmergletsels in het algemeen op MRI verband houden met progressie van klinische knieartrose. Het bewijs voor de meerderheid van de determinanten was echter beperkt (inclusief 'range of motion (ROM)' van de knie of serum markers) of tegenstrijdig (waaronder leeftijd, geslacht en een pijnlijke gewrichtsspleet). De review maakt duidelijk dat er een grote verscheidenheid in definities van (progressie van) klinische knieartrose bestaat. De pathofysiologie van radiografische factoren en hun relatie met symptomen moet verder worden onderzocht.

In **Hoofdstuk 3** hebben we een systematische review herzien van beschikbaar bewijs over prognostische factoren voor progressie van radiografische knieartrose. De oorspronkelijke review uit 2003 bevat 36 artikelen. Een nieuwe zoekstrategie over de periode 2003 tot 2013 leverde 1.912 artikelen op waarvan er 43 konden worden geincludeerd, waardoor in totaal 79 artikelen in de herziene review zijn opgenomen. De 'pooled odds ratio' (OR) van twee determinanten vertoonde associaties met progressie van knieartrose: baseline kniepijn (OR, 2,38 [95% CI, 1,74-3,27) en 'Heberden nodes' (OR, 2,66 [95% CI, 1,46-8,84]). Onze 'best evidence synthesis' gaf sterk bewijs dat een varus stand van de knie, serum hyaluronzuur en tumornecrosefactor-α geassocieerd zijn met progressie van knieartrose. Er is eveneens sterk bewijs dat geslacht, voormalige knieblessures, quadriceps kracht, roken, hardlopen en regelmatige sportuitoefening geen associatie hebben met progressie van knieartrose. Het bewijs voor de meerderheid van de overig onderzochte associaties was echter beperkt, tegenstrijdig of onvoldoende. Grote variatie blijft in definities van knieartrose en progressie van knieartrose. Klinische studies dienen meer consistente definities van artrose te gebruiken om data pooling in toekomstige meta-analyses mogelijk te maken.

Pijnprogressie

Pijn is het meest kenmerkende symptoom bij personen met artrose. Maar pijn door knie- of heupartrose staat erom bekend te fluctueren, wat zich kenmerkt door perioden van ernstige gewrichtspijn en perioden met minder of zelfs geen pijn in de aangedane gewrichten. Het beoordelen van de (gemiddelde) ernst van pijn bij een individu met artrose kan uitdagend zijn, omdat pijn erg subjectief is, en het dus zo tijdsafhankelijk is. Het vaker beoordelen van pijn over de tijd zou een betere aanduiding kunnen geven van de mate van pijn, in tegenstelling tot een enkel moment van pijnbeoordeling in individuen met artrose. Dit pijnbeloop zou een nauwkeuriger voorstelling kunnen weergeven van de ernst van de symptomen van de aandoening, oftewel de progressie van klinische knieartrose.

In **Hoofdstuk 4** definiëren we afzonderlijke pijnbelopen bij personen met vroeg-symptomatische knieartrose en bepalen we risicofactoren voor deze pijnbelopen. We hebben 5 jaars follow-up data gebruikt van een prospectieve cohort studie, de Cohort Heup en Cohort Knie studie (CHECK) in Nederland. In de CHECK studie werden 1.002 deelnemers in de leeftijd van 45 tot 65 jaar met vroeg-symptomatische knie- en/of heupartrose gedurende 10 jaar gevolgd. Voor onze uitkomstmaat werd gebruik gemaakt van de jaarlijkse *Numeric Rating Scale* (NRS) voor pijn scores. Pijnbelopen werden gecreeerd door middel van de analyse techniek van *Latent Class Growth Analyses* (LCGA). Er waren in totaal 705 deelnemers. Zes verschillende pijnbelopen werden geïdentificeerd. We vonden significante verschillen in baseline kenmerken tussen de verschillende pijnbelopen, waaronder body mass index (BMI); ernst van symptomen; en *pain-coping* stra-

tegieën. Hogere BMI, lager onderwijs, meer co-morbiditeit, hogere scores van functie beperking en een pijnlijke gewrichtsspleet werden vaker geassocieerd met belopen die gekenmerkt werden door meer pijn bij eerste presentatie en pijnprogressie - in vergelijking met de referentiegroep met een mild pijnbeloop. Er werden geen associaties gevonden voor baseline radiografische kenmerken. Deze resultaten kunnen helpen bij het onderscheiden van die patiënten met vroeg-symptomatische knieartrose die meer specifieke monitoring nodig hebben vergeleken met patiënten bij wie een afwachtend beleid gerechtvaardigd lijkt.

HEUPARTROSE

In **Hoofdstuk 5** hebben we vergelijkbare analyses uitgevoerd als in het vorige hoofdstuk, maar dan bij heuppijn. In dit hoofdstuk definiëren we verschillende belopen van heuppijn bij personen met vroeg-symptomatische heupartrose en bepalen we risicofactoren voor deze pijnbelopen. Opnieuw werden gegevens verkregen uit de CHECK studie. Deelnemers met heuppijn of -stijfheid en een voltooide 5 jaars follow-up werden geïncludeerd. Voor de uitkomstmaat werd gebruik gemaakt van de jaarlijkse pijnscore (NRS, *Numeric Rating Scale*). Pijnbelopen werden gecreëerd door middel van *Latent Class Growth Analyses* (LCGA). Er werden 545 deelnemers geïncludeerd. Vier verschillende pijnbelopen werden geïdentificeerd door LCGA. We vonden significante verschillen in baseline kenmerken tussen de verschillende pijnbelopen, waaronder BMI; ernst van symptomen; *pain-coping* strategieën en classificatie criteria voor klinische heupartrose. Lager onderwijs niveau, hogere scores van functie beperkingen, frequent gebruik van de *pain-coping* strategie 'pijn transformatie' en pijnlijke endorotatie van de heup werden vaker geassocieerd met pijnbelopen gekenmerkt door ernstigere pijn. Net als bij de resultaten van het vorige hoofdstuk werden geen associaties gevonden voor baseline radiografische kenmerken. Het kunnen identificeren van vier verschillende pijnbelopen suggereert dat er verschillen bestaan in de manier waarop symptomatische heupartrose verloopt.

KNIE- & HEUPARTROSE

Zoals eerder vermeld, lopen een toenemend aantal patiënten het risico op progressie van knie- en heupartrose, wat uiteindelijk kan resulteren in het ondergaan van gewrichtsvervangende operaties indien de symptomen dusdanig invaliderend worden. Echter, niet alle patiënten die artrose hebben in de onderste extremiteiten ondergaan een operatie, wat suggereert dat progressie van artrose afhankelijk is van patiënten

karakteristieken; of varieert tussen zogenaamde fenotypes van artrose; of variabiliteit tussen chirurgen over de redenen om wel of niet te opereren. In **Hoofdstuk 6** bepalen we de patiënt- en ziektekarakteristieken die verband houden met het ondergaan van een gewrichtsvervangende operatie binnen zes jaar follow-up bij deelnemers van de CHECK studie, kort na de eerste symptomen van knie en/of heupartrose. Gewrichtsafhankelijke eigenschappen werden vergeleken met behulp van de analyse techniek *Generalized Estimating Equations* (GEE). Ook werden verschillen in symptomatische en radiografische progressie bepaald tussen baseline en na twee jaar follow-up (T2). In totaal werden 751 deelnemers (1.502 knieën) geïncludeerd in de knie-subgroep; 538 deelnemers in de heup subgroep (1.076 heupen). 19 deelnemers (22 knieën) kregen een Totale Knie Prothese (TKP) en 53 deelnemers (62 heupen) een Totale Heup Prothese (THP). Deelnemers die een TKP kregen, hadden een hogere baseline BMI, pijnlijke knie flexie en ernstigere radiografische artrose scores (zogenaamde *Kellgren & Lawrence* (K/L) score). Deelnemers die een THP kregen, hadden een pijnlijke endorotatie van de heup en hadden ook ernstigere radiografische artrose scores. Deelnemers die een TKP of THP kregen, vertoonden een snellere symptomatische en radiografische progressie van artrose na twee jaar follow up. In alle deelnemers met recent ontstane knie- of heuppijn zijn al eigenschappen van radiografische artrose zichtbaar en een aanzienlijk aantal deelnemers voldeden reeds aan bestaande criteria voor knie- en heupartrose.

Pijn is het meest voorkomende symptoom bij personen met artrose. Pijn ervaring is echter subjectief en heeft vele dimensies, zoals psychologische stress of verminderde onafhankelijkheid. Individuen met knie- en heupartrose gebruiken verschillende *pain-coping* strategieën om met hun pijn om te gaan. Deze strategieën spelen een essentieel onderdeel in pijnervaring. In **Hoofdstuk 7** testen we of *pain-coping* strategieën fungeren als *mediating factors* tussen ernst van pijn en rolbeperkingen bij personen met vroeg-symptomatische artrose van de onderste extremiteiten. Dit zijn deelnemers van de CHECK studie met knie- en / of heuppijn. We bepalen ook het mogelijke mediërend effect op de langere termijn (longitudinaal). De *Western Ontario and McMaster universities osteoarthritis index* (WOMAC) score voor pijn en 'Rolbeperkingen door fysieke gezondheid' werden herhaaldelijk gemeten gedurende 5 jaar follow-up. Rolbeperkingen werden beoordeeld door de SF-36 subschaal. De analyse techniek *Structural Equation Modeling* (SEM) werd gebruikt om de directe associatie tussen pijn en rolbeperkingen te bepalen en het mediërend effect van 6 soorten *pain-coping* strategieën. Daarnaast werd het mediërende effect van coping strategieën getest in een longitudinale SEM-model. Er werden in totaal 920 deelnemers geïncludeerd (gemiddelde leeftijd 55,9 ± 5,1 jaar, 79% vrouw). 705 deelnemers meldden kniepijn; 545 deelnemers meldden heuppijn op baseline. De univariate associaties tussen WOMAC Pijn en rolbeperkingen bleven statistisch significant tijdens de follow-up, wat aangeeft dat een hogere WOMAC Pijn score wordt

geassocieerd met meer beperkingen. Alle zes coping strategieën toonden significante mediërende effecten in de associaties tussen WOMAC Pijn en rolbeperkingen in cross-sectionele analyse. Longitudinaal waren de mediërende effecten klein en alleen de strategie 'worrying' (zorgen maken over pijn) bleef statistisch significant. Hieruit wordt geconcludeerd dat *pain-coping* strategieën een essentiële rol spelen in het verband tussen de ernst van pijn en rolbeperkingen bij personen met (chronische) pijn door artrose van de onderste extremiteiten. Deze resultaten onderstrepen het mogelijke belang van het al in een vroeg stadium van artrose beoordelen van *pain-coping* gedrag.

Tenslotte reflecteren we in **Hoofdstuk 8** over de belangrijkste bevindingen van dit proefschrift en verdiepen we ons in de implicaties voor de praktijk en voor wetenschappelijk onderzoek.

About the author

Alex Bastick was born on April 3rd 1984 in Scarborough, Canada. He and his family moved to The Netherlands in 1992. He attended secondary school at Mgr. Frencken College in Oosterhout and graduated in 2002. He studied medicine at the faculty of Erasmus MC, University Medical Center in Rotterdam and graduated in 2008. After his graduation he worked as a volunteer MD at Nawanyago Medical Health Care Clinic in Uganda for three months. Later, he worked for a year as an intern at Maasstad Hospital in Rotterdam for the departments of nephrology & dialyses, gastroenterology and emergency care. In 2010 he began his specialty training for general practitioners (GP) at Erasmus MC in Rotterdam, combining this with a PhD-project in 2011 for the department of General Practice under the supervision of prof.dr. Sita Bierma-Zeinstra and prof.dr. Patrick Bindels. His research data were mainly obtained from a nationwide, 10-year follow-up cohort study of 1,002 participants with early symptomatic knee and/or hip osteoarthritis (the Cohort Hip & Cohort Knee, or *CHECK* study). In 2012 he obtained a Master of science (MSc) degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES, Erasmus MC Rotterdam). During his GP-training he was also a member and later chairman of *LOVAH Rotterdam* (the Rotterdam division of the National Organization of GP-Trainees) from 2011 to 2014.

In 2014 he completed his GP-training. After working at various practices and emergency departments as a GP, he and a fellow GP purchased their own practice in Oosterhout in 2017.

Alex met his wife Marly in 2002, whom he married in 2010. They live in Breda with their three children Liam (2011), Libby (2013) and Owen (2015).

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PhD Portfolio

PHD TRAINING	YEAR	ECTS
Courses		
Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2011-2012	70
Professional education		
Vocational training for general practitioner, Erasmus MC, Rotterdam	2010-2014	
Conferences		
Awards		
Young Investigator Award, OARSI World Congress, Amsterdam	2016	
Oral presentations		
The XVI Cochrane Colloquium, Freiburg, Germany	2008	2
OARSI World Congress, Amsterdam, The Netherlands	2016	2
NHG Congres, Leeuwarden, The Netherlands	2016	2
Poster presentations		
OARSI World Congress, Philadelphia, USA	2013	1
NAPCRG, Ottowa, Canada	2013	1
NHG Wetenschapsdag, Leiden, 2013	2013	1
TEACHING ACTIVITIES		
Supervising medical student sessions 'How to judge a paper'	2011	2

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