CHECK, A MULTICENTER COHORT OF PERSONS WITH EARLY OSTEOARTHRITIS

Janet Wesseling

CHECK,
A MULTICENTER COHORT OF PERSONS WITH EARLY OSTEOARTHRITIS

CHECK, een multicenter cohort van personen met beginnende artrose
(met een samenvatting in het Nederlands)

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1

INTRODUCTION

photo's from the internet

OSTEOARTHRITIS IS NOT A SIMPLE CONSEQUENCE OF AGEING. At the end of the twentieth century it became clear that osteoarthritis (OA) can no longer be regarded as a simple consequence of ageing and cartilage degeneration. The label of degenerative joint disease is now recognized to be incomplete, or even a misnomer. In understanding osteoarthritis it helps to make a distinction between the disease process as such, leading to structural changes in the different joint tissues, and patients complaints associated with osteoarthritis: the illness OA. The disease process usually involves progressive changes in synovial joints, ultimately leading to damage of the whole joint. This implies that any tissue of the joint can be involved: articular cartilage, bone tissue, such as underneath the cartilage and marginal outgrowths –osteophytes–, soft tissue structures in and around the joint (muscles, ligaments and menisci) and in most patients synovial tissue.[1] It is now well recognised that OA is not one disease entity: characteristics of late stage disease may reflect final common pathways of different phenotypes, that may differ in (early) symptoms and pathogenic mechanisms.[2]

DISEASE PROCESS AND ILLNESS OF OA ARE NOT THE SAME

Patients complaints associated with OA are pain, stiffness, limitations in function, influencing daily life activities (walking, getting up, sitting down) and restrictions in work and household activities.[3] Particularly in early stages of the disease, there is a weak correlation between complaints and structural damage.[4] This limited overlap between the disease process OA (structural changes) and the illness OA (patients' complaints) in early disease was one of the reasons to start an early OA cohort and ensuing research. Other reasons included poorly understood course of complaints and mechanisms in the early stage of disease, ultimately leading to structural damage. From the perspective of prevention and early intervention, it is important to diagnose the disease at an early stage and to recognise its prognostic signs. This early stage of presentation of OA without recognizable structural damage is often referred to as 'early or symptomatic OA'. To address the many gaps in these areas, the Dutch Arthritis Foundation (DAF) initiated and funded an inception cohort of patients with early symptomatic osteoarthritis (OA) of the hip and/or knee: CHECK (Cohort Hip & Cohort Knee). CHECK set out to study clinical, biochemical and radiographic signs and symptoms of early OA with 10-year follow-up, to identify prognostic factors for diagnosis and progression, and to study the underlying mechanisms that may cause these symptoms.

Apart from focussing on the course (evolution) of the complaints and structural damages of the total patient population, it is also important to study individual development of complaints and/or structural changes over time to subsequently identify groups of subjects with comparable trajectories. Better understanding of more homogeneous trajectories in OA patients could offer important insights into clinical prognosis and could even form a starting point for specific treatment.

NO SINGLE DEFINITION FOR OA, NOR FOR EARLY OA

There is no single accepted definition or classification system for (early) OA. Despite the fact that OA is frequently diagnosed by the general practitioner, there are no criteria which are developed and validated in primary care. The clinical criteria that are commonly used are those produced some years ago by the American College of Rheumatology (ACR), but they were derived from data that compared hospital patients with a diagnosis of OA with those who had inflammatory joint disease. One has to consider that criteria which are developed in a clinical setting are of limited use for primary care. It should be emphasized that there are no criteria available for early OA, which is of relevance for early diagnosis and possible targeted treatment to prevent or limit progression.

In 2000, when the Cohort Hip & Cohort Knee (CHECK) study was designed, this was one of the reasons to evaluate in the CHECK study whether it would be feasible to establish criteria for early OA, that are broader than the ACR (American College of Rheumatology) criteria for the classification of OA of hip and knee.[5,6]

The prevalence of OA varies and depends on the joints of interest and the definition used: from purely radiographic OA based on structural changes versus only symptomatic OA.[7] Data derived from general practice registrations in the Netherlands estimate the number of patients that are actually being treated for hip and knee OA as 359,000 men and 594,000 women.[8]

DEFINING AN EARLY OA COHORT

Pain is the first and predominant symptom of OA that causes patients to visit their general practitioner. They also experience stiffness, which generally resolves in minutes when the affected joints are used.[2,9] These complaints are part of the clinical ACR criteria and are also of relevance for early OA. However, also bony tenderness and crepitus are part of the clinical ACR criteria of knee OA, but they are seldom present early in the disease. Limitation of hip movements (ACR criteria: internal rotation ‹ 15°) is not seen as a characteristic of early OA either, based on the results of diagnosing hip OA in primary care research.[10] Being older than 50 years is also part of the ACR criteria for OA of hip or knee. Since OA often starts before this age, the age criteria for early OA should perhaps be reduced. The period between

TABLE 1 | Criteria of early osteoarthritis cohort CHECK

Inclusion criteria of early osteoarthritis cohort: CHECK
pain of knee and/ or hip
age of 45-65 years
at or within 6 months of their first visit to the general practitioner for these symptoms
Exclusion criteria
any other pathological condition that could explain the symptoms (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, Bakers cyste)
co-morbidity precluding physical evaluation and/or follow-up of at least 10 years
malignancy in the last 5 years
inability to understand the Dutch language

45-65 years is interesting to evaluate, since many persons in this category still participate in paid work. There is a lack of knowledge about work status in relation to early OA.

The knee and hip are most affected by OA and are the most important cause of pain.[2,11] Disease in these weight-bearing joints has great functional impact and is frequently associated with disability in activities of daily living (ADL) involving lower extremity functions such as walking, transferring, and using the bathroom. The hip and knee are therefore the relevant joints for an early OA study. These and other thoughts ultimately led to the following inclusion criteria of the early osteoarthritis Cohort Hip & Cohort Knee study (see *table 1*).

INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH AS FRAMEWORK

To categorise a wide range of information concerning disease process, complaints and health status, the World Health Organisation (WHO) designed the ICF (International Classification of Functioning, Disability and Health). The ICF model provides an integrative framework, combining biological, psychological and social aspects of health and disease.[12] The ICF model identifies three main distinct outcomes: Impairment (I), Activity limitations (A) and Participation restrictions (P) and their respective opposites: Body Function and Structure, Activity and Participation. The ICF framework emphasizes that an individual's health experience is the interaction between the health condition (biological dysfunction) and social, personal and environmental factors.

In CHECK data are collected on these different outcomes, by assessing clinical, biochemical and radiographic variables. Clinical variables include parameters of body function and structure, performed activities and participation as well as factors of environment and personal factors. Measurements of biochemical and radiographic variables are mainly focused on changes in biological function, to study the underlying mechanisms that may cause the symptoms and complaints, as well as to identify prognostic factors for diagnosis and progression of early OA.

THE UNIQUENESS OF CHECK

As stated above, to address the many gaps in the area of early symptomatic OA, the Dutch Arthritis Foundation initiated an inception cohort of early symptomatic OA of the hip or knee: CHECK. A systematic review on the course of functional status and pain in OA of the hip and knee reported that the number of longitudinal studies on functional outcome in OA is limited.[13] Most cohorts, such as the Johnston County OA project, the Framingham study, or Bristol OA 500 study, recruited on radiological criteria, thus creating cohorts with radiological evidence of OA.[14,15,17] Other cohorts had another design, such as the Chingford study, Clinical Assessment Study Knee (CAS[K]), Multicenter Osteoarthritis Study (MOST) and the Osteoarthritis Initiative (OAI) studies that focus on knee OA; included only women (Chingford) or radiographic OA or subjects at high risk for developing the disease (MOST), or had a follow-up of 3 years.[16,18-20] There was no cohort of hip and knee OA with a long (ten years) follow-up and collecting the clinical, biochemical and radiographic outcomes of OA.

An important additional objective of the CHECK study is to create an infrastructure for osteoarthritis research. Basis of the study is 10-year follow-up of a cohort of 1,000 participants with early symptomatic OA of hip or knee, thereby offering the possibility to add spin-off studies to this infrastructure. During follow-up of the CHECK-cohort, CHECK became also unique in the sense that there was only a very limited drop-out (88% was still in the study at 8 years follow-up).

OUTLINE AND SCOPE OF THIS THESIS

The research described in this thesis is a small part of the CHECK study. The overall aim is to analyze disease characteristics (pain, physical functioning) of early symptomatic OA and to examine evolution of structural damage in relation with disease characteristics. As an introduction we provide up-to-date details of CHECK, also to enable researchers worldwide to start collaborations and to maximize use of existing resources (*chapter 2*).

In *part I* of the thesis differences between two cohorts of persons with early osteoarthritis are described. As already mentioned above, parallel to CHECK, an observational study on OA was initiated by the National Institutes of Health: the Osteoarthritis Initiative. This 4-year follow-up study had also the objective to study the natural history of, and risk factors for, the onset and progression of knee OA. In fact both initiatives, CHECK and the OAI, search answers to similar questions in different populations. We wondered whether CHECK and on comparable inclusion criteria selected study populations of the OAI are similar and if detailed information from both cohorts can be used as a basis for further research (*chapter 3*). To answer this question first only baseline data were analyzed, and more differences then expected were observed. Therefore, we compared longitudinal data of both cohorts to question how the observed differences in the relation of joint damage and evolution of pain and physical functioning developed in these two cohorts (*chapter 4*).

In *part II* we focus on differences in evolution of disease characteristics within the CHECK-participants. OA has a very high number of comorbidities, significantly more than non-OA patients.[21-23] First the question is discussed what the relationship might be between comorbidity (absolute number as well as the presence of specific comorbidities) and pain, physical functioning and mental health status of participants with early symptomatic OA (*chapter 5*). We know that the level and course of the main clinical symptom pain can be very different between patients over time.[24] We wondered whether we could identify homogeneous subgroups of pain trajectories in patients with symptomatic knee OA, and whether we could explain these different pain trajectories by disease characteristics (*chapter 6*). An obvious next question was whether homogenous subgroups also exist with regard to structural damage. Could we identify subgroups of CHECK-participants with homogeneous patterns of osteophyte formation over time (trajectories), and could we identify prognostic factors for these different trajectories (*chapter 7*)?

It is evident that these questions are only part of the large amount of research within CHECK. In the general discussion (*chapter 8*) our findings will be placed into perspective and suggestions for future research will be given. —

REFERENCES

1. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011; 19:478-82.

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

3. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994; 84:351-8.

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

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

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

7. Pereira D, Peleteiro B, Araujo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartilage 2011; 19:1270-85.

8. Artrose: prevalentie en incidentie naar leefijd en geslacht. Nationaal Kompas Volksgezondheid 2014. www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/bewegingsstelsel-en-bindweefsel/artrose/prevalentie-en-incidentie-naar-leeftijd-en-geslacht/

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

10. Bierma-Zeinstra S, Bohnen A, Ginai A, Prins A, Verhaar J. Validity of American College of Rheumatology criteria for diagnosing hip osteoarthritis in primary care research. J Rheumatol 1999; 26: 1129-33.

11. Corti MC, Rigon C. Epidemiology of osteoarthritis: prevalence, risk factors and functional impact. Aging Clin Exp Res 2003; 15:359-63.

12. Cieza A, Stucki G. New approaches to understanding the impact of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2004; 18:141-54.

13. van Dijk GM, Dekker J, Veenhof C, Van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: A systematic review of the literature. Arthritis Rheum 2006; 55:779-85.

14. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007; 34:172-80.

15. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997; 40:728-33.

16. Goulston LM, Kiran A, Javaid MK, Soni A, White KM, Hart DJ, et al. Does obesity predict knee pain over fourteen years in women, independently of radiographic changes? Arthritis Care Res (Hoboken) 2011; 63:1398-406.

17. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol 'OA500' study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthritis Cartilage 1997; 5:87-97.

18. Peat G, Thomas E, Handy J, Wood L, Dziedzic K, Myers H, et al. The Knee Clinical Assessment Study-CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population: baseline recruitment and retention at 18 months. BMC Musculoskelet Disord 2006;7:30.

19. Roemer FW, Zhang Y, Niu J, Lynch JA, Crema MD, Marra MD, et al. Tibiofemoral joint osteoarthritis: risk factors for MR-depicted fast cartilage loss over a 30-month period in the multicenter osteoarthritis study. Radiology 2009; 252:772-80.

20. Osteoarthritis Initiative (OAI). 2009. http://www.oai.ucf.edu/

21. Caporali R, Cimmino MA, Sarzi-Puttini P, Scarpa R, Parazzini F, Zaninelli A, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug prescriptions by general practitioners and specialists. Semin Arthritis Rheum 2005; 35(Suppl 1):31-7.

22. Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JT, van Weel C. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 1993; 46:469-73.

23. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Ann Rheum Dis 2004; 63:408-14.

24. Yusuf E, Bijsterbosch J, Slagboom PE, Kroon HM, Rosendaal FR, Huizinga TW, et al. Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis. PLoS One 2011;6:e25426.

2

COHORT PROFILE: COHORT HIP & COHORT KNEE (CHECK) STUDY

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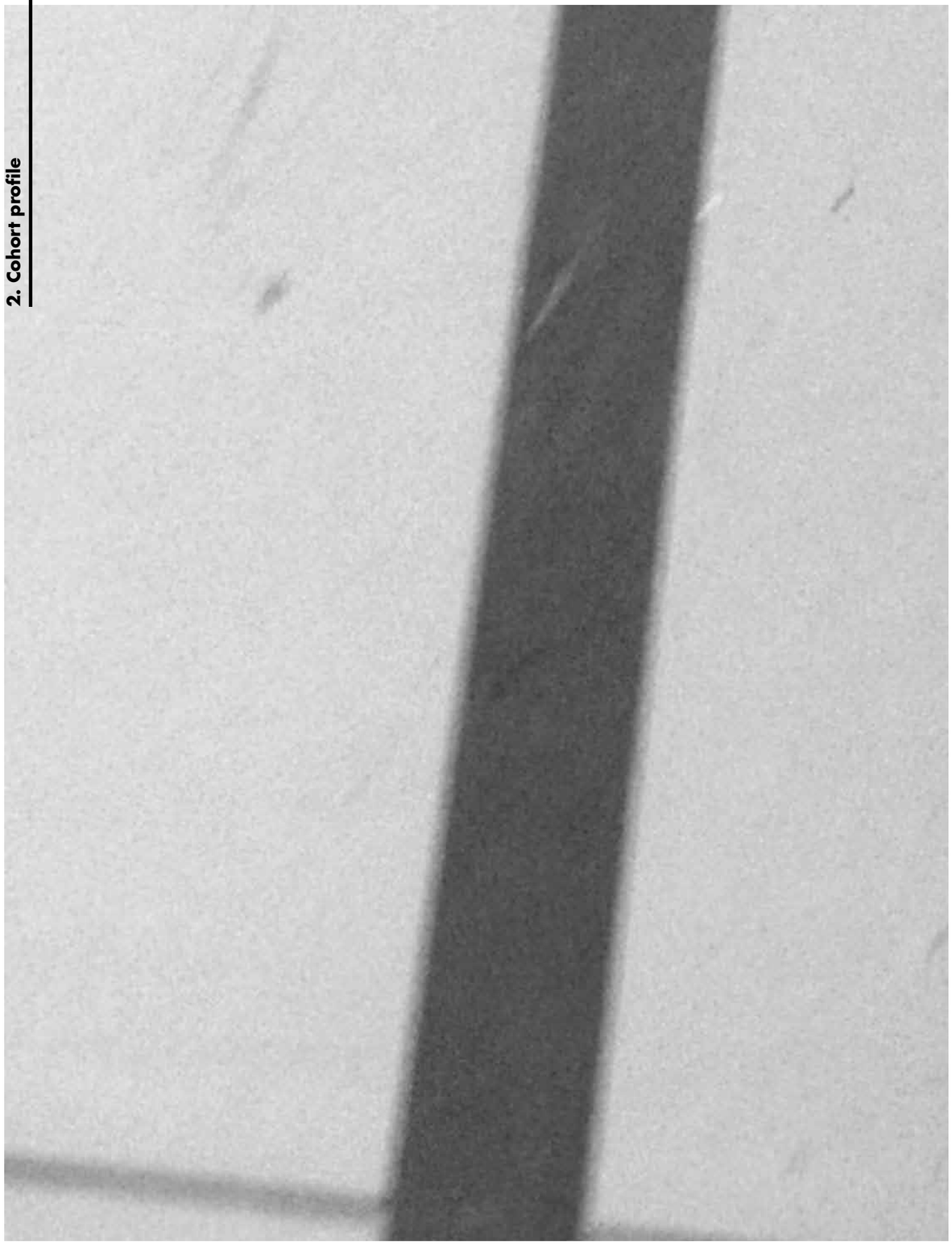

ABSTRACT

The Cohort Hip & Cohort Knee (CHECK) study included participants with early symptomatic osteoarthritis (OA) of the hip or knee and evaluated clinical, radiographic and biochemical variables in order to establish the course, prognosis and underlying mechanisms of early symptomatic osteoarthritis. A total of 1,002 participants aged 45-65 years, with symptomatic OA characterized by pain of knee and/ or hip, entered the cohort in the period October 2002 – September 2005. They were included at or within 6 months of their first visit to the general practitioner for these symptoms. An overview of measures that are included in the study can be found on the website *www.check-research.com*. On the basis of their presenting symptoms, participants were divided into two groups. Participants with mild symptoms visited the research center at year 0, 2, 5, 8 and 10 (variable visiting group) and participants with more serious symptoms visited the research center each year (annual visiting group). After 7 years only 105 participants (10%) had dropped out; their baseline characteristics did not differ significantly from other participants. CHECK is a valuable source of information on early symptomatic OA that allows the examination of high-quality data on clinical, radiographic and biochemical variables. The CHECK steering group welcomes collaboration with national and international colleagues. Request for collaboration or access to data can be sent to *checkreu@umcutrecht.nl*.

WHY WAS THE COHORT SET UP? The course of clinical symptoms and radiographic changes, prognosis and underlying mechanism of osteoarthritis (OA) is poorly understood, despite it is being the most common diagnosis in older patients with knee and hip pain. For instance, a systematic review summarized the available evidence on predictive factors for the course of hip OA, and concluded that prospective cohort studies with an adequate follow-up time were missing to strengthen the conclusions.[1] In a study on radiological progression of knee OA it became clear that further work is also needed in the selection and detection of subjects with poor prognosis.[2] From the perspective of prevention and early intervention, it is important to diagnose the disease at an early stage and recognise its prognostic signs. To address the many gaps in this area, the Dutch Arthritis Foundation (DAF) initiated and funded an inception cohort of early symptomatic osteoarthritis (OA) of the hip or knee with 10-year follow-up: CHECK (Cohort Hip & Cohort Knee).

CHECK set out to study clinical, biochemical and radiographic signs and symptoms of early OA, to identify prognostic factors for diagnosis and progression, and to study the underlying mechanisms that may cause these symptoms.

An obvious side product of the study is the creation of a Dutch infrastructure for studying osteoarthritis. CHECK offers the possibility to add spin-off studies that require access to CHECK participants (whether from a single clinical center or from the entire cohort) to collect measurements or data that are not part of the core protocol. At present 15 spin-off studies have been added to CHECK. We give a few examples of these spin-off studies. One study investigated the association between baseline hip shape assessed on radiographs, and both clinical hip OA and total hip replacement at 5 year follow-up.[3] Another spin-off study evaluated whether pentosidine can predict radiographic progression and burden of OA over 5 years follow-up. One of the major age-related changes in cartilage is the accumulation of advanced glycation endproducts (AGE). Since cartilage tissue is not readily available from subjects for studying these AGE- levels, skin pentosidine may be used as a surrogate marker for cartilage pentosidine. In this study all 300 participants of three participating centers were asked for a skin biopsy from the lower back.[4,5] In another spin-off study, the aim was to assess the validity of the avoidance model. All CHECK participants recruited through Reade, Centre for Rehabilitation and Rheumatology in Amsterdam, were invited for additional measurements (muscle strength and a performance –based measure of activity limitation).[6]

WHO IS IN THE COHORT?

From October 2002 until September 2005 a cohort was formed of 1,002 participants. Ten general and university hospitals in the Netherlands are participating, located in (semi-)urbanised regions. *Table 1* lists the inclusion and exclusion criteria. General practitioners near the participating centers were invited to refer eligible persons to these centers. Additionally, participants were recruited through advertisements and articles in local newspapers and on the Dutch Arthritis Foundation website. Most CHECK participants were recruited by advertisements or articles in newspaper (69%), 6% by their physicians, 12% by flyer/ family/ friend (12% not recorded). Medical ethics committees of all participating centers approved the study, and all participants gave written informed consent.

HOW OFTEN HAVE THEY BEEN FOLLOWED UP?

After inclusion participants were divided into two groups on the basis of their presenting symptoms *(table 2)*. Participants in the annual visiting group (with more serious symptoms) visited the research center each year; participants in the variable visiting group (with mild symptoms) visited the research center at years 0, 2, 5, 8 and 10. Participants in the variable visiting group were shifted to the annual visiting group when they met the criteria of that group. At baseline, 861 participants were classified into the annual visiting group and 141 into the variable group; after 2 years 50 participants, and after 5 years another 29 participants were shifted to the annual visiting group *(figure 1)*.

After 7 years 105 participants had been lost to follow-up. Reasons comprised loss of motivation (21%), serious comorbidity (18%), death (12%), loss of contact (11%), costs incurred (5%) and other (33%, including death of partner, move out of the area, unduly burdensome). Apart from one year difference in mean age, there were no statistically significant differences in baseline characteristics between dropouts and participants who were still participating at year 7 *(table 3)*.

WHAT HAS BEEN MEASURED?

Data collection includes clinical, radiological and biochemical data *(table 4)*. A coordinator visits the centers every three months to check and support complete and accurate data gathering.

Clinical variables

Clinical assessment comprises self-reported questionnaires, medical history questions and physical examination (clinical features of hip, knee and hands) by a trained health professional. Self-reported

TABLE 1 | The eligibility criteria of CHECK

Inclusion criteria

pain of knee and/or hip
age of 45-65 years
at or within 6 months of their first visit to the general practitioner for these symptoms

Exclusion criteria

any other pathological condition that could explain the symptoms
(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, Bakers cyste)
co-morbidity precluding physical evaluation and/or follow-up of at least 10 years
malignancy in the last 5 years
inability to understand the Dutch language

TABLE 2 | Subgroup criteria of knee and hip, used to divide participant into the variable or annual visiting group

Criteria of knee

Knee pain
Morning stiffness < 30 minutes
Crepitus
Bony tenderness

Criteria of hip

Hip pain
Morning stiffness < 60 minutes
Pain on hip internal rotation or internal rotation < 15°

Annual visiting group: participant fulfill two or more of criteria of the hip or knee
Variable visiting group: participant fulfill only one of criteria of the hip and only one of the criteria of the knee

questionnaires evaluate hip and knee symptoms,[7,8] hand symptoms,[9] pain severity,[10] coping,[11] health-related quality of life,[12-14] leisure activities and employment,[15] economic consequences,[16] social support,[17] and comorbidities[18] *(table 4)*.

Radiographic variables

Severity of knee and hip osteoarthritis is scored according to Kellgren and Lawrence (0-4 scale)[19] on the posterior-anterior radiograph of the knee and the anterior-posterior radiograph of the pelvis. Separate features of the knee and hip are scored on other radiographs according to Altman et al.[20] and the radiographic atlas of Burnett et al.,[21] both on a 0-3 scale. These radiographs are independently scored by five trained observers. Readers score all consecutive radiographs at the same time with known sequence, but blinded to the clinical status. Interobserver variability was tested in a subset of 38 participants scored by all five observers yielding moderate to substantial interobserver agreement (kappa 0.60 for presence of K&L 0 versus K&L 1- 2 - 3 in the knees, and kappa 0.67 for presence of K&L 0 versus K&L 1-2-3 in the hips, mean kappa's over three measurements: T0- T2- T5).[22] Knee Images Digital Analysis (KIDA) assesses more detailed quantitative

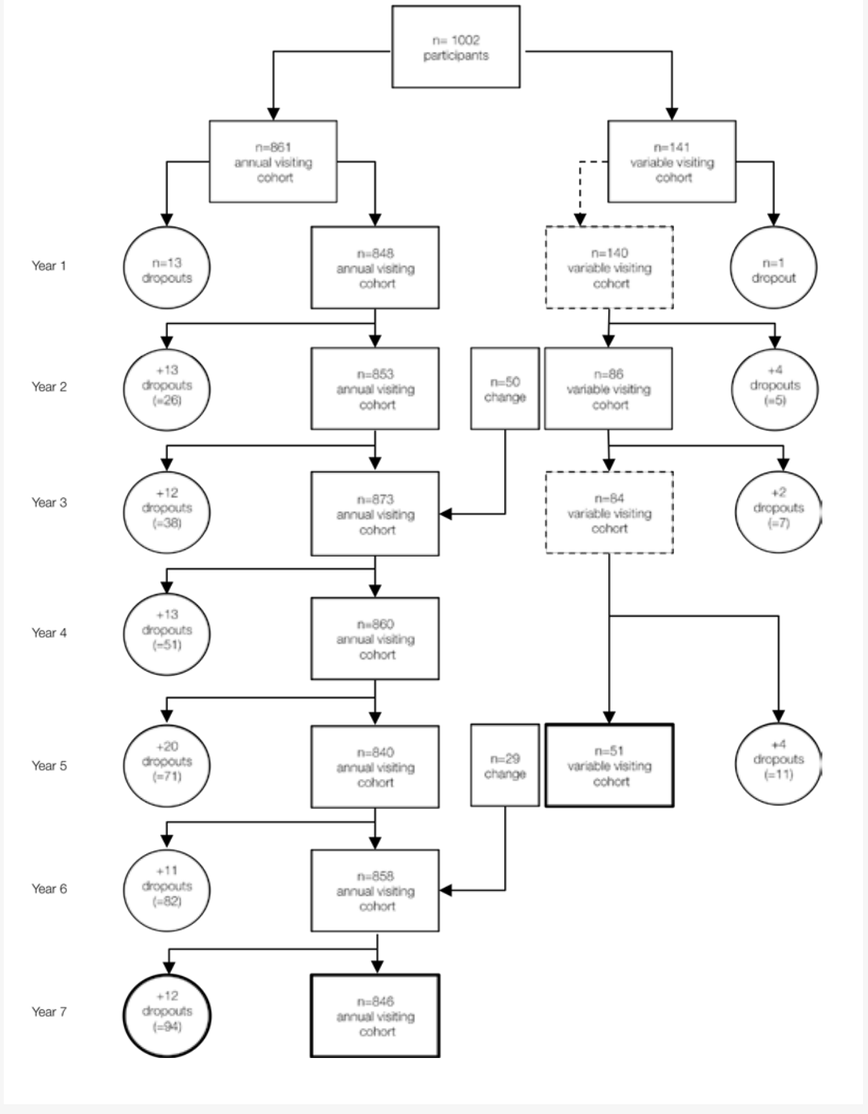

FIGURE 1 | Flowchart of the CHECK study

TABLE 3 | Comparison of baseline characteristics between people still participating after 7 years of follow-up and those who had dropped out

	Subjects participating	Dropouts	p-value	95% Confidence interval
n	897	105		
Age	56 (5)	57 (6)	0.05	-2.1 – 0.004
Sexe, female, %	79	81	0.70	
BMI	26 (4)	26 (4)	0.23	-0.3 – 1.4
Education level			0.58	
Primary school, %	2	4		
Secondary school, %	60	61		
High profession education/ university, %	35	31		
Missings, %	3	4		
WOMAC subscales				
Pain (0-20)	5 (3)	5 (4)	0.19	-1.2 – 0.2
Stiffness (0-8)	3 (2)	3 (2)	0.86	-0.4 – 0.3
Function (0-68)	16 (11)	17 (14)	0.19	-4.0 – 0.8
Pain intensity (0-10)	4 (2)	4 (2)	0.96	-0.4 – 0.4
Hip pain, %	59	57	0.79	
Knee pain, %	83	82	0.75	
Highest K&L score knee			0.89	
Grade 0, %	68	66		
Grade 1, %	25	26		
Grade 2, %	6	8		
Grade 3, %	1	1		
Missings	1	0		
Highest K&L score hip			0.74	
Grade 0, %	79	78		
Grade 1, %	14	17		
Grade 2, %	5	4		
Grade 3, %	1	1		
Missings, %	1			
Comorbidities			0.23	
0, %	31	37		
1, %	30	27		
2, %	20	12		
≥ 3, %	17	20		
Missings, %	2	4		

Continuous variables are given as mean values, standard deviation between brackets and categorical variables as percentages.
BMI | body mass index, K&L | Kellgren and Lawrence grade, WOMAC | Western Ontario and McMaster Universities OA index with higher scores indicating worst health.
p- values are given.

TABLE 4 | Summary of collected data during 10 years in all participants (all) and in the subgroup of the annual visiting group (A) of CHECK

Year	0	1	2	3	4	5	6	7	8	9	10
Questionnaires											
Demographics	all	A	all	A	A	all	A	A	all	A	all
SF-36: Short Form 36-item health status survey	all	A	all	A	A	all	A	A	all	A	all
EQ5D: EuroQol	all	A	all	A	A	all	A	A	all	A	all
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index	all	A	all	A	A	all	A	A	all	A	all
NRS for pain intensity (numeric rating scale)	all	A	all	A	A	all	A	A	all	A	all
Comorbidity list	all	A	all	A	A	all	A	A	all	A	all
Health care use	all	A	all	A	A	all	A	A	all	A	all
Pain Coping Inventory list	all		all			all			all		all
Social Support scale	all		all			all			all		all
Lifestyle: tobacco and alcohol use	all		all			all			all		all
AUSCAN: Australian Canadian Osteoarthritis Hand Index									all		
ICOAP: Measure of Intermittent and Constant Osteoarthritis pain									all	A	all
Clinical assessment											
Knee examination											
Palpable warmth	all	A	all	A	A	all	A	A	all	A	all
Refill test	all	A	all	A	A	all	A	A	all	A	all
Bony tenderness	all	A	all	A	A	all	A	A	all	A	all
Patella grinding test	all	A	all	A	A	all	A	A	all	A	all
Range of Motion- flexion/ extension	all	A	all	A	A	all	A	A	all	A	all
Crepitus	all	A	all	A	A	all	A	A	all	A	all
Hip examination											
Range of motion- flexion/internal/ external rotation/	all	A	all	A	A	all	A	A	all	A	all
adduction/abduction	all	A	all	A	A	all	A	A	all	A	all
Hand examination											
DIP/ PIP bony enlargements	all	A	all	A	A	all	A	A	all	A	all
CMC I bony enlargements							A	A	all	A	all
Soft tissue swelling MCP I-V							A	A	all	A	all
Deformity CMC I, DIP, PIP							A	A	all	A	all
Radiographic assessment											
Knee: unilateral posterioranterior fixed flexion view (both knees)	all		all			all			all		all
Knee: unilateral lateral view (both knees)	all		all			all			all		all
Knee: bilateral skyline view (supine)	all		all			all			all		
Hip: anteriorposterior pelvis view	all		all			all			all		all
Hip: unilateral faux profile view (both hips)	all		all			all					
Hand: bilateral posterioranterior view									all		
Lumbar spine: lateral view (supine)									all		
Biochemical assessment											
DNA	all										
Plasma	all		all			all			all		
Serum	all		all			all			all		
Urine	all		all			all			all		

parameters on radiographs.[23] These KIDA parameters are measured without knowing the sequence of the radiographs.

Biochemical variables

Blood and urine samples have been collected from each participant following a standardised protocol at all sites. Multiple aliquots of serum, plasma, and urine are centrally stored at -80°C. DNA was collected at baseline and was stored at -20°C. A systematic review of the currently available biochemical markers in knee and hip OA was the basis for composing the

spectrum of biochemical markers to be assessed at baseline in the CHECK study: uCTX-II, uCTX-I, uNTX-I, sCOMP, sPIIANP, sCS846, sC1,2C, sOC, sPINP, sHA, sPIIINP, pLeptin, pAdiponectin, pResistin *(table 5)*.[24]

WHAT HAS IT FOUND? KEY FINDINGS AND PUBLICATIONS

An actual list of publications can be found on our website *(www.check-research.com)*. Here we summarize the key findings.

Clinical variables

The course of pain and physical function in patients with early symptomatic OA remains, on average, fairly stable over five years, especially in participants with a slow progression (radiographic change of 0 or 1 grade in K&L grading). In participants with a rapid progression (radiographic change of ≥ 2 in K&L grading) pain increased and function declined. Already in an early stage of the disease large inter-individual differences appear in course of activity limitations and pain,[25] which is in concordance with the literature.[26] Based on 5 years data of activity limitations homogeneous subgroups of subjects were identified with comparable trajectories of activity limitations: 'good', 'moderate' and 'poor outcome'.[27] The following baseline characteristics distinguished poor and moderate outcome from good outcome: younger age, higher BMI, greater pain, bony tenderness, reduced knee flexion, hip pain, osteophytes on X-rays, ≥ 3 comorbidities, and lower or avoidance of activity. Distinguishing these baseline characteristics might have implications for treatment.

A combined psychological and neuromuscular model was developed to explain clinical characteristics of OA. According to this model, a person experiences pain during activities, expects renewed activities to result in more pain and consequently avoids activities. In the long term, inactivity results in muscle weakness, that leads to an increase in activity limitations.[28,29] In patients with early stage OA this model appears to offer a valid explanation for the associations between pain, negative affect (i.e., feeling of fatigue, low vitality, depression, and nervousness), avoidance of activities, muscle weakness, and activity limitations.[6]

At baseline 67% of participants reported one or more comorbidities. Additional problems in the musculoskeletal system (apart from knee and hip problems) and obesity have a negative effect on pain and physical health status. Also mental health status is affected in early symptomatic OA by the presence of specific comorbidities.

Besides the course of pain and activity limitations, also the course of work participation was analysed. The 2-year course of work participation was similar to that of the general Dutch population. Sustained work participation was predicted by lower age, not by OA related factors.[30]

Radiographic variables

The gold standards to evaluate radiographic OA are K&L grading and grading according to the Altman atlas. The newer method, KIDA, appeared sensitive to detect early progression of radiographic knee damage, especially through the measurement of separate quantitative features of radiographic knee OA.[31] Based on KIDA features, 5 phenotypes of radiographic progression can be identified. These represent the level of disease progression (Severe or No progression), the phase of progression (Early or Late) and the prominent involvement of Bone density.[32]

Statistical Shape Modelling (SSM) assessed the radiographic shape of the hip, to test whether the morphology of the hip joint could be a risk factor for OA. Evaluation of the hip radiographs of CHECK participants showed that the SSM-modelled shape of the hip can predict total hip replacement, but variation in shape cannot predict clinical OA.[3] In addition, individuals with severe cam-type deformity (hip incongruity by non-spherical head) and reduced internal rotation were at high risk of fast progression to end stage OA.[33] Finally, pincer deformity (acetabulum over-coverage) did not lead to OA of the hip, but acetabulum under-coverage did.[34]

Biochemical variables

In CHECK 14 markers of cartilage, bone and synovial metabolism *(table 5)* were assessed to improve understanding of pathophysiology and as potential prognostic predictors. None proved sufficiently discriminating to predict diagnosis or prognosis of

TABLE 5 | Description of biomarkers

Category biochemical marker	Biomarker	Description biomarker
Cartilage degradation	CTX-II sC1,2C sCOMP	C-terminal telopeptide of type II collagen collagen of type I and II cartilage oligomeric matrix protein
Cartilage synthesis	sPIIANP sCS846	collagen N-propeptide of type IIA chondroitin sulphate 846
Bone degradation	uCTX-I uNTX-I	C-terminal telopeptide of collagen I N-terminal telopeptide of collagen I
Bone synthesis	sOC sPINP	osteocalcin aminoterminal propeptide of type I procollagen
Synovium degradation	sHA	Hyaluronic acid
Synovium synthesis	sPIIINP	N-terminal propeptide of type III procollagen
Adipokines	pLeptin pAdiponectin pResistin	

OA. Two reflected a broader spectrum than expected. The cartilage degradation marker, CTX-II, showed striking similarities with markers of bone metabolism, suggesting that CTX-II also originates from bone. The cartilage degradation marker COMP (Cartilage Oligomeric Matrix Protein) may also originate from (inflamed) synovial tissue in early-stage OA.[35] Biomarkers, confirmed cartilage degradation and synovitis as processes underlying the development of radiographic signs in early-stage knee and hip OA. Markers of bone turnover and bone mineral density suggest these are relevant factors in the development of radiographic OA, but their effect may differ between knee and hip.

WHAT ARE THE MAIN STRENGTHS AND WEAKNESSES?

CHECK's main strength is the combination of high-quality data in the clinical, radiographic and biochemical domain. Second, CHECK is an inception cohort: observations started at the same point in the course of OA in all participants. Third, CHECK has a follow-up of 10 years and thereby provides a huge data set to answer longitudinal research questions on OA of the hip or knee. Fourth, CHECK has a remarkably low loss to follow-up due to a special retention program.

This program is aimed at optimizing the compliance of CHECK participants and motivating health professionals involved in the participating hospitals (physicians, researchers, X-ray technicians, research nurses). Activities include: twice-yearly newsletters for participants and health professionals, separate websites for participants and health professionals, organizing symposia for both groups to present preliminary results and progress of CHECK, and sending birthday cards to all participants.

The main weakness of the study is related to the fact that no diagnostic criteria of early OA exist; this may hamper generalizing results. CHECK participants are subjects with early OA, defined as having pain in hip or knee at or within 6 months of their first visit to the general practitioner for these symptoms, and complaints were not attributable to another rheumatic disease. There are however criteria for OA; 76% of the CHECK participants with knee pain fulfilled the clinical American College of Rheumatology classification criteria for knee OA, 24% fulfilled the clinical

classification criteria of hip OA. These criteria for OA were developed in cases of established disease. None of the CHECK participants had radiographic OA (i.e. K&L grade ≥ 2). The transition from early to established OA is gradual. That is why we decided to call the situation at presentation 'symptomatic OA'.

CAN I GET HOLD OF THE DATA? WHERE CAN I FIND OUT MORE?

The CHECK steering group welcomes collaboration and the interest of national and international colleagues. More information of CHECK can be found on *www.check-research.com* while from *(http://www.check-research.com/images/upload/english/spin-offformuliereng.doc)* a sign-up form can be downloaded to describe a proposal for collaboration or a request for access to data, to be sent to *checkreu@umcutrecht.nl*. The CHECK steering committee will evaluate all proposals for spin-off studies, for access to data, and for use of biological samples. —

REFERENCES

1. Lievense AM, Bierma-Zeinstra SM, Verhagen AP, Verhaar JA, Koes BW. Prognostic factors of progress of hip osteoarthritis: a systematic review. Arthritis Rheum 2002; 47:556-62.
2. Spector TD, Dacre JE, Harris PA, Huskisson EC. Radiological progression of osteoarthritis: an 11 year follow up study of the knee. Ann Rheum Dis 1992; 51:1107-10.
3. Agricola R, Reijman M, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). Osteoarthritis Cartilage 2013; 21:559-64.
4. Vos PA, Welsing PM, DeGroot J, Huisman AM, Oostveen JC, Reijman M et al. Skin pentosidine in very early hip/knee osteoarthritis (CHECK) is not a strong independent predictor of radiographic progression over 5 years follow-up. Osteoarthritis Cartilage 2013; 21:823-30.
5. Vos PA, DeGroot J, Huisman AM, Oostveen JC, Marijnissen AC, Bijlsma JW et al. Skin and urine pentosidine weakly correlate with joint damage in a cohort of patients with early signs of osteoarthritis (CHECK). Osteoarthritis Cartilage 2010; 18:1329-36.
6. Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF et al. Avoidance of Activities in Early Symptomatic Knee Osteoarthritis: Results from the CHECK Cohort. Ann Behav Med 2012; 44:33-42.
7. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of womac: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15:1833-40.
8. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW et al. Satisfactory cross cultural equivalence of the Dutch womac in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63:36-42.
9. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002; 10:863-9.
10. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240-S252.
11. Kraaimaat FW, Evers AW. Pain-coping strategies in chronic pain patients: psychometric characteristics of the pain-coping inventory (PCI). Int J Behav Med 2003; 10:343-63.
12. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998; 316:736-41.
13. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.
14. Salaffi F, Carotti M, Grassi W. Health-related quality of life in patients with hip or knee osteoarthritis: comparison of generic and disease-specific instruments. Clin Rheumatol 2005; 24:29-37.
15. Rijken PM, Foets M, Peters L, de Bruin AF, Dekker J. Patiëntenpanel Chronisch Zieken: kerngegevens 1998 (Panel of patients with chronic diseases: core figures). Utrecht, The Netherlands: Nivel, 1999.
16. Verstappen SM, Boonen A, Verkleij H, Bijlsma JW, Buskens E, Jacobs JW. Productivity costs among patients with rheumatoid arthritis: the influence of methods and sources to value loss of productivity. Ann Rheum Dis 2005; 64:1754-60.
17. Fink P, Jensen J, Borgquist L, Brevik JI, Dalgard OS, Sandager I et al. Psychiatric morbidity in primary public health care: a Nordic multicentre investigation. Part I: method and prevalence of psychiatric morbidity. Acta Psychiatr Scand 1995; 92:409-18.
18. Botterweck A, Frenken F, Janssen S, Rozendaal L, Vree Md, Otten F. [Plausibility new measurements general health and lifestyles.] Plausibiltiet nieuwe metingen algemene gezondheid en leefstijlen.

Heerlen, The Netherlands: Centraal Bureau voor de Statistiek; 2001.

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

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

21. Burnett DJ, Hart DJ, Cooper C, Spector A. A radiographical Atlas of Osteoarthritis. London: Springer Verlag; 1994.

22. Damen J, Schiphof D, ten Wolde S., Cats H, Bierma-Zeinstra S, Oei EHG. Inter-observer reliability for radiographic assessment of osteoarthritis features: the CHECK (Cohort Hip & Cohort Knee) study (under Revission). Osteoarthritis and Cartilage 2014; 22:969-74.

23. Marijnissen AC, Vincken KL, Vos PA, Saris DB, Viergever MA, Bijlsma JW et al. Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis Cartilage 2007; 16:234-43.

24. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage 2010; 18:605-12.

25. Holla JF, Steultjens MP, Roorda LD, Heymans MW, ten Wolde S, Dekker J. Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee. Arthritis Care Res (Hoboken) 2010; 62:1415-25.

26. Yusuf E, Bijsterbosch J, Slagboom PE, Kroon HM, Rosendaal FR, Huizinga TW et al. Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis. PLoS One 2011; 6:e25426.

27. Holla JF, van der Leeden M, Heymans MW, Roorda LD, Bierma-Zeinstra SM, Boers M et al. Three trajectories of activity limitations in early symptomatic knee osteoarthritis: a 5-year follow-up study. Ann Rheum Dis 2013; 73:1369-75.

28. Steultjens MP, Dekker J, Bijlsma JW. Avoidance of activity and disability in patients with osteoarthritis of the knee: the mediating role of muscle strength. Arthritis Rheum 2002; 46:1784-8.

29. Bot SD, Terwee CB, van der Windt DA, Feleus A, Bierma-Zeinstra SM, Knol DL et al. Internal consistency and validity of a new physical workload questionnaire. Occup Environ Med 2004; 61:980-6.

30. Bieleman HJ, Reneman MF, Drossaers-Bakker KW, Groothoff JW, Oosterveld FG. Prognostic factors for sustained work participation in early osteoarthritis: a follow-up study in the Cohort Hip & Cohort Knee (CHECK). J Occup Rehabil 2013; 23:74-81.

31. Kinds MB, Marijnissen AC, Vincken KL, Viergever MA, Drossaers-Bakker KW, Bijlsma JW et al. Evaluation of separate quantitative radiographic features adds to the prediction of incident radiographic osteoarthritis in individuals with recent onset of knee pain: 5-year follow-up in the CHECK cohort. Osteoarthritis Cartilage 2012; 20:548-56.

32. Kinds MB, Marijnissen AC, Viergever MA, Emans PJ, Lafeber FP, Welsing PM. Identifying Phenotypes of Knee Osteoarthritis by Separate Quantitative Radiographic Features May Improve Patient Selection for More Targeted Treatment. J Rheumatol 2013; 40:891-902.

33. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis 2013; 72:918-23.

34. Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SM, Verhaar JA et al. Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage 2013; 21:1514-21.

35. van Spil WE, Drossaers-Bakker KW, Lafeber FP. Associations of CTX-II with biochemical markers of bone turnover raise questions on its tissue origin: data from CHECK, a cohort study of early osteoarthritis. Ann Rheum Dis 2013; 72:29-36.

CHECK is an inception cohort study of clinical, radiographic and biochemical variables in early symptomatic OA of the hip or knee.

The study provides a valuable data set to answer many longitudinal research questions regarding OA of the hip or knee.

PART I

DIFFERENCES BETWEEN COHORTS OF PERSONS WITH EARLY OSTEOARTHRITIS

3

CHECK: COHORT HIP & COHORT KNEE; SIMILARITIES AND DIFFERENCES WITH THE OA INITIATIVE

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ABSTRACT

Objective

To describe the osteoarthritis study population of CHECK (Cohort Hip & Cohort Knee) in comparison with relevant selections of the study population of the Osteoarthritis Initiative (OAI) based on clinical status and radiographic parameters.

Methods

In The Netherlands a prospective 10-year follow-up study was initiated by the Dutch Arthritis Association on participants with early osteoarthritis related complaints of hip and/or knee: CHECK. In parallel in the US an observational 4-year follow-up study, the OAI, was started by the National Institutes of Health, on patients with or at risk for symptomatic knee osteoarthritis. For comparison with CHECK, the entire cohort and a subgroup of individuals excluding those with exclusively hip pain were compared with relevant subpopulations of the OAI.

Results

At baseline, CHECK included 1,002 participants with in general similar characteristics as described for the OAI. However, significantly fewer individuals in CHECK had radiographic knee osteoarthritis at baseline when compared to the OAI ($p<0.0001$). In contrast, at baseline, the CHECK cohort reported higher scores on pain, stiffness, and functional disability (Western Ontario and McMaster osteoarthritis Index) when compared with the OAI (all $p<0.0001$). These differences were supported by physical health status in contrast to mental health (Short Form 36/12) was at baseline significantly worse for the CHECK participants ($p<0.0001$).

Conclusions

Although both cohorts focus on the early phase of osteoarthritis, they differ significantly with respect to structural (radiographic) and clinical (health status) characteristics, CHECK expectedly representing participants in an even earlier phase of disease.

THE DIAGNOSIS OSTEOARTHRITIS (OA) CAN BE BASED ON SYMPTOMS, SIGNS, AND RADIOGRAPHIC FINDINGS AND AS SUCH BE DEFINED BY VARIOUS SETS AND COMBINATIONS OF CRITERIA.[1,2] It is the most common diagnosis made in older patients with knee or hip pain. The prognosis of osteoarthritis for the individual patient is uncertain; the course of symptoms, clinical signs, disability and radiographic changes is difficult to predict.[3] Besides, it has been demonstrated that there is inconsistency between the radiographic change and severity of joint pain with accompanying disability.[4] Clearly, to understand more about the disease and its course, large independent detailed observational studies starting (very) early in the stage of the disease are necessary.

Therefore, in The Netherlands, a prospective 10-year follow-up study was recently initiated by the Dutch Arthritis Association in order to establish the onset and progression of osteoarthritis in participants with early complaints of hip and/or knee pain: CHECK (Cohort Hip & Cohort Knee), using the International Classification of Functioning, Disability and Health (ICF) as a conceptual framework. The ICF model provides an integrative framework, combining biological, psychological, and social aspects of health and disease.[5] The objective of CHECK is to study the course of complaints, the mechanisms that cause joint damage, and to identify markers for diagnosis and course of joint damage, as well as to identify prognostic factors that predict and explain the course of osteoarthritis. In parallel, an observational study on osteoarthritis was initiated by the National Institutes of Health: the Osteoarthritis Initiative (OAI). This 4-year follow-up study will create a public archive of data, biological samples, and joint images to study the natural history of, and risk factors for, the onset and progression of knee osteoarthritis. In fact, both initiatives, CHECK and the OAI, seek answers to the same questions in comparable populations. In the present report the CHECK population is described at baseline and compared with relevant subpopulations of the OAI to provide a basis for further research and a comparison of both cohorts in the future.

METHODS

CHECK cohort

Design

From October 2002 to September 2005 a cohort was formed of 1,002 participants with pain and/ or stiffness of knee and/ or hip, which is to be followed prospectively for a period of at least 10 years. Nationwide, 10 general and academic hospitals in The Netherlands are participating, located in urbanised and semi-urbanised regions. The study was approved by the medical ethics committees of all participating centres, and all participants gave their written informed consent before entering the study.

Study population

General practitioners (GP) in the surroundings of the participating centres were invited to refer eligible persons to these centres. All patients that visited the GP on their own initiative, potential fulfilling the inclusion criteria, were referred to one of the 10 participating centres. In addition, participants were recruited through advertisements and articles in the local newspapers and on the Dutch Arthritis Association website. The physicians in the participating centres checked whether referred patients as well as patients from their outpatient clinic fulfilled the inclusion criteria.

Inclusion criteria

Individuals were eligible if they had pain and/or stiffness of the knee and/or hip, were aged 45-65 years, and had never or not longer than 6 months ago visited the GP for these symptoms for the first time. Exclusion criteria were: 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) or co-morbidity that did not allow physical evaluation and/or follow-up of at least 10 years, malignancy in the last 5 years, and inability to understand the Dutch language.

Baseline Measurements

Variables categorised according to the ICF model (*table 1)*.

Body function and structures: articular and kinesiologic factors

To assess cartilage and bone at baseline, imaging techniques were employed and samples of blood and urine collected. During follow-up this is also done at 2, 5, and 10 years. At baseline both knees and hips were analysed in all participants, independent of symptoms and signs.

Radiographs of tibio-femoral joints (TF) joints were made by a weight-bearing (WB) posterioranterior (PA) view, semi-flexed (7-10°) according to Buckland-Wright and colleagues.[6-8] Radiographs of the patellofemoral joints were made by a single standing mediolateral view in 30° flexion and a skyline (inferior superior) view in 30° flexion.[9,10] For the hip, weight-bearing anterioposterior (AP) radiographs of the pelvis were made.[11,12] In addition, a weight-bearing single faux profile radiograph of both hips was obtained.[13]
All radiographs were made without fluoroscopy, and were digitalised and centrally stored. Radiographs of PA, TFJ and AP pelvic views at baseline were scored according to Kellgren & Lawrence (K&L).[14] Blood and urine samples were collected, using a standardised protocol at all sites. Multiple aliquots of serum, plasma, and urine were centrally stored at -80°C. DNA was collected at baseline and was stored at -20°C.

Kinesiologic factors *(table 1)* were assessed each year by a protocol that was established to measure clinical features of knee, hip, and hands.

Body function and structures: pain, stiffness, and fatigue

Questionnaires were selected based on the following criteria: validated in participants with osteoarthritis; demonstrated reliability, validity and, if applicable, responsiveness; the questionnaire is internationally accepted, is available in the Dutch language, and has a high feasibility. Questionnaires are administered annually.

The Western Ontario and McMaster osteoarthritis Index (WOMAC),[15,16,17] a questionnaire with well-known and good clinimetric properties and recommended by OMERACT is utilised to measure pain (five items), stiffness (two items), and physical functioning (see below).[18,19] The five point Likert version of the WOMAC

TABLE 1 | The assessment of the variables, categorized according to the dimensions of the ICF, comparison of CHECK and OAI

	CHECK	OAI
Body function and structures	**Physiological functions of body systems and anatomical part of the body**	
Articular factors	Single PA view TFJ, mediolateral view TFJ,	Bilateral PA view TFJ
	bilateral skyline view PFJ	AP view pelvis
	AP pelvis view, faux profil view of hip	PA view dominant hand
Kinesiologic factors	Pain during joint motion of the hip and knee. Assisted active range of joint motion of the hip and knee (in degrees) with a goniometer	Knee flexion pain/ tenderness
Knee	Palpable warmth, refill-test, bony tenderness, crepitus, patellofemoral grinding test	Effusion, bony tenderness, crepitus patellar tenderness, alignment, medial-lateral laxity
Hip	Sign of Thomas	NA
Hand	DIP and PIP bony enlargements	DIP bony enlargements
Pain	Pain scale WOMAC	Pain scale WOMAC
	Knee/ hip pain intensity 0-10 rating scale	Knee pain 0-10 rating scale
		KOOS knee pain and symptoms
Stiffness	Stiffness scale WOMAC	Stiffness scale WOMAC
Other joint symptoms	Hip pain, stiffness, Foot/toe symptoms	Symptoms of hip, shoulder, elbow, wrist, hand/finger, ankle, foot/toe
Fatigue	Vitality scale of the Short Form 36-item health status survey questionnaire (SF-36)	NA
Activities	**Execution of a task or action by an individual**	
Limitations in activity	Functioning scale WOMAC	Functioning scale WOMAC
Participation	**Involvement in life situation**	
Working status	Employment, current and past	Employment, current and past
	Participants with paid employment were asked whether they would like to change their working environment	Work disability due to health problems
Environmental and personal factors	**Complete background of an individual's life and living situation**	
Socio-demographic characteristics	Age, sex, ethnicity, marital status, household composition	Age, sex, ethnicity, marital status, residency, income
	Height, weight, education	Height, weight, education
Utility	EuroQol	
Quality of life	SF-36	SF-12, KOOS Quality of life
Co-morbidity	List of complaints and diseases	Comorbidity Index
Psychological factors		
Pain coping	Pain Coping Inventory (PCI)	NA
Fear and depression	Scale form the SF-36: emotional role- functioning	CES-D (depressive symptoms)
Social support	Social Support Scale (SOS)	NA
Physical workload	Based on the Dutch Musculoskeletal Questionnaire	Frequent knee bending activities
Physical activity during leisure	Physical activity, qualitative and quantitative	KOOS sport, recreation
		Physical activity (PASE)
		Limitation of activity due to knee symptoms
Health care use	Medical consumption, to have and use aids	Medication consumption
Lifestyle	Tobacco, alcohol use	Tobacco, alcohol use
	Changes in feeding habits	Dietary nutrient intake

AP | anteriorposterior, CHECK | Cohort Hip & Cohort Knee, KOOS | Knee Outcomes in Osteoarthritis Survey, NA | not available, OAI | Osteoarthritis Initiative, PA | posterioranterior, PASE | Physical Activity Scale for the Elderly, PFJ | patellofemoral joint, SF-12 | Short Form 12-item medical outcome study, SF-36 | Short Form 36-item health status questionnaire, TFJ | tibiofemoral joint, WOMAC | Western Ontario and McMaster Osteoarthritis Index.

TABLE 2 | Demographic and disease characteristics in CHECK and selections of the OAI

	CHECK	OAI incidence cohort	p-value	CHECK-knee subgroup	OAI incidence subgroup	p-value
N	1002	3285	NA	829	1578	NA
Age in years	56 (52-60)	61 (53-69)	< 0.001	56 (52-60)	56 (51-61)	0.8
Gender, female	79%	59%	< 0.001	80%	64%	< 0.001
BMI, kg/m^2	26 (23-28)	28 (25-31)	< 0.001	26 (24-28)	28 (25-32)	< 0.001
Educational level			0.1			0.006
Primary school	3%	3%		3%	2%	
Secondary school	70%	65%		71%	65%	
High prof. education/ univ.	27%	32%		26%	33%	
Site of pain			< 0.001			0.002
Knee only	41%	37%		50%	43%	
Hip only	17%	7%		NA	NA	
Knee and hip	42%	48%		50%	57%	
No hip or knee pain	NA	37%	NA	NA	NA	NA
Pain intensity (range 0-10)	3 (3-5)	2 (0-3)	< 0.001	3 (2-5)	2 (0-4)	< 0.001
K&L rating score for knee			< 0.001			< 0.001
Grade 0	68%	14%		65%	19%	
Grade 1	25%	46%		27%	50%	
Grade 2	6%	16%		7%	16%	
Grade 3	1%	19%		1%	13%	
Grade 4	NA	5%		NA	2%	
K&L rating score for hip						
Grade 0	79%	NA	NA	83%	NA	NA
Grade 1	15%	NA	NA	13%	NA	NA
Grade 2	5%	NA	NA	4%	NA	NA
Grade 3	1%	NA	NA	0%	NA	NA
WOMAC subscales						
Pain (range 0-20)	5 (2-7)	1 (0-3)	< 0.001	5 (2-7)	1 (0-3)	< 0.001
Stiffness (range 0-8)	3 (2-4)	1 (0-2)	< 0.001	3 (2-4)	1 (0-2)	< 0.001
Physical function (range 0-68)	14 (7-24)	2 (0-8)	< 0.001	14 (7-24)	3 (0-9)	< 0.001
Present employment			< 0.001			< 0.001
Paid job/volunteer	53%	70%		52%	79%	
no paid job	47%	30%		48%	21%	
SF-36 subscales (range 0-100)						
Physical function	80 (65-90)	NA	NA	75 (65-85)	NA	NA
Physical role	100 (50-100)	NA	NA	100 (38-100)	NA	NA
Bodily pain	67 (57-80)	NA	NA	67 (57-80)	NA	NA
Fatigue	65 (55-75)	NA	NA	65 (55-75)	NA	NA
Social function	88 (63-100)	NA	NA	88 (63-100)	NA	NA
Fear and depression	100 (100-100)	NA	NA	100 (100-100)	NA	NA
Mental health	80 (68-88)	NA	NA	80 (68-88)	NA	NA
PCS	47 (40-51)	53 (46-56)	< 0.001	47 (40-51)	53 (46-56)	< 0.001
MCS	55 (50-59)	55 (50-58)	0.4	55 (50-59)	55 (49-58)	0.3
EuroQol Utility	0.7 (0.7-0.8)	NA	NA	0.7 (0.7-0.8)	NA	NA

Median values with 25th-75th percentiles between brackets and categorical variables as percentages (%) are given. BMI | body mass index, K&L | Kellgren and Lawrence grade, WOMAC | Western Ontario and McMaster Universities OA index with higher scores indicating worst health, SF36 | Short Form 36-item health status survey questionnaire with higher score indicating a better health related quality of life, PCS | Physical Component Scale, MCS | Mental Component Scale (in CHECK both scales calculated without general health scale), NA | not available /applicable

was used; item responses range from 'none' to 'extreme' and are summed to produce subscales (pain 0-20, stiffness 0-8, functioning 0-68) with higher scores indicating worse health.

Fatigue was assessed with the vitality subscale of the Short Form 36-item health status survey questionnaire (SF-36). This questionnaire is a generic instrument yielding scores on eight scales, with two summary scores, the physical component summary (PCS) and the mental component summary (MCS). The physical functioning, role limitations due to physical health and bodily pain, scale contributes most to the scoring of the PCS. The mental health, role limitations due to emotional problems and social functioning scales contributes most to the MCS. These summary scores of the SF-36 are equivalent to the summary scores of the SF-12,[20] as used in the OAI. Scores on the scales range from 0 to 100, with a higher score indicating a better health-related quality of life.[21]

Activities

The WOMAC was used to assess physical functioning (17 items).[18,19]

Participation

To assess the involvement in life situation, the employment and the leisure activities were measured with the questionnaire from the Patient Panel Chronic Diseases (The Netherlands Institute for Health Services Research; NIVEL) and the questionnaire 'economic aspects in rheumatoid arthritis.[22]

Environmental factors and personal factors

Table 1 provides an overview of the environmental and personal factors collected at baseline. Co-morbidity was assessed with a standard consensus-based list.[23] Pain-coping behaviour was measured with the pain coping inventory, assessing both behavioural and cognitive coping strategies.[24] To assess a person's distress and fear, a subscale of the SF-36 was used. Social support was measured with the Dutch 'Social support scale'.[25] Physical load and economic consequences were assessed with the Dutch musculoskeletal questionnaire and the questionnaire 'economic aspects in rheumatoid arthritis, respectively.[26,22]

Each 3 months, the 10 institutes were visited by a single central coordinator to support complete and accurate data gathering.

Osteoarthritis Initiative

All details of the OAI are available on the internet *(http://www.oai.ucs.edu)*. In short: Individuals were eligible if they had or were at risk for symptomatic TF knee osteoarthritis and aged between 45 and 79 years. Individuals with inflammatory arthritis, bilateral end-stage knee osteoarthritis, inability to walk and contraindication for magnetic resonance imaging were excluded. Recruitment of 4,796 individuals was realised from March 2004 to May 2006. At baseline the cohort was divided into two subcohorts, one with symptomatic knee osteoarthritis (defined as in at least one knee frequent knee symptoms and radiographic TF knee osteoarthritis, defined as K&L ≥2; progression cohort) and a second cohort of 3,285 individuals without symptomatic knee osteoarthritis, selected on the basis of having specific characteristics that give them an increased risk of developing symptomatic knee osteoarthritis (incidence cohort). For the incidence cohort age-specific eligibility criteria were defined. Individuals aged 45-49 were eligible when they had frequent knee symptoms, or made frequent use of medication for the treatment of knee symptoms or had infrequent knee symptoms, and in addition had one or more other eligible risk factor such as knee injury, knee surgery, overweight, positive family history, etc. Individuals aged 50-69 were eligible if they had frequent knee symptoms, or made frequent use of medication for the treatment of knee symptoms, or were overweight, or had two or more of the eligible risk factors.

At baseline materials for identification of joint imaging, biomarkers, and genetic markers were collected. Also data on the clinical and joint status of

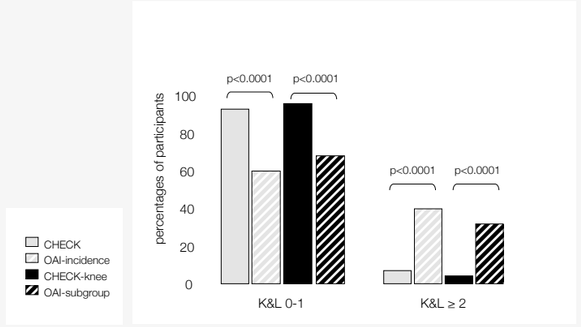

FIGURE 1 | Comparison of radiographic joint damage between Cohort Hip & Cohort Knee (CHECK) and Osteoarthritis Initiative (OAI) and their subpopulations at baseline. The bars depict the percentage of knees with a Kellgren and Lawrence (K&L) score of 0-1 and a K&L ≥ 2. P values for statistical comparison are given.

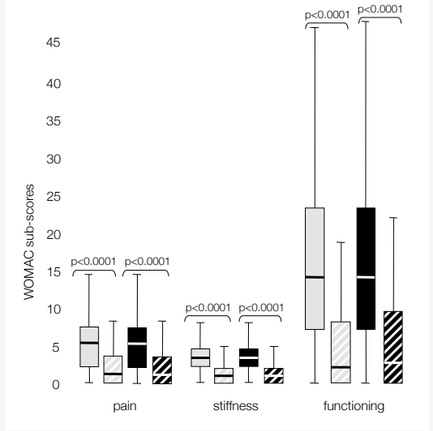

FIGURE 2 | Comparison of the three Western Ontario and McMaster osteoarthritis Index (WOMAC) subscales for pain, stiffness and functional disability between Cohort Hip & Cohort Knee (CHECK) and Osteoarthritis Initiative (OAI) and their subpopulations at baseline. Box- whisker plot (median and 25th-75th percentiles) and p values are given. A higher score indicates more pain, stiffness, and problems in physical functioning.

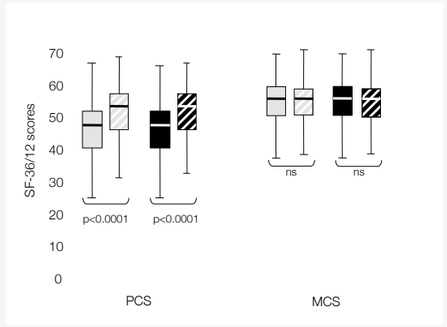

FIGURE 3 | Comparison of the physical component summary scale (PCS) and mental component summary scale (MCS) of the Short Form 36-item health status survey questionnaire (SF-36/12) between Cohort Hip & Cohort Knee (CHECK) and Osteoarthritis Initiative (OAI) and their subpopulations at baseline. Box whisker plot (median and 25th- 75th percentiles) and p values are given. A higher score indicates a better health-related quality of life.

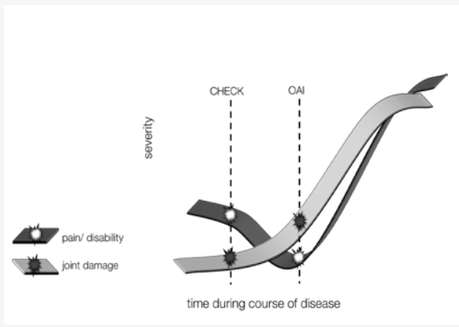

FIGURE 4 | Schematic presentation of the hypothesis as put forward in the discussion explaining the (apparent) discrepancy between both cohorts with respect to pain and joint damage.

subjects and on risk factors for the progression and development of knee osteoarthritis were collected by questionnaires and examination (categorised according to the dimensions of the ICF depicted in *table 1*).

In the present report baseline CHECK data of the entire cohort were compared with data of the OAI incidence cohort. To make the cohorts more comparable, in addition, CHECK participants with knee problems (excluding those with exclusively hip problems; n=829) were compared with participants of the OAI incidence cohort within the same age range (45-65 years) who had at least frequent or infrequent knee symptoms excluding those who e.g. just had overweight without symptoms and excluding those who had previous knee surgery (n=1,578).

Statistical analyses

Baseline characteristics of both cohorts are presented using descriptive statistics: median and 25th-75th percentiles or percentages. Differences between groups are analysed using Mann Whitney U-tests or the χ^2 test, when appropriate.

RESULTS

More than 75% of participants were selected based on advertisement including website. The baseline characteristics of the participants from CHECK and the relevant populations of the OAI are presented in *table 2*. With respect to radiological osteoarthritis (K&L score) and health status there were some striking differences between the cohorts.

Radiographic joint damage was clearly more notable in the OAI compared with CHECK *(table 2)*. In *figure 1* the percentage of participants with a knee K&L grade 0-1 and ≥ 2 is depicted. Based on the definition of K&L grade ≥ 2, at baseline only 7% of CHECK participants had radiographic knee osteoarthritis compared with 40% in the OAI incidence cohort ($p<0.0001$). Evidence for radiographic hip osteoarthritis was only present in 7% of the participants of CHECK. The significant difference in knee K&L grade was also clear when the subgroups of both cohorts were compared (8% and 32%; $p<0.0001$). Even when the participants with K&L grade 4 were omitted from the calculations, the difference in severity of radiographic joint damage between both cohorts remains evidently significant. This difference in severity of joint damage between both cohorts was not based on differences in gender (data not shown).

Despite the limited number of participants with radiographic knee osteoarthritis in CHECK, 76% of the patients with knee symptoms could be diagnosed as osteoarthritis according to the clinical American College of Rheumatology criteria for the classification of osteoarthritis.[1,2] Only a minority of CHECK participants with hip symptoms (24%) fulfilled the clinical classification criteria of hip osteoarthritis.

The evident difference in radiographic joint damage between both cohorts was not accompanied by a similar difference in pain and physical function. On the contrary, as shown in *figure 2*, on each of the WOMAC subscales participants of CHECK presented with more pain, stiffness, and problems in function than patients in the OAI. This was observed for the whole cohorts as well as the subgroups of both cohorts (all $p<0.0001$). Women reported more pain and functional disability than men, which was almost identical with the OAI (all $p<0.05$; data not shown).

The specific difference in physical function, contrasting the radiographic difference between both cohorts, was underscored by the difference in PCS in contrast to MCS of the SF-36/12 scale *(figure 3)*; CHECK participants scoring less than patients from the OAI ($p<0.0001$) for the PCS but not for the MCS (not significant). Also for these scales, in both cohorts women scored worse compared to men (all $p<0.05$; data not shown).

DISCUSSION

The CHECK study is the first prospective 10 year follow-up study of osteoarthritis in an early phase of the disease that combines biological, psychological, and social aspects of osteoarthritis. Radiographic knee osteoarthritis was present only in a small number of the CHECK participants when compared with the OAI. In contrast, the participants in CHECK had more pain, more stiffness, more limitations in activities, and a worse health status. The worse clinical health status is supported by the use of pain medication: At baseline, only 9% of the participants in OAI had taken any pain medication, whereas this was 46% for CHECK (data not shown). Other characteristics such as body mass index or gender appeared not explanatory for this observed characteristic difference between both cohorts (data not shown). It could be that the difference in radiographic joint damage between both cohorts is due to differences in implementation of the K&L grading method. However, grading of a random sample of the OAI knee radiographs by those who performed the grading for CHECK, excluded this possibility (data not shown). Although not expected to be explanatory, it should be kept in mind that radiographs were taken, although according to standard protocols, in 10 different centres, whereas in the OAI only 4 centres are involved. It can not be ruled out that the social, cultural, and healthcare system differences between the US and Europe, in particular The Netherlands, account for (part of) the difference in reported health status. Also differences in inclusion between both cohorts can not be ruled out.

The OAI incidence cohort is recognized as an early osteoarthritis cohort. Taking the radiological findings into account, we conclude that CHECK was started in an even earlier phase of the disease compared with the OAI. Although this is apparently in discordance with the more severe clinical symptoms, the relation between radiographic damage and clinical symptoms has never been clear[27] and is subject of study in both cohorts. Therefore, it is hypothesised that in the early phase of osteoarthritis pain, stiffness, and disability (of still unknown origin) are prominent, and, not yet accompanied by radiographic findings of osteoarthritis (CHECK). In the subsequent phase (OAI) patients are coping with the pain and physical disability, leading to a decrease in report of these characteristics, while independently (or maybe as a consequence) structural changes, visible on radiographs, develop. In other words earlier recruitment of patients may carry more perceived symptoms of osteoarthritis (as also seen in rheumatoid arthritis), while in a later stage coping with a new disease may ameliorate symptoms *(figure 4)*. In the final course of the disease the structural (radiographic) changes progress and lead to further pain and disability. It should be taken into account that in addition, several other factors, as described in the ICF model, may add to the apparent discrepancy observed between pain and structural joint damage over time.[28] Our hypothesis can be tested in future follow-up of patients in both cohorts, in particular those with the more severe complaints (still) without radiographic joint damage. If it appears that the CHECK population with respect to pain and joint damage, independent of factors like, social background, healthcare system differences, cultural difference, variance in methodology etc, follows the OAI population, then our hypothesis may hold true. Of course other factors, independent of symptoms and joint damage, need to be evaluated regarding observed differences between both cohorts, as such giving both cohorts their surplus value. —

Fewer participants in CHECK had radiographic knee OA compared with the OAI.

The participants in CHECK had more pain, more stiffness, more limitations in activities and a worse health status.

REFERENCES

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

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

3. van Dijk GM, Dekker J, Veenhof C, Van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: A systematic review of the literature. Arthritis Rheum 2006; 55:779-85.

4. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol 1999; 26:1785-92.

5. Cieza A, Stucki G. New approaches to understanding the impact of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2004; 18:141-54.

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

7. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995; 54:872-80.

8. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999; 26:2664-74.

9. Chaisson CE, Gale DR, Gale E, Kazis L, Skinner K, Felson DT. Detecting radiographic knee osteoarthritis: what combination of views is optimal? Rheumatology (Oxford) 2000; 39:1218-21.

10. Laurin CA, Dussault R, Levesque HP. The tangential x-ray investigation of the patellofemoral joint: x-ray technique, diagnostic criteria and their interpretation. Clin Orthop 1979;16-26.

11. Auleley GR, Duche A, Drape JL, Dougados M, Ravaud P. Measurement of joint space width in hip osteoarthritis: influence of joint positioning and radiographic procedure. Rheumatology (Oxford) 2001; 40:414-9.

12. Conrozier T, Bochu M, Gratacos J, Piperno M, Mathieu P, Vignon E. Evaluation of the 'Lequesne's false profile' of the hip in patients with hip osteoarthritis. Osteoarthritis Cartilage 1999; 7:295-300.

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

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

15. Veenhof C, Bijlsma JW, Van den Ende CH, van Dijk GM, Pisters MF, Dekker J. Psychometric evaluation of osteoarthritis questionnaires: a systematic review of the literature. Arthritis Rheum 2006; 55:480-92.

16. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at omeract III. J Rheumatol 1997; 24:799-802.

17. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998; 25:198-9.

18. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63:36-42.

19. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of womac: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15:1833-40.

20. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34:220-33.

21. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.

22. Verstappen SM, Boonen A, Verkleij H, Bijlsma JW, Buskens E, Jacobs JW. Productivity costs among patients with rheumatoid arthritis: the influence of methods and sources to value loss of productivity. Ann Rheum Dis 2005: 64:1754-60.

23. Picavet HS, van Gils HWV, Schouten JSAG. Musucloskeletal complaints in the Dutch population, prevalences, consequences and risk groups (in Dutch: Klachten van het bewegingsapparaat in de Nederlandse bevolking, prevalenties, consequenties en risicogroepen) RIVM rapportnummer 266807002. 2000. Bilthoven, CBS/RIVM.

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

25. Fink P, Jensen J, Borgquist L, Brevik JI, Dalgard OS, Sandager I, et al. Psychiatric morbidity in primary public health care: a Nordic multicentre investigation. Part I: method and prevalence of psychiatric morbidity. Acta Psychiatr Scand 1995; 92:409-18.

26. Hildebrandt V.H., Douwes M. Physical load and work: questionnaire on musculoskeletal load and health complaint (in Dutch: lichamelijke belasting en arbeid: vragenlijst bewegingsapparaat). Directoraat-Generaal van de Arbeid 1991; S122-S123.

27. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000; 27:1513-7.

28. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000; 133:635-46.

62885 Vragenlijst Check

Onderstaande vragen betreffen uw dagelijks functioneren. Hiermee bedoelen we het vermogen u te verplaatsen en voor uzelf te zorgen. Wilt u voor elk van de onderstaande activiteiten aangeven hoeveel moeite u **tijdens de afgelopen 48 uur** heeft ervaren als gevolg van klachten aan uw heup en/of knie. (Geef uw antwoord alstublieft aan met een kruisje in het passende hokje)

4. Hoeveel moeite had u.....

	Geen	Gering	Matig	Veel	Erg veel
a. Bij de trap *aflopen*?	☐	☒	☐	☐	☐
b. Bij trap *oplopen*?	☐	☒	☐	☐	☐
c. Bij het opstaan vanuit een stoel?	☒	☐	☐	☐	☐
d. Bij het staan?	☐	☐	☒	☐	☐
e. Bij het bukken naar de grond?	☐	☐	☒	☐	☐
f. Bij het lopen op een vlakke ondergrond?	☐	☐	☒	☐	☐
g. Bij het instappen/ uitstappen van een auto?	☐	☐	☒	☐	☐
Met *één* uur lopen	☐	☐	☒	☐	☐
twee uur lopen?	☐	☐	☒	☐	☐
winkelen?	☐	☐	☒	☐	☐
sokken/ kousen *aantrekken*?	☐	☐	☒	☐	☐
l. Bij het opstaan van bed?	☐	☐	☒	☐	☐
m. Bij het sokken/ kousen *uittrekken*?	☐	☐	☒	☐	☐
n. Bij het in bed liggen?	☐	☐	☒	☐	☐
o. Bij het in/ uit bad gaan?	☐	☐	☒	☐	☐
p. Bij het onder de douche gaan?	☐	☐	☒	☐	☐
q. Bij het zitten?	☐	☐	☒	☐	☐
r. Bij het gaan zitten op/ opstaan van het toilet?	☐	☐	☒	☐	☐
s. Bij zware activiteiten in en om het huis?	☐	☐	☒	☐	☐
t. Bij *zware* huishoudelijke werkzaamheden?	☐	☐	☒	☐	☐
u. Bij *lichte* huishoudelijke werkzaamheden?	☐	☐	☒	☐	☐
v. Bij de trap op- of aflopen *met iets in handen*?	☐	☐	☒	☐	☐
w. Bij *vijf* kilometer lopen?	☐	☐	☒	☐	☐
x. Bij het gaan zitten op/ opstaan van de grond?	☐	☐	☒	☐	☐

4

WORSENING OF PAIN AND FUNCTION OVER 5 YEARS IN INDIVIDUALS WITH 'EARLY' OA IS RELATED TO STRUCTURAL DAMAGE: DATA FROM THE OSTEOARTHRITIS INITIATIVE AND CHECK (COHORT HIP & COHORT KNEE) STUDY

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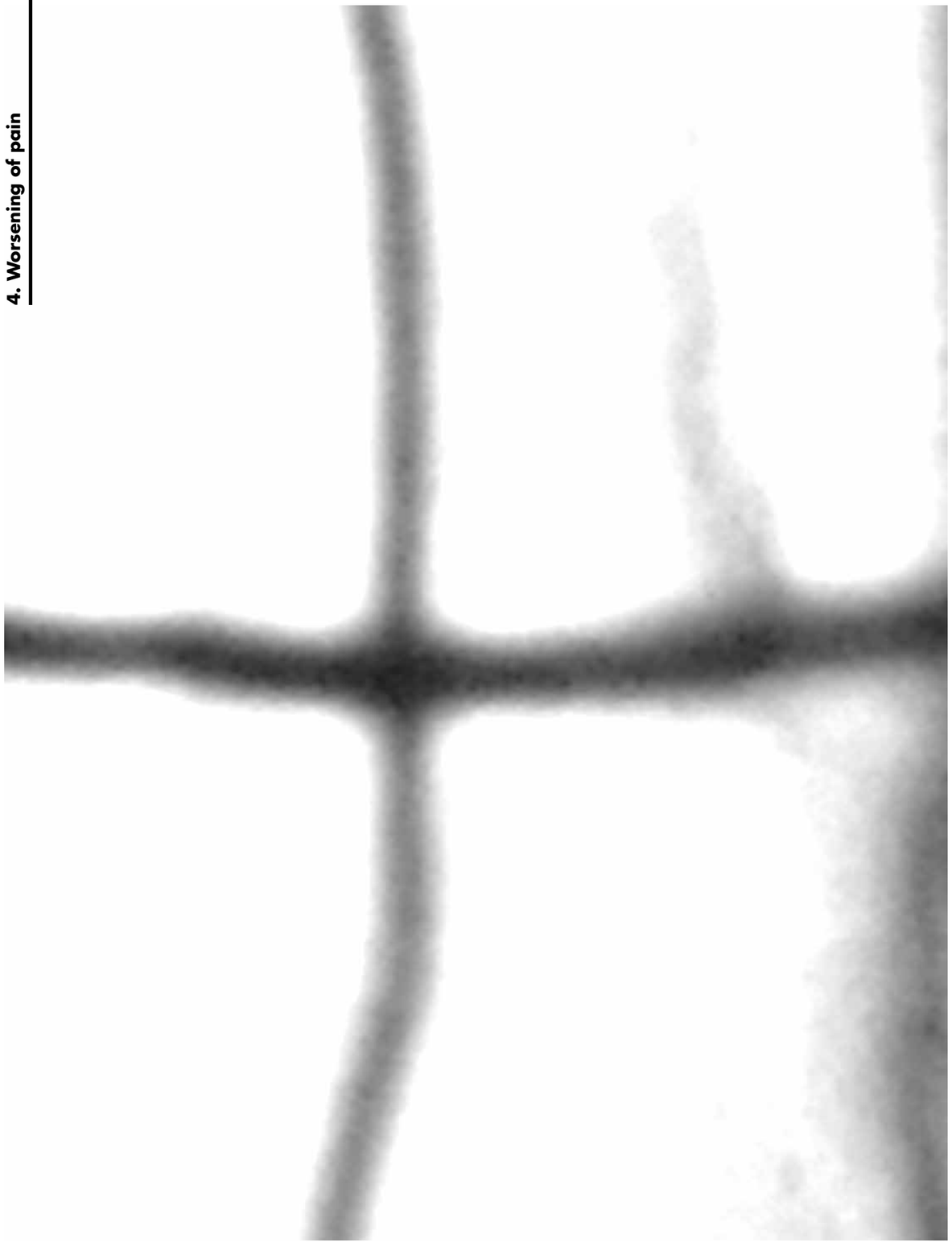

ABSTRACT

Objective

To analyse the relation of joint damage on evolution of pain and physical functioning in two different cohorts of early phase of osteoarthritis (OA): Osteoarthritis Initiative (OAI) and Cohort Hip & Cohort Knee study (CHECK).

Methods

Longitudinal data of 4 to 5 years follow-up (= medium term) of CHECK study and OA Initiative were used. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was utilized to measure pain and physical functioning. For comparison with CHECK a subgroup of the OAI Incidence cohort was selected Generalized estimating equations (GEE) were used and all models were adjusted for gender, BMI, age, amount of working hours, racial background and hip pain at baseline. Finally, an interaction term was added to assess a possible differential effect of radiological progression on evolution of pain and function in the two cohorts.

Results

At baseline CHECK had less radiographic OA (K&L ≥ 2) compared to OAI Incidence subgroup, but at follow-up CHECK had more radiographic change (51% us 15% ≥1 K&L point increase; p‹ 0.001). Over 4 years of follow-up, evolution of pain and physical functioning remained fairly stable in both cohorts, however at different levels: OAI participants had less pain and less problems with physical functioning compared to CHECK participants. Both cohorts showed the same negative effect of rapid radiological change (K&L change of 2 points) on pain and physical function.

Conclusions

In participants with 'early symptomatic OA' rapid radiological change (change of ≥2 grades of K&L in 4 or 5 years) is related to worsening of pain and function.

KNEE PAIN IS OFTEN THE FIRST SIGN OF KNEE OSTEOARTHRITIS (OA)[1] AND IT IS KNOWN THAT ITS EVOLUTION CAN BE VERY DIFFERENT BETWEEN PATIENTS.

Besides pain, OA causes on the long term decline in physical function.[2] Studies to analyse the natural evolution of pain and physical function in the early stage of OA are sparse. Osteoarthritis Initiative Incidence cohort (OAI) and Cohort Hip & Cohort Knee study (CHECK) focus both on the early phase of OA; we compared baseline characteristics of both cohorts and described that at baseline radiographic knee OA was more present in OAI-Incidence subgroup compared to CHECK knee pain group. This radiological observation is in discordance with the more severe clinical symptoms reported by the CHECK participants. Discrepancies between radiological findings and clinical symptoms in OA are well described, but the actual relation between radiographic damage and clinical symptoms over time has never been clear and is subject of this study in both cohorts.[3] The present study aims to identify the evolution of pain and physical functioning on medium term in these different OA cohorts and to analyze the relation of structural damage with this evolution.

METHODS

Design and study population of CHECK

From October 2002 till September 2005 a cohort was formed of 1,002 participants with pain and/ or stiffness of knee and/ or hip. The study was approved by the medical ethics committees of the 12 participating centres, and all participants gave their written informed consent before entering the study. A complete description of the CHECK study has been reported elsewhere.[3] Individuals were eligible if they had pain or stiffness of knee or hip, were aged 45-65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry.[3] For the analyses in this study, only longitudinal data on medium term of CHECK participants with knee pain at baseline were included, irrespective of their annual or variable schedule to visit the study centre.

Design and study population of OAI

From March 2004 to May 2006 the OAI cohort was formed and divided into two sub cohorts: progression cohort and an incidence cohort. For the incidence cohort age-specific eligibility criteria were defined. All details of the OAI are available on the internet (*http://www.oai.ucs.edu*). For the present study longitudinal data on medium term was used of participants within age range 45-65 years, which had at least frequent or infrequent knee symptoms, excluding those that had overweight without symptoms and excluding those that had previous knee surgery.

Outcome variables

Evolution of pain and physical functioning over medium term was assessed with the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire. The WOMAC[4-6] is a disease specific questionnaire with well-known and good clinimetric properties and recommended by OMERACT.[7,8] The five point Likert version of the WOMAC was used; item responses range from 'none' to 'extreme' and are summed to produce subscales (pain 0-20, functioning 0-68) with higher scores indicating worse health. In both cohorts the WOMAC pain and physical function were assessed at baseline and at follow-up after 1, 2, 3 and 4 years. CHECK assessed per participant a WOMAC score for pain and physical problems; they were asked to answer the WOMAC for their knee as well as hip complaints together. OAI assessed per knee per participant a WOMAC score for pain, and physical function. In the analyses the highest WOMAC score of the OAI participant is used.

Independent variables

In both cohorts, at baseline and at follow-up, posterior-anterior weight-bearing radiographs of both tibio-femoral joint were obtained to assess radiographic OA features of the knee. Follow-up time for the radiographs was in CHECK 5 years and in OAI 4 years. All views were scored according to Kellgren & Lawrence (K&L) and original description of K&L criteria was used.[9] For each knee the radiographic change from baseline to follow-up was measured and the greatest radiographic change in one of the knees was used in the analyses. Severity of radiographic OA at baseline was defined as the worst knee, defined by the knee with higher K&L grade.[1]

The radiographs of CHECK were scored by trained observers independently. CHECK readers scored all consecutive radiographs at the same time knowing the sequence (baseline, 2 year and 5 year). OAI readers know the true baseline visit X-ray, but were blinded to the chronological order of follow-up visits (12 month, 24 month, 36 month and 48 month), with grouped images from all available time points viewed simultaneously. All readers were blinded to the clinical data of the participant.

Statistical analyses

In the present report CHECK participants with knee problems (excluding those with exclusively hip problems) were compared with participants of the OAI incidence cohort within the same age range (45-65 years). All analyses were performed in the participants of CHECK and OAI who had data of at least 2 visits (CHECK n= 805; OAI n= 1,483). The post-surgery WOMAC data of participants who underwent total knee replacement during 4 or 5 year follow-up were coded as missing. Baseline characteristics of both cohorts are presented separately using descriptive statistics: mean or percentages. Differences between cohorts are analysed using T-tests or Chi-Square test, where appropriate.

To analyse the evolution of pain and function in the two OA cohorts, we selected participants in both

cohorts with K&L grade 0 or 1, because only these 2 grades were present at baseline in both cohorts.

To investigate the longitudinal relationship between change in pain and function and the independent variables of two OA cohorts, generalized estimating equations (GEE) were carried out. The correction for dependency of the individual observations is performed by assuming a working correlation structure; an exchangeable structure was used. To assess differential effects between the two cohorts' data of CHECK and OAI were merged into one dataset. To analyse the evolution of pain and function over time, time variable is added to the GEE model. The linearity of the relationship between these outcomes and time is analysed by adding time^2 to the GEE model. In a quadratic relationship, or another non- linear relationship between outcome and independent variable, the independent variable is included in the model as a categorical variable.

All GEE models were adjusted for gender, BMI, age, amount of working hours, racial background and hip pain at baseline. Finally, possible differential effects of radiological joint damage on the evolution of pain and physical functioning in both cohorts was investigated by introducing the interaction term 'max K&L change x cohort'.

RESULTS

Patient population

At baseline 805 CHECK participants had knee pain and data of at least two visits. The subgroup of OAI Incidence cohort consisted of 1,483 participants *(figure 1)*. The characteristics of both cohorts are given in *table 1*. At baseline CHECK knee subgroup had less radiographic OA (K&L ≥ 2) and more pain and function problems compared to OAI Incidence subgroup. During follow-up CHECK participants developed more radiographic changes (51% us 15% K&L grade change ≥1; p<0,001), with constant mean scores of pain and function over time *(figure 2 and 3)*. In both cohorts increase of 2 and 3 grades of K&L, were combined as K&L≥2, as a result of low numbers of 3 grades increase of K&L.
In CHECK knee subgroup there were after five years of follow-up 33 joint replacements (17 hip- and 16 knee replacements) performed and in the OAI Incidence subgroup after 4 years 30 replacements (18 hip- and 12 knee replacements). In the subgroup with K&L 0 or 1, the number of replacements in CHECK was the same; in OAI there were only 12 hip replacements performed.

Effect of change in joint damage in evolution of pain and function

In *table 2* univariate beta coefficients of variables which are included in the multivariate longitudinal model are presented. There was an univariate association of radiological change from baseline to follow-up with pain and physical functioning. Compared to no radiological change, the pain and function score increase with more radiological change from baseline to follow-up.

In *table 3* the results of the longitudinal regression model with evolution of pain as outcome variable are presented. There was a slight decrease of pain over time for the total group (OAI and CHECK together), but at a lower level of 2.6 points in OAI participants (less pain). In the model with evolution of function as outcome variable, there was over time a slight decrease of physical function in the total group, but at a lower score for function of 9.7 points in OAI participants (better function). The results presented in *table 3* indicate that in all participants for example first year of follow-up is associated with a 0.3 lower pain score compared to baseline pain score; besides that, an OAI participant has a 2.6 lower pain score compared to a CHECK participant.

In the total group a significant association of the radiological change with evolution of pain and function was noted. The pain or function score of participants with a radiological K&L change of 1 point compared to those without changes was not influenced by this change in radiological damage. In

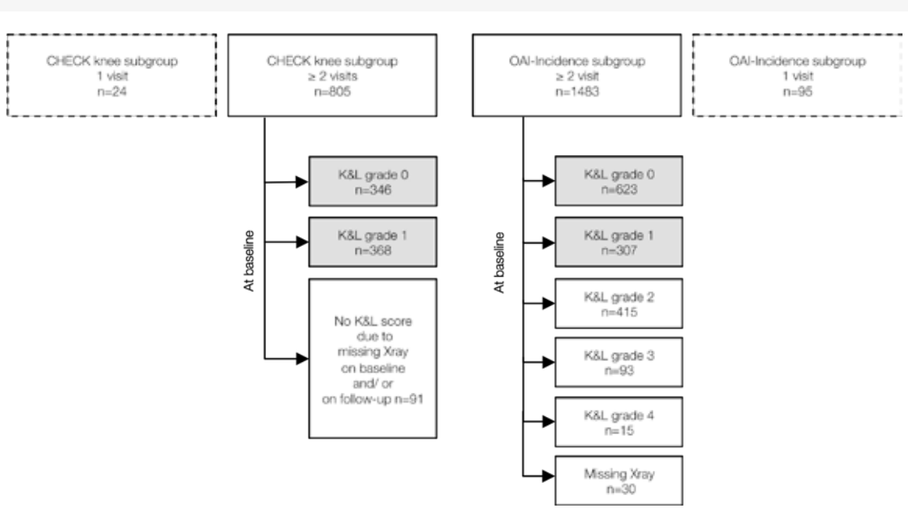

FIGURE 1 | Flow diagram from the baseline study population selected for the present study

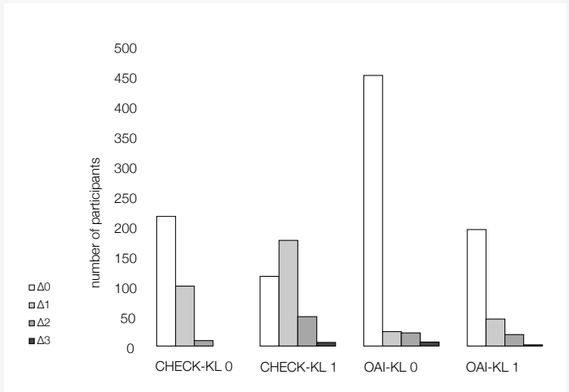

FIGURE 2 | Number of participants with radiological changes (Δ0 – Δ3 points) from baseline to follow-up by baseline K&L score in CHECK and OAI participants with K&L 0 or 1 at baseline

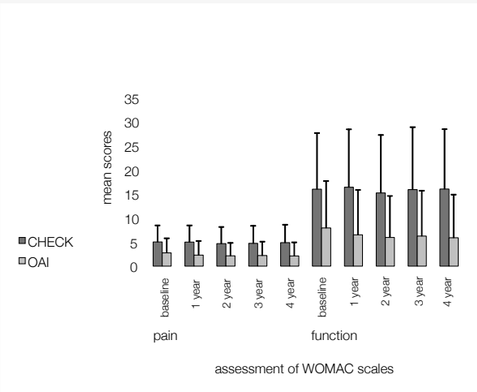

FIGURE 3 | Mean scores (with standard deviations) at baseline, after 1,2,3 and 4 years follow-up on WOMAC pain and physical function scale of participants with K&L 0 or 1 at baseline. Higher scores indicates more pain and physical function problems

TABLE 1| Baseline demographic and disease characteristics in CHECK knee subgroup with ≥ 2 visits, OAI-incidence subgroup with ≥ 2 visits, CHECK knee subgroup with K&L grade 0 or 1 at baseline and OAI-incidence subgroup with K&L grade 0 or 1 at baseline

	CHECK-knee subgroup	OAI incidence subgroup	p-value	K&L 0/1 at baseline CHECK	K&L 0/1 at baseline OAI	p-value
n	805	1483		714	930	
Age in years	56 (5)	56 (6)	0.9	56 (5)	55 (6)	0.003
Gender, female (%)	80	64	< 0.001	80	62	< 0.001
BMI, kg/m^2	25 (7)	28 (5)	< 0.001	26 (7)	28 (5)	< 0.001
Educational level (%)			0.006			0.001
Primary school	3	2		3	2	
Secondary school	71	65		71	64	
High prof. education/ univ.	26	33		26	34	
Racial background (%)			< 0.001			
White or Caucasian	97	77		97	79	< 0.001
Black or African American	1	19		1	18	
Asian	2	1		2	1	
Other, non-white		2			2	
Hip pain (%)						
No pain	50	43	0.002	49	42	0.003
Yes pain	50	57		51	58	
K&L rating score for knee (%)			< 0.001			
Grade 0	48	43		49	68	< 0.001
Grade 1	52	21		52	32	
Grade 2		28				
Grade 3		6				
Grade 4		1				
WOMAC subscales						
Pain (range 0-20)	5 (3)	3 (3)	< 0.001	5 (3)	3 (3)	< 0.001
Stiffness (range 0-8)	3 (2)	2 (2)	< 0.001	3 (2)	2 (2)	< 0.001
Physical function (range 0-68)	16 (12)	9 (10)	< 0.001	16 (12)	8 (10)	< 0.001
Present employment (%)			< 0.001			
No paid job/volunteer?	46	22		46	20	< 0.001
> 36 hour work/week	11	23		11	60	
8-36 hour/week	43	55		43	20	
Healthcare provider consultation < 3 months ago for knee complaints (CHECK) or seeing a healthcare provider for knee arthritis (OAI) (%)						
Yes	46	3	< 0.001	46	2	< 0.001
No	54	97		54	98	

Mean values, standard deviation between brackets and categorical variables as percentages (%) are given.
BMI | body mass index; K&L | Kellgren and Lawrence grade, WOMAC | Western Ontario and McMaster Universities OA index with higher scores indicating worst health; p values are given.

TABLE 2| Univariate regressions in CHECK and OAI participants adjusted for age, BMI, gender, working hours, racial background and hip pain at baseline in participants with K&L score 0 or 1 at baseline

	WOMAC pain evolution			WOMAC function evolution		
	Beta	**CI**	**p-value**	**Beta**	**CI**	**p-value**
Time (per year)	-0.1	-0.1 – -0.02	< 0.001	-0.3	-0.4 – -0.2	< 0.001
Time^2	-0.01	-0.02 – -0.008	< 0.001	-0.04	-0.06 – -0.02	< 0.001
Cohort (CHECK=0; OAI=1)	-2.6	-2.8 – -2.3	< 0.001	-9.5	-10.5 – -8.5	< 0.001
Max K&L change T4-T0						
Δ score = 0	Reference			Reference		
Δ score = 1	0.7	0.4 – 1.1	< 0.001	3.1	1.8 – 4.4	< 0.001
Δ score = 2 and 3	1.2	0.7 – 1.7	< 0.001	4.6	2.7 – 6.5	< 0.001
Overall			< 0.001			< 0.001

WOMAC | Western Ontario and McMaster Universities OA Index, CI | confidence interval Negative beta values = decrease in WOMAC pain evolution or WOMAC function evolution (better health).

TABLE 3| Regression model adjusted for age, BMI, gender, working hours, racial background and hip pain at baseline in participants with K&L score 0 or 1 at baseline

	WOMAC pain evolution			WOMAC function evolution		
	Beta	**CI**	**p-value**	**Beta**	**CI**	**p-value**
Intercept	5.8	4.0; 7.6	< 0.001	14.3	8.0; 20.5	< 0.001
Time						
Baseline	Reference			Reference		
1 year	-0.3	-0.5 – -0.2	< 0.001	-0.8	-1.2 – -0.4	< 0.001
2 year	-0.4	-0.6 – -0.3	< 0.001	-1.2	-1.7 – -0.8	< 0.001
3 year	-0.4	-0.6 – -0.3	< 0.001	-1.0	-1.5 – -0.5	< 0.001
4 year	-0.4	-0.5 – -0.2	< 0.001	-1.0	-1.5 – -0.5	< 0.001
overall			< 0.001			< 0.001
Cohort (CHECK=0; OAI=1)	-2.6	-3.0 – -2.3	< 0.001	-9.7	-10.7 – -8.6	< 0.001
Max K&L change T4-T0						
Δ score = 0	Reference			Reference		
Δ score = 1	-0.2	-0.5 – 0.2	0.3	-0.1	-1.3 – 1.1	0.9
Δ score = 2 and 3	0.8	0.3 – 1.3	0.002	3.0	4.8 – 11.1	0.001
Overall			0.002			0.003

WOMAC | Western Ontario and McMaster Universities OA Index, CI | confidence interval Negative beta values = decrease in WOMAC pain evolution or WOMAC function evolution (better health).

participants with a K&L change of at least 2 points compared to those with zero K&L change, a reinforcing association with evolution of pain (increase of pain) and function (decline of function) was observed.

The interaction term: 'max K&L change x cohort' for the outcome pain and function was not statistically significant (overall effect with p-value 0.2). This indicates that no differential effect of change in joint damage from baseline to follow-up on the evolution of pain and function between CHECK and OAI participants was observed.

DISCUSSION

The objective of our study was to identify the evolution of pain and physical functioning on medium term in two different OA cohorts (CHECK and OAI) and especially to analyze the relation of structural damage with this evolution. Participants of CHECK and OAI included for the analysis were aged 45-65 years, had knee pain at baseline and had at baseline K&L 0 or 1. It can be concluded that in the total groups the evolution of pain and physical function remains fairly stable over medium term in participants with early symptoms of symptomatic OA in the Netherlands as well as in the US. It was noted that the level of these outcome variables are different: OAI participants had less pain and less problems with physical functioning compared to CHECK participants. In literature others also described a stable course of limitations in activity over a period of 5 years. At individual level a considerable variation (indicated by large standard deviations of the change scores) was found.[10,11] Also in CHECK and OAI considerable individual variation was found.

From baseline to follow-up, half of the CHECK participants showed radiological change of at least one K&L grade and in the OAI only one sixth of the participants showed radiological change of at least one point. In literature change of K&L grade is divided into incidence and progression, both with different definitions. Incidence is defined as a change from K&L grade 0 to grade ≥ 1 or more from baseline to follow-up. Progress is defined as a change from K&L 1 to any higher grade.[1] This definition differs from a definition by Felson, who defined incidence as new-onset K&L grade 2 and progression when K&L grade increases (≥2) or joint replacement occurs.[12] Additionally, it is described that knees that are progressing are far more likely to continue to progress than knees which have been stable in terms of structural deterioration: state of inertia.[13] In this study, when we used the first definition of incidence and progression, there were 16% in CHECK and 4% in OAI who changed from K&L grade 0 to grade ≥1, so have incidence knee OA. In CHECK 34% of participants with K&L grade ≥1 progressed, compared to 6% of OAI participants. According to Felson's definition much lower percentages were found in incidence.

Importantly, in this study we found an association between radiological change and the evolution of pain and function, which was comparable between both cohorts. These findings suggest it was not so much the presence of joint damage at the knee that was important for the evolution of pain and function, but rather the worsening of joint damage on medium term. A limited radiographic change of 1 point in K&L grade did not have an association with the evolution of pain and function. This limited change could be characterized as slow progression. However, an increase of 2 points or more in K&L grade is associated with more pain and function problems. Apparently there must be a larger change in structural deterioration to have effect on the evolution of pain and function. This radiological change could be characterized as rapid progression. In literature it has been suggested that individuals with slow progression could have more opportunity to adapt to the changes in physiology and decreases in pain.[14] The reported differences in pain and function levels could not be explained by difference in BMI, age, gender, working hours, racial background or hip pain at baseline. The approaches to recruit participants differed slightly: only 6% of the CHECK participants were recruited by a healthcare provider, compared to 1% in OAI. Further, it cannot be ruled out that the social, cultural, and health care system differences between the US and Europe, specifically the Netherlands, account for (part of) the difference in reported WOMAC levels. There are factors which could limit the relevance of the findings of this study. First the follow-up time for radiological change is slightly different between the cohorts. Radiological change in CHECK is measured after 5 years and in OAI after 4 years. It is unlikely that the observed radiological change between the cohorts can be caused by a difference of 1 year follow-up. The difference in radiological change is probably caused by a higher frequency of participants with K&L 1 at baseline in the CHECK group. Knees with grade K&L 1 have a higher chance to progress in comparison to K&L 0.[15,16]

Second, the reading of the X-rays in the US is performed by other readers than the readers who performed the reading in the Netherlands. Both groups used the same original description of K&L, however it is known that cohort studies disagree between each other on the interpretation of grading according to K&L.[17] Importantly, in both cohorts it was known if the X-rays represented baseline or follow-up, and in both cohorts they were read in a paired fashion. It has been suggested that progression might be overestimated when reading paired radiographs with sequence known, but that effect was similar in both cohorts.[18]

Third, there were missing data in the longitudinal data of the WOMAC. The advantage of GEE is, that subjects with missing WOMAC data are not excluded from the analyses and imputation methods are not necessary to analyse longitudinal dataset with missing data.[19] The baseline characteristics of the included CHECK participants were compared with CHECK participants who were excluded from this study, because they had only one visit or a missing radiograph. There was no statistical significant difference between these variables (data not shown). Also baseline characteristics of the included OAI participants were compared with the OAI participants who were excluded for the same reason in this study. At baseline there was a difference, the excluded participants had more pain (mean 3.5 with SD 3.4) and more functional problems (mean 10.7 with SD 10.9). Besides, this group consisted of a different racial background (28% black) and a differential education level (4% primary school). The other baseline variables were not different. So, it could be that the level of pain and function evolution of the excluded OAI participants is higher than the level of the included OAI participants. However baseline values of pain and function of the excluded OAI participants is still lower than the level of the CHECK participants.

Besides these possible methodological limitations, there are other variables that are related to evolution of pain and functional problems. People vary in their reporting of pain and their pain related behavior; however in this study only severity of pain and physical function are analyzed. It should be interesting to evaluate different aspects of pain itself, and for example to evaluate intermittent and constant pain.[20,21] However, this is not possible in this report, because the ICOAP (measure of intermittent and constant OA pain) is not measured in CHECK and OAI at baseline. It would also be interesting to analyze the use of different coping strategies between OAI and CHECK, because lower levels of pain and function could be caused by better coping strategies. Unfortunately coping was not measured in OAI. Also of interest are the comorbidities, since they may have a negative effect on pain and physical health status.[22] Unfortunately, comorbidities were measured in both cohorts using different questionnaires. This underscores the importance of international, common databases which consist of the same items measured at the same time points. Hopefully, in future answers can be given which factors contribute to the observed difference in evolution in pain and function between CHECK and OAI.

We conclude that on average in patients with early symptomatic OA pain and physical function remain fairly stable over 4 to 5 years, and especially in participants with a slow progression (radiological change of K&L grade 1). In participants with a rapid progression (radiological change of K&L grade ≥2) pain will increase and function will decline. For the physician, these findings, which are based on analyses on groups' level, may provide a legitimation for symptomatic treatment. —

REFERENCES

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

2. Felson DT, Lawrence RC, Dieppe pa, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000; 17;133:635-46.

3. Wesseling J, Dekker J, van den Berg wb, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip & Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68:1413-9.

4. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at omeract III. J Rheumatol 1997; 24:799-802.

5. Boers M, Brooks P, Strand CV, Tugwell P. The omeract filter for Outcome Measures in Rheumatology. J Rheumatol 1998; 25:198-9.

6. Veenhof C, Bijlsma JW, Van den Ende CH, van Dijk GM, Pisters MF, Dekker J. Psychometric evaluation of osteoarthritis questionnaires: a systematic review of the literature. Arthritis Rheum 2006; 55:480-92.

7. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. Satisfactory cross cultural equivalence of the Dutch womac in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63:36-42.

8. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of womac: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15:1833-40.

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

10. Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JW, Dekker J. The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. Osteoarthritis Cartilage 2012; 20:503-10.

11. Yusuf E, Bijsterbosch J, Slagboom PE, Kroon HM, Rosendaal FR, Huizinga TW, et al. Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis. PLoS One 2011;6:e25426.

12. Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis 2011; 70:1884-6.

13. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt MC. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2013; 72:924-9.

14. White DK, Zhang Y, Niu J, Keysor JJ, Nevitt MC, Lewis CE, et al. Do worsening knee radiographs mean greater chances of severe functional limitation? Arthritis Care Res (Hoboken) 2010; 62:1433-9.

15. Hart DJ, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee--doubtful or definite? Osteoarthritis Cartilage 2003 Feb; 11:149-50.

16. de Klerk BM, Willemsen S, Schiphof D, van Meurs JB, Koes BW, Hofman A, et al. Development of radiological knee osteoarthritis in patients with knee complaints. Ann Rheum Dis 2012; 71:905-10.

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

18. Spector TD, Dacre JE, Harris pa, Huskisson EC. Radiological progression of osteoarthritis: an 11 year follow up study of the knee. Ann Rheum Dis 1992; 51:1107-10.

19. Twisk J, de VW. Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol 2002; 55:329-37.

20. Hawker GA. Experiencing painful osteoarthritis: what have we learned from listening? Curr Opin Rheumatol 2009; 21:507-12.

21. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (icoap). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240-S252.

22. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip & Cohort Knee) study. Rheumatology (Oxford) 2013; 52:180-8.

In patients with early symptomatic OA, pain and physical function remain stable over 4-5 years.

In participants with a rapid progression pain will increase and function will declin

PART II

DIFFERENCES IN EVOLUTION OF DISEASE CHARACTERISTICS IN CHECK

5

IMPACT OF SELF-REPORTED COMORBIDITY ON PHYSICAL AND MENTAL HEALTH STATUS IN EARLY SYMPTOMATIC OSTEOARTHRITIS: THE CHECK (COHORT HIP & COHORT KNEE) STUDY

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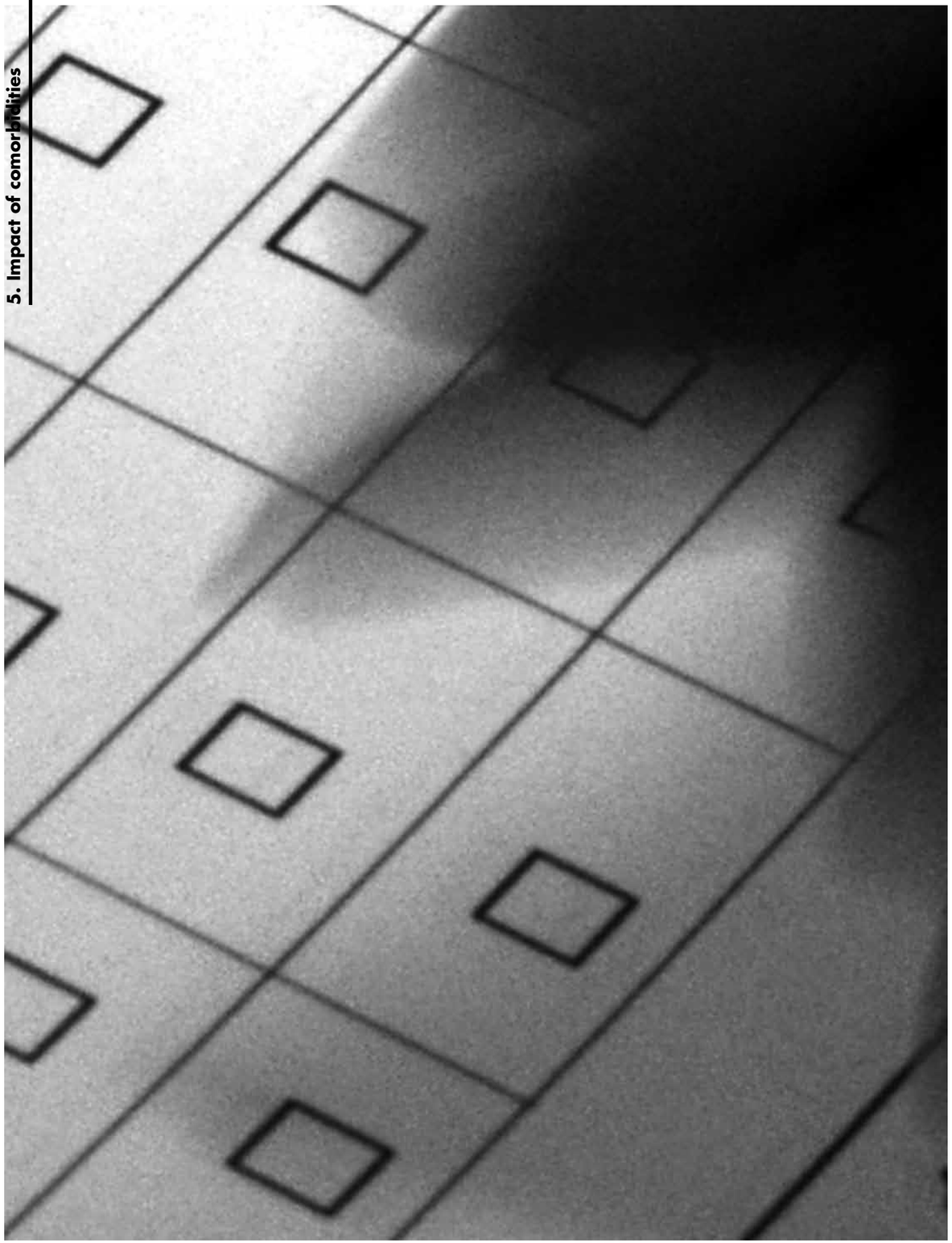

ABSTRACT

Objective

To describe the relationship between comorbidity (absolute number as well as the presence of specific comorbidities) and pain, physical functioning and mental health status of participants with early symptomatic OA of hip or knee.

Methods

In the Netherlands a prospective 10-year follow-up study was initiated by the Dutch Arthritis Association in participants with early symptomatic OA of hip or knee: CHECK (Cohort Hip & Cohort Knee), which consists of 1,002 individuals. At baseline, linear regression analysis was used to determine the influence of comorbidity on the outcome variables: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC physical functioning, Medical Outcomes Study Short Form 36 (SF-36) Physical Component Summary and Mental Component Summary.

Results

Of 979 subjects, 67% reported one or more comorbidities. After controlling for age, gender, social status and severity of radiographic OA (Kellgren and Lawrence score), back disorders have the largest effect on WOMAC pain, physical functioning, and one of the largest effects on physical status of SF-36, besides obesity. Mental status was negatively influenced by the additional presence of duodenal ulcer, thyroid disease, and migraine or chronic headache.

Conclusions

In early stage of OA, the presence of additional problems in the musculoskeletal system and of obesity have a negative effect on pain and physical health status. Also mental status is affected in early symptomatic OA by the presence of specific comorbidities. Comorbidity should be assessed and treated to improve the burden of illness of patients with early symptomatic OA.

OA IS THE MOST COMMON DIAGNOSIS MADE IN ELDERLY PATIENTS WITH KNEE OR HIP PAIN. The prevalence of many other disabling conditions increases with age and (with increasing age) many chronic conditions occur together with OA.[1,2] OA has a very high rate of comorbidities[1,3] and patients with OA are significantly more likely to have comorbidity than non-OA patients.[4] In a large representative network of general practices, the Netherlands Information Network of General Practice (LINH), 75% of the OA patients aged ≥ 55 years had one or more comorbid diseases. Twenty-seven per cent of these patients had chronic disorders of the neck or back.[5] Combinations of back disorders with OA and hypertension with OA are most reported in absolute values.[6,7] The consequences of combinations of specific diseases and OA are diverse and not very well known. Previous research in OA patients,[1,8-10] has shown that the number of (co)morbidities ('comorbidity count') is associated with limitations in activities and perceived health. Although the majority of studies on comorbidity have focused on 'comorbidity count' only, it was found that specific (combinations of) chronic diseases have a different influence on physical functioning.[8,9,11-13] With regard to mental functioning, it is reported that mental health deteriorates less than physical health with increasing comorbidity and remains relatively high and stable.[12,13] Other disease characteristics, such as illness duration and disease stage or activity, may be more important for mental health than the type or number of comorbidities.[11] None of the former studies assessed the impact of the presence of specific diseases and complaints of patients in the early stage of OA.

Studying comorbidity in this early phase of OA is important, because it influences the burden of illness of OA for a large part. Health gain can be achieved by prevention or early recognition and adequate treatment of comorbid diseases, especially in the early stage of OA. Therefore it is necessary to further increase our knowledge of comorbidity in patients with early symptomatic OA. This might enable us to define strategies to prevent a further negative effect on the symptoms of OA. The objective of the present report is to describe the relationship of comorbidity (absolute number as well as the presence of specific comorbidities) with pain, physical and mental health status of participants with early symptomatic OA of knee or hip.

METHODS

Study design

For the current cross-sectional evaluation, baseline data of the CHECK (Cohort Hip & Cohort Knee) study were used. The CHECK study is a Dutch prospective 10-year follow-up study, initiated by the Dutch Arthritis Association, to study progression of OA in participants with early symptomatic OA of knee or hip. This multicentre study (10 centres across the Netherlands) was approved by the medical ethical committees of all participating centres, and all participants gave their written informed consent before entering the study. Participants were recruited by general practitioners and through advertisements, articles in the local newspapers and on the website. A complete description of the CHECK study has been reported elsewhere.[14]

Study population

Individuals were eligible if they had pain or stiffness of knee or hip, were aged 45-65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months of entry.[14] Exclusion criteria were any non-OA condition that could explain the existing complaints (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, IA fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome, Bakers cyst). The physicians assessed by protocol a physical examination to exclude any non-OA condition.

Outcome variables

Pain and physical functioning were measured using two subscales of the Western Ontario and McMaster Universities Osteoarthritis Index, (WOMAC), which is a disease-specific self-report questionnaire with subscales ranging from 0 to 100 and higher scores indicating worse health.[15,16] The 5-point Likert version of the WOMAC was used. Besides mental health status, physical status (physical functioning) is also measured with the Medical Outcomes Study Short Form 36 (SF-36). This is a generic instrument with eight scales and two summary scores (scales range from 0 to 100 with higher scores indicating a better health status), the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[17] Country-specific scores have been established to interpret scale scores. Normative data come from a sample from the general Dutch population, aged 18-74 years, mean PCS is 49.7 (SD 9.3) and mean MCS is 52.1 (SD 9.6).[18] Generic and disease-specific instruments measure different dimensions of health status, and the use of both in quality of life studies has been recommended. However, the SF-36 has a higher correlation with comorbidities than the WOMAC.[19] To gain general insight into a patient's health, and in particular when comorbidity is common, the SF-36 should also be used.[19]

Independent variables

Comorbidity has been defined as the existence or occurrence of any distinct additional entity during the clinical course of a patient who has the index disease under study.[20,21] In the present study, comorbidity is assessed with a self-reported health module of the Central Bureau of Statistics (CBS) in the Netherlands with encompasses 24 chronic diseases.[22] The participants are asked: do you have any other chronic disease or disorder besides your knee or hip complaints? If the participants answer yes, they are asked: would you please mark, if you have or have had in the last 12 months the next disease or disorder? Along with this, height and weight were determined to calculate BMI. Obesity, defined as a BMI ≥ 30 kg/m^2 was added as a separate comorbidity. Individual comorbidities were scored and the total number of comorbidities was calculated per participant (comorbidity count).

To assess radiographic OA features, weight-bearing radiographs of tibio-femoral joint were made in posterioanterior view with semi-flexed (7-10°) knee, according to Buckland-Wright.[23-25] For the hip, weight-bearing anterioposterior radiographs of the pelvis were made.[26,27] Radiographs of posterioanterior tibio-femoral joint and anterioposterior pelvic views were scored according to Kellgren and Lawrence.[28] The severity of radiographic OA was defined as the maximum Kellgren and Lawrence (K&L) score assessed in one of the four joints (hips and knees).

Statistical analyses

Baseline characteristics of the total CHECK population and separately for participants with and without comorbidity are presented using descriptive statistics: mean and SD or frequency and proportions.

TABLE 1 | Baseline characteristics

	CHECK all	Early OA without comorbidity	Early OA with comorbidity	p-value
n	979	321	658	
Age, mean (SD), years	56 (5)	56 (5)	56 (5)	0.961
Female gender, %	79	73	82	< 0.001
BMI, mean (SD) kg/m^2	26 (4)	25 (2)	27 (5)	< 0.001
Education level, %				
Primary school	3	2	3	
Secondary school	70	67	72	0.073
High professional education/ university	27	31	25	
K&L grade, %				0.190
Grade 0	55	56	54	
Grade 1	33	29	35	
Grade 2	11	13	10	
Grade 3	1	2	1	
WOMAC subscales (range 0-100)				
Pain, mean (SD)	25.3 (17.1)	20.8 (15.2)	27.5 (17.6)	< 0.001
Physical function, mean (SD)	23.5 (17.1)	18.5 (15.0)	26.0 (7.6)	< 0.001
SF-36 subscales (range 0-100), mean (SD)				
PCS	45.6 (7.9)	48.2 (6.6)	44.4 (8.2)	< 0.001
MCS	53.0 (8.6)	54.4 (7.1)	52.4 (9.2)	< 0.001
Comorbidity counts (n=979), n (%)				
0	321 (32.8)	NA	NA	NA
1	295 (30.1)			
2	188 (19.2)			
3	105 (10.7)			
4	42 (4.3)			
5	18 (1.8)			
6	7 (0.7)			
7	3 (0.3)			

Value are mean (SD), except for categorical variables which are presented as n (%); p-value: χ^2 tests for dichotomous variables and t-tests for continuous variables.
K&L score is maximum K&L score of the four joints assessed; WOMAC, with higher score indicating worse health; SF-36 | health status survey questionnaire, with higher score indicating a better health status. NA | not applicable.

Differences in baseline characteristics between participants with and without comorbidity were compared by χ^2 tests for dichotomous variables and t-tests for continuous variables.

Linear regression analysis was used to determine the relationship between comorbidity count and outcome variables: WOMAC pain score, WOMAC physical functioning score, SF-36 PCS and SF-36 MCS. All regression models were adjusted for age, gender, social status and severity of radiographic OA.

To analyse the relationship between specific comorbidities and outcome variables, first a univariate regression analysis was performed. For this analysis only those diseases or disorders with a frequency in the CHECK population of ›5% or diseases or disorders that were thought to have a large influence on outcome were used. Next, the diseases that had a statistically significant association ($p<0.05$) with the outcome in the univariate analyses were all simultaneously added in a linear regression model, after it was checked if two or more diseases were highly correlated (collinearity). If specific diseases were no longer statistically significantly associated with the outcome and/or did not add to the explained variance (R^2), they were removed from the model one by one to arrive at a final model. The sample size justifies

TABLE 2 | Frequency of self- reported comorbidities (prevalence › 1%)

n= 979	Prevalence, n	(%)
Disorders of neck, shoulder, elbow, wrist or hand*	222	(22.2)
Hypertension*	198	(19.8)
Back disorders (including slipped disc)*	172	(17.2)
Obesity*	161	(16.1)
Migraine or chronic headache*	124	(12.4)
Asthma, chronic bronchitis, pulmonary emphysema or chronic non-specific lung disease*	90	(9.1)
Pharyngitis, sinusitis	91	(9.0)
Thyroid disease*	53	(5.3)
Prolaps uteri	42	(4.2)
Chronic inflammation of joints (such as RA)	37	(3.7)
Diabetes Mellitus*	35	(3.5)
Other chronic rheumatic diseases, longer than three month	29	(2.9)
Cholelithiasis	18	(1.8)
Dizziness with falls	17	(1.7)
Chronic urolithiasis	16	(1.6)
Peptic ulcer or duodenal ulcer*	14	(1.4)
Severe heart disease or myocardial infarction/ stroke*	14	(1.4)
Skin disease	13	(1.3)
Other, e.g. ear problems, eye problems, bowel disorders, psycho disorders	276	(27.5)

* Comorbidities were used to build the final regression model (table 4).

TABLE 3 | Results of univariate regression with pain, physical and mental health status as outcome

n=979	WOMAC pain Beta	WOMAC function Beta	SF-36 PSC Beta	SF-36 MSC Beta
Disorders of neck, shoulder, elbow, wrist or hand	5.4*	6.1*	-4.4*	-0.2
Hypertension	2.9*	3.7*	-0.98	-1.4*
Back disorders (including slipped disc)	8.1*	8.6*	-4.6*	0.006
Obesity	6.0*	7.2*	-3.4*	-0.2
Migraine or chronic headache	3.6*	5.1*	-1.0	-2.9*
Asthma, chronic bronchitis, pulmonary emphysema or chronic non-specific lung disease	4.4*	3.0	-2.6*	-1.4
Pharyngitis, sinusitis	4.1*	5.3*	-2.6*	-1.4
Thyroid disease	3.7	4.8*	-2.6*	-3.5*
Diabetes Mellitus	4.9	9.5*	-4.3*	-1.0
Peptic ulcer or duodenal ulcer	3.2*	8.7	-2.0	-6.0*
Severe heart disease or myocardial infarction/ stroke	1.9	3.2	-4.8*	0.6

Regression coefficients Beta are presented. For WOMAC, a higher scores implies a worse health status. For SF-36, a higher score implies better health status.
* p-value ≤0.05.

having a p-value cut-off point of 5%.[29] SPSS version 15 was used for all analyses and p<0.05 was considered statistically significant.

RESULTS

Study population

At baseline 1,002 participants were included. For 979 participants data on comorbidity were present, and these participants were used in the present analysis. Participants with and without complete data on comorbidity did not differ on demographic and clinical variables. The characteristics of the participants of CHECK are presented in *table 1*. More than 67% of the total study population reported one or more comorbidity. Disorders of the neck, shoulder, elbow, wrist or hand (23%), hypertension (20%) and back disorders (18%) were most prevalent *(table 2)*. Remarkably, physical examination of the musculoskeletal system did not show any clear abnormalities underlying self-reported rheumatic diseases. As shown in *table 1*, there was a significant difference in WOMAC pain, WOMAC physical functioning, SF-36 PCS and SF-36 MCS between participants with and without comorbidities (all p< 0.001).

Impact of comorbidity count

Figure 1 shows that with an increasing number of comorbidities pain as well as physical functioning deteriorates. Health status (*figure 2*) also deteriorates with an increasing number of comorbidities. *Table 4* reports the results of the linear regression analyses with WOMAC pain, WOMAC physical functioning, SF-36 PCS and SF-36 MCS as outcome variables. After controlling for age, gender, social status and K&L score, there was a significant association of the number of comorbidities with the pain and physical function subscales of WOMAC, and PCS and MCS of SF-36. The pain score and physical function score on the WOMAC deteriorate by about 3 and 4 points, respectively, with every (extra) comorbidity; the physical and mental components of the SF-36 deteriorate by about 2 and 1 point, respectively, with every (extra) comorbidity.

Impact of specific comorbidities

Based on results of univariate analyses *(table 3)*, we selected these items for further analyses in the regression model. The regression model of specific comorbidities *(table 4, controlling for age, gender, social status, K&L score)* indicates that back disorders have the greatest effect on WOMAC pain, and physical functioning scores and one of the largest effects on physical status of SF-36, besides obesity, neck and upper extremities disorders. The presence of back disorders increases WOMAC pain score on average by about 7 points, the WOMAC function score by 8 points, and SF-36 PCS score by 4 points. Obesity and the presence of disorders of the neck, shoulder, elbow, wrist and hand also independently negatively associate with scores on pain and physical functioning. Diabetes only negatively associates with physical functioning, not with pain. These diseases do not associate with the mental health status of participants. The mental health status was, however, negatively associated with less frequently occurring duodenal ulcer, thyroid disease, and migraine or chronic headache.

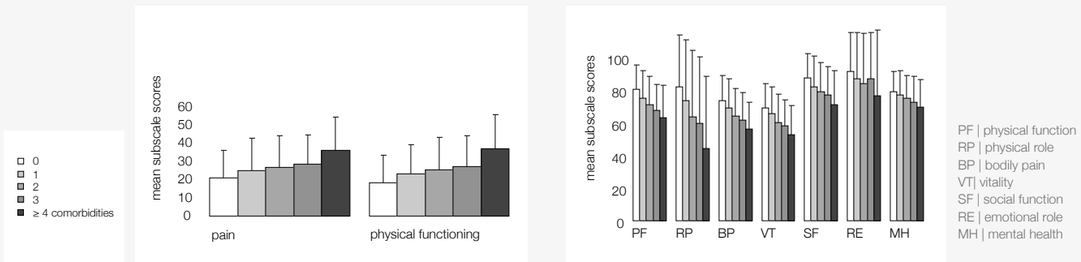

FIGURE 1 | Mean (SD) WOMAC subscale scores (0-100) in participants with 0, 1, 2, 3 and ≥ 4 comorbidities. Higher WOMAC scores indicating worse health.

PF | physical function
RP | physical role
BP | bodily pain
VT| vitality
SF | social function
RE | emotional role
MH | mental health

FIGURE 2 | Mean SF-36 subscales scores (0-100) in participants with 0, 1, 2, 3 and ≥ 4 comorbidities. SF-36 health status survey questionnaire, with higher score indicating a better health status.

TABLE 4 | Results of linear regression model with pain, physical and mental health status as outcome

Variable	Beta	p-value	95% CI	R^2
WOMAC pain				
Comorbidity count	2.8	< 0.001	2.0 – 3.8	0.10
Model-specific comorbidities				
Back disorders (including slipped disc)	7.4	< 0.001	4.7 – 10.2	
Disorders of neck, shoulder, elbow, wrist or hand	4.0	0.002	1.5 – 6.6	0.10
Obesity	4.4	< 0.001	1.5 – 7.2	
Adjusted variables				0.05
WOMAC function				
Comorbidity count	3.5	< 0.001	2.7 – 4.2	0.13
Model-specific comorbidities				
Back disorders (including slipped disc)	7.9	< 0.001	5.2 – 10.7	
Disorders of neck, shoulder, elbow, wrist or hand	4.4	0.001	1.9 – 6.9	0.13
Obesity	5.3	< 0.001	2.5 – 8.1	
Diabetes Mellitus	6.9	0.018	1.2 – 12.5	
Adjusted variables				0.06
SF-36 PCS				
Comorbidity count	-1.7	< 0.001	-2.1 – -1.3	0.12
Model-specific comorbidities				
Disorders of neck, shoulder, elbow, wrist or hand	-3.9	< 0.001	-5.0 – -2.7	
Back disorders (incl. slipped disc)	-3.7	< 0.001	-5.0 – -2.5	0.15
Obesity	-2.9	< 0.001	-4.2 – -1.6	
Diabetes Mellitus	-2.8	0.039	-5.4 – -0.1	
Adjusted variables				0.04
SF-36 MCS				
Comorbidity count	-0.8	< 0.001	-1.2 – -0.39	0.04
Model-specific comorbidities				
Duodenal ulcer	-5.8	0.011	-10.3 – -1.3	
Thyroid disease	-3.4	0.007	-5.8 – -0.9	0.04
Migraine or chronic headache	-2.2	0.009	-3.8 – -0.5	
Adjusted variables				0.02

Regression coefficients Beta are presented. All models are adjusted for age, gender, social status and K&L score. Adjusted variables | model with adjusted variables only.
R^2 | explained variance. For WOMAC, a higher score implies a worse health status. For SF-36, a higher score implies better health status.

DISCUSSION

The objective of the present study was to describe the relationship between comorbidity, pain and the physical and mental health status of participants with early symptomatic OA.

More than 67% of participants suffered from at least one comorbid disease, with disorders of neck, shoulder, elbow, wrist or hand, hypertension and back disorders being most prevalent. Comparing different studies on self-reported comorbidity different prevalence can be found. These differences can be explained by defining the inclusion and exclusion of diseases in the assessment of comorbidity lists used in individual studies and by differences in population of interest. Generally the higher the number of possible diseases included in a study, the higher the frequency of comorbidities found.[20] This is apparent for instance in an OA study in which almost all patients (98.6%) suffered from one or more coexistent diseases. In this study, the Cumulative Illness Rating Scale was used, which consists of 13 domains (organ systems) related to different body systems, also including the presence of diseases of ear, eye, nose and larynx.[8] In another study, the prevalence of comorbidity in subjects with arthritis (RA or OA) was 44.8%. This study used a list of seven specific chronic diseases: chronic non-specific lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, malignancies and arthritis (RA or OA).[9] When comparing the frequency of self-reported comorbidities of the present study with the prevalence of chronic diseases in an age-matched sample of the Dutch population, almost the same frequencies are found.[7]

Before studying the impact of specific disease conditions, we first assessed the impact of the number of coexisting diseases (i.e unspecified comorbidity, comorbidity count) in early OA on pain, physical and mental functioning. Participants with more comorbidities reported worse pain, more problems in physical functioning and a worse mental health status as compared with participants without comorbidity. These results confirm earlier research in patients with more advanced OA, in which comorbidity was associated with pain, and limitations in activities and a poorer physical health status.[1,8]

The influence of specific chronic diseases was assessed by means of linear regression analyses. After adjusting for age, gender and radiographic severity of OA, the presence of disorders of back, neck, shoulder, wrist or hand or obesity negatively associate with pain and physical functioning. The results were identical when using summed K&L grades instead of maximum K&L grade. There are possible mechanisms that can explain the influence of the presence of specific comorbidity. Probably, in participants with early OA, coexistent disorders in the musculoskeletal system will aggravate pain and physical functioning, whereas diseases present in the cardiovascular system or pulmonary system will probably not (yet) influence these outcomes. In this concept, obesity is seen as a mechanical loading factor and an inflammatory environment response that also will have a negative influence on the musculoskeletal system. Adipose tissue is now recognised as an organ with the capacity to secrete adipocytokines. These adipocytokines may play an important role in cartilage homeostasis and in the modulation of inflammatory processes. However, there is little to support a role of these cytokines in relation to pain.[30,31]

An explanation for the higher pains scores and physical functions scores of painful comorbidities in the musculoskeletal system could be the role of central sensitization, suggesting that more than just the receptor area for the painful joint is involved in nociception.[31,32] Croft et al. also give this explanation for their findings that knee-specific pain and disability, measured with WOMAC, are worse in the presence of pains elsewhere than the knee. [33] Probably the avoidance model, which explains the association between pain, avoidance of activities, muscle strength and activity limitations in participants with early OA, will be reinforced by these painful comorbidities.[34] Other OA studies also showed that low-back pain influences a worsening in WOMAC physical functioning.[35,36] Back pain can in part be explained by a change in mechanical loading caused by the painful hip or knee joint.

Another explanation for the influence of comorbidity that is described in literature, but not confirmed in this study, could be that specific combinations of chronic diseases that both influence physical functioning, but through different mechanism (such as musculoskeletal system and decreased endurance capacity), are perhaps more detrimental than other types of combinations. An example of such a combination includes arthritis (RA or OA) and cardiac disease; suggested mechanisms are chronic inflammation, but also the use of medication.[8,9,11] Initially, in the first analysis the influence of cardiac diseases was not assessed because of the low prevalence in this population as a consequence of the low mean age (57 years), but when we added this disorder to the final multivariate model, cardiac diseases was not associated with any of the outcomes (data not shown). This corresponds with another study, which concluded that there was no significant relationship between cardiac diseases and pain, and limitation in activity[37] in patients with OA. The conflicting results on coexisting disorders in other body systems than musculoskeletal system in established OA makes it important to test the influence of these disorders in the prospective follow-up of these CHECK participants with very early disease.

We also analysed the influence of comorbidity count and specific diseases on mental functioning; duodenal ulcer, thyroid disease and migraine or chronic headache negatively influenced mental functioning. Contrary to previous research, which shows that mental functioning in patients with arthritis is not influenced by the presence of comorbidity,[11] this study suggests that mental health is vulnerable to comorbidities outside the musculoskeletal system during the early stages of the disease.

In the present study mental health also deteriorates less than the physical health with an additional disease. These findings led to the conclusion that among patients with early OA with comorbidity, the focus of the physician should be not only on OA, but also on worsening pain and physical and mental health status due to a second disease. Significant health gain can be achieved by prevention or early recognition and adequate treatment of comorbid diseases.[38]

Some limitations of our study should be mentioned before drawing final conclusions. Data on comorbidity and health status were based on subject self-reports, which might be influenced by personal or mood characteristics. Nevertheless, positive correlations have been found between self –reported comorbidity measures and comorbidity from medical record reviews.[39]

Second, our study focussed on the impact of specific prevalent chronic diseases without taking disease stage and severity of these diseases into account. Thirdly, the health module of the Central Bureau of Statistics (CBS) which is used in this study did not include psychiatric disorders. Among older adults with OA, the prevalence of depressive symptoms is high and these symptoms may result in limitation in activity and increased pain.[40] The mental health scale of SF-36 has been shown to be useful in detecting major depression, affective disorders generally, and anxiety disorders.[41] However, after adjusting the final model with pain and functioning as outcome for mental health, the same results were found. The beta coefficient of the mental health scale was not statistically significant and the explained variance of the outcome variables pain, function and PCS did not change.

Fourth, although significant associations were found, comorbidity count and specific disorders accounted for a small part of the variation in the outcome variables pain, physical functioning and mental health status. The explained variance ranged from 0.03 to 0.013 for comorbidity count, and from 0.03 to 0.14 for the coexistence of specific comorbidities in the models with different outcomes. The statistically significant increases in WOMAC pain and physical function by comorbidity count or the presence of specific comorbidity are small; for pain, 3 points for comorbidity and 4 to 7 points for specific comorbidity; and for function, 4 points for comorbidity and 4 to 8 points for specific comorbidity. These are meaningful differences in this stage of the disease. In the early stage of the disease, small differences are expected that might develop into greater differences in the course of the disease. Fifth, although significant association between mental health and comorbidity was found, the mean score on MCS in the present study is ›52,1, indicating that mental functioning was almost comparable to the general Dutch population (with a mean age of 47.6 years). Mental summary scores generally increased slightly with age.[42]

In conclusion, in the early stage of symptomatic OA especially (other) disorders in the musculoskeletal system have a negative effect on pain, physical functioning and mental health status. The clinical implications are that to improve pain and physical health status of participants with early symptomatic OA, not only these complaints have to be treated, but also the additional conditions, especially back, neck, shoulder, elbow, wrist or hand disorders and obesity. Also the mental status can be affected in the early stage of OA by additional comorbidities, especially by the presence of duodenal ulcer, thyroid disease and migraine or chronic headache. This is a further argument to take comorbidity into account in the management of early OA. —

REFERENCES

1. Caporali R, Cimmino MA, Sarzi-Puttini P, Scarpa R, Parazzini F, Zaninelli A, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug prescriptions by general practitioners and specialists. Semin Arthritis Rheum 2005; 35:31-7.

2. Kadam UT, Croft PR. Clinical comorbidity in osteoarthritis: associations with physical function in older patients in family practice. J Rheumatol 2007; 34:1899-904.

3. Schellevis FG,van der Velde J, van de Lisdonk E, van Eijk JT, van Weel C. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 1993; 46:469-73.

4. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Ann Rheum Dis 2004; 63:408-14.

5. van Oostrom SH, Picavet HS, van Gelder BM, Lemmens LC, Hoeymans N, Verheij RA, et al. [Multimorbidity and comorbidity in the Dutch population--data from general practices]. Ned Tijdschr Geneeskd 2011;155:A3193.

6. Statistics Netherlands. [Prevalence of chronic diseases 2001-2008]. 2011.

7. Statistics Netherlands. [Health and services in numbers] Gezondheid en zorg in cijfers 2009. The Hague: Centraal Bureau voor de Statistiek; 2009.

8. van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95.

9. Kriegsman DM, Deeg DJ, Stalman WA. Comorbidity of somatic chronic diseases and decline in physical functioning:; the Longitudinal Aging Study Amsterdam. J Clin Epidemiol 2004; 57:55-65.

10. Reichmann WM, Katz JN, Kessler CL, Jordan JM, Losina E. Determinants of self-reported health status in a population-based sample of persons with radiographic knee osteoarthritis. Arthritis Rheum 2009 15;61:1046-53.

11. Rijken M, van Kerkhof M, Dekker J, Schellevis FG. Comorbidity of chronic diseases: effects of disease pairs on physical and mental functioning. Qual Life Res 2005;14:45-55.

12. Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. Qual Life Res 2006; 15:83-91.

13. Hopman WM, Harrison MB, Coo H, Friedberg E, Buchanan M, VanDenKerkhof EG. Associations between chronic disease, age and physical and mental health status. Chronic Dis Can 2009;29:108-16.

14. Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip & Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68:1413-9.

15. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at omeract III. J Rheumatol 1997; 24:799-802.

16. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. Satisfactory cross cultural equivalence of the Dutch womac in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63:36-42.

17. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.

18. Ware JE, Jr., Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51:1167-70.

19. Salaffi F, Carotti M, Grassi W. Health-related quality of life in patients with hip or knee osteoarthritis: comparison of generic and disease-specific instruments. Clin Rheumatol 2005; 24:29-37.

20. van den Akker M., Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. J Clin Epidemiol 2001; 54:675-9.

21. Feinstein A.R. The pre-therapeutic classification of co-morbidity in chronic disease. J Chron Dis 1970;23:455-68.

22. Botterweck A, Frenken F, Janssen S, Rozendaal L, Vree Md, Otten F. [Plausibility new measurements general health and lifestyles.] Plausibiltiet nieuwe metingen algemene gezondheid en leefstijlen. Centraal Bureau voor de Statistiek; 2001.

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

24. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995; 54:872-80.

25. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26 :2664-74.

26. Auleley GR, Duche A, Drape JL, Dougados M, Ravaud P. Measurement of joint space width in hip osteoarthritis: influence of joint positioning and radiographic procedure. Rheumatology (Oxford) 2001; 40:414-9.

27. Conrozier T, Bochu M, Gratacos J, Piperno M, Mathieu P, Vignon E. Evaluation of the 'Lequesne's false profile' of the hip in patients with hip osteoarthritis. Osteoarthritis Cartilage 1999; 7:295-300.

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

29. Twisk J.W.R. [Introduction in applied Biostatistics] Inleiding in de toegepaste biostatistiek. Maarssen: Elsevier Gezondheidszorg; 2007.

30. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol 2010; 22:533-7.

31. Ordeberg G. Characterization of joint pain in human OA. Novartis Found Symp 2004;260:105-15.

32. Geenen R, Bijlsma JW. Psychological management of osteoarthritic pain. Osteoarthritis Cartilage 2010; 18:873-5.

33. Croft P, Jordan K, Jinks C. "Pain elsewhere" and the impact of knee pain in older people. Arthritis Rheum 2005; 52:2350-4.

34. Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF, et al. Avoidance of Activities in Early Symptomatic Knee Osteoarthritis: Results from the CHECK Cohort. Ann Behav Med 2012; 44:33-42.

35. Botha-Scheepers S, Riyazi N, Kroon HM, Scharloo M, Houwing-Duistermaat JJ, Slagboom E, et al. Activity limitations in the lower extremities in patients with osteoarthritis: the modifying effects of illness perceptions and mental health. Osteoarthritis Cartilage 2006; 14:1104-10.

36. Wolfe F. Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. Rheumatology (Oxford) 1999 Apr;38(4):355-61.

37. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? Clin Rheumatol 2010; 29:739-47.

38. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. J Clin Epidemiol 2001; 54:661-74.

39. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Med Care 1996; 34:73-84.

40. Sale JE, Gignac M, Hawker G. The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. J Rheumatol 2008; 35:335-42.

41. Berwick DM, Murphy JM, Goldman PA, Ware JE, Jr., Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. Med Care 1991; 29:169-76.

42. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the sf-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51:1171-8.

In early OA additional musculoskeletal diseases have a negative effect on pain and physical functioning.

Comorbidity should be assessed and treated to improve the burden of illness of early OA.

check
concrete knowledge for concrete value

41278

Heup (altijd pijn meten)

Links

Pijn (verplicht): Niet ☑ | Beetje ☐ | Duidelijk ☐ | Heftig ☐

ROM

	Start °	Eind °
Actief endo-rotatie	10°	23° verplicht
Actief exo-rotatie	10°	16°
Actief flexie	0°	114° verplicht
Actief abductie	0°	45°
Actief adductie	0°	25°

Flexiecontractuur (verplicht): Aanwezig ☐ | Niet aanwezig ☒

Teken van Thomas

Hand

Links

Benige zwelling

	Aanwezig	Afwezig
n. van Heberden DIP	☐	☐
n. van Bouchard PIP	☐	☐

Rechts

Pijn (verplicht): Niet ☐ | Beetje ☑ | Duidelijk ☐

ROM

	Start °	Eind °
Actief endo-rotatie	10°	41° verplicht
Actief exo-rotatie	0°	20°
Actief flexie	0°	116° verplicht
Actief abductie	0°	40°
Actief adductie	0°	20°

Flexiecontractuur (verplicht): Aanwezig ☐ | Niet aanwezig ☒

Teken van Thomas

Hand

Rechts

Benige zwelling

	Aanwezig	Afwezig
n. van Heberden DIP	☐	☐
n. van Bouchard PIP	☐	☐

DIG II

6

GOOD, MODERATE AND POOR OUTCOME TRAJECTORIES OF PAIN SEVERITY IN EARLY SYMPTOMATIC KNEE OA; 5 YEAR FOLLOW-UP OF CHECK (COHORT HIP & COHORT KNEE)

submitted for publication

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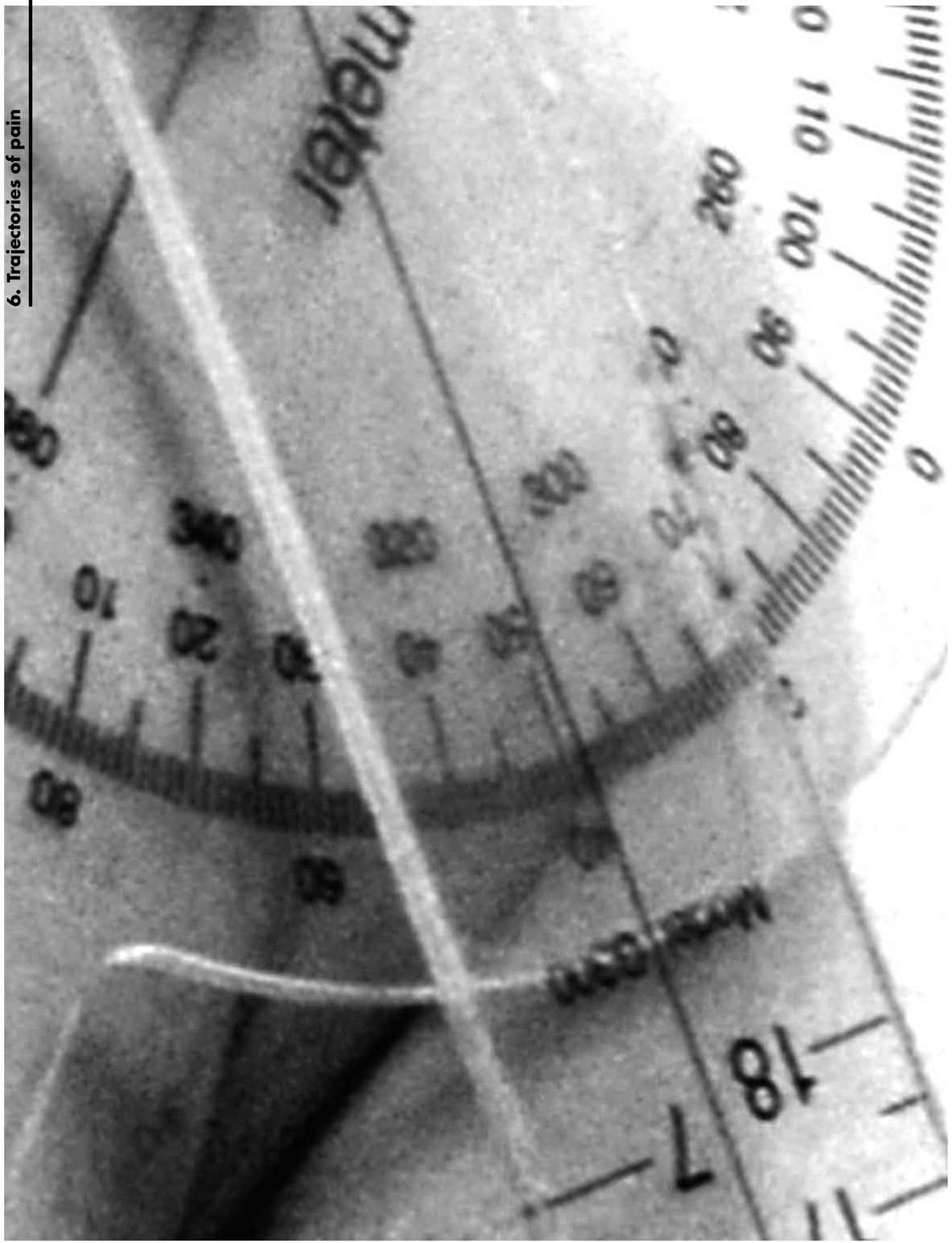

ABSTRACT

Objective

This study sets out to identify subgroups of pain trajectories in patients with symptomatic knee osteoarthritis (OA), and to explain these different trajectories by patient characteristics, lifestyle and coping factors as well as radiographic features.

Methods

Longitudinal data of pain severity (0-10) of five years follow-up of CHECK (Cohort Hip & Cohort Knee) study was used. Latent Class Growth Analysis identified homogenous subgroups with distinct trajectories of pain. Multinomial regression analysis was used to examine different lifestyle and coping characteristics between the trajectories.

Results

In longitudinal pain data of 5 years follow-up of 705 participants three pain trajectories were identified: good, moderate and poor outcome trajectory. Compared to the good outcome group, the moderate and poor outcome groups can be characterized by the following baseline variables: BMI›25, additional hip pain, low education level, using coping strategy 'worrying' and having ≥3 comorbidities, supplemented with radiological change of Kellgren & Lawrence grade ≥2.

Conclusions

Three trajectories of pain exist, which can be explained by different clinical features, coping strategies and lifestyle factors. In the management of knee pain in people with early symptomatic OA attention should also be given to additional factors, like hip pain, other comorbidities, passive coping strategy and obesity.

KNEE PAIN IS OFTEN THE FIRST SIGN OF KNEE OSTEOARTHRITIS (OA) AND IT IS KNOWN THAT ITS LEVEL AND COURSE CAN BE VERY DIFFERENT BETWEEN PATIENTS OVER TIME.[1] It is helpful to study individual development of pain severity over time to subsequently identify groups of subjects with comparable pain trajectories. Next step after identifying different trajectories, is to study determinants which could explain these different trajectories. In the end this could lead to different treatment modalities targeted to the identified trajectories. The individual development of knee pain severity over time might depend on the radiographic OA severity, but may also be dependent on patient characteristics such as gender and age,[2] additional comorbidities[3] and pain coping strategies.[4] Pain coping can be defined as people's behavioral and cognitive attempts to manage or tolerate pain and its effects[5] and can be classified into active and passive coping strategies. Passive strategies are generally negative (maladaptive), but some are probably more negative than others, whereas some active strategies could be more worthwhile than others.[6] Analyses of pain coping strategies in patients with OA may be important to minimize the impact of symptoms and to establish appropriate disease management.[7] Besides, stimulating or discouraging specific coping strategies as treatment modalities, influencing lifestyle factors might be important in strategies aimed at prevention, since they are modifiable in nature. As yet the role of lifestyle and coping factors in modifying different pain trajectories in early OA is unclear.

Radiographic joint damage has emerged as one of the risk factors for reported joint pain.[8] OA structural progression over time has been reported to occur in diverse patterns: knees that are progressing in structural deterioration versus knees which are stable.[9] Rapid radiological deterioration (change of ≥2 grades of K&L in 4 or 5 years) is related to worsening of pain and function.[10] Therefore, to explain differences in pain trajectories, it is important to take not just the presence, but rather the change in radiographic damage) into account.[11]

This study sets out to identify subgroups of pain trajectories in patients with early symptomatic knee OA, and to explain these different trajectories by baseline lifestyle, coping factors and radiographic features as well as changes over time in radiographic features.

METHODS

Study population

From October 2002 till September 2005 a cohort was formed of 1,002 participants with pain and/ or stiffness of knee and/ or hip. Individuals were eligible if they had pain or stiffness of knee or hip, were aged 45-65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry. No other obvious reason to explain participants complaints should be present. The study was approved by the medical ethics committees of all participating centres, and all participants gave their written informed consent before entering the study. A complete description of the CHECK study has been reported elsewhere.[12] For the analyses in this study, longitudinal data of five years follow-up of CHECK participants with knee pain at baseline were included.

Outcome variables

Pain severity (during last week) was measured annually with the Numeric Rating Scale (NRS) rating from 0-10, with a higher score indicating more pain. The NRS for pain is an one dimensional single-item scale that provides an estimate of patients' pain intensity.[13] The post-surgery pain severity data of participants who underwent total knee replacement during 5 year follow-up were coded as missing.

Independent variables

At baseline and after 5 years follow-up lifestyle factors, coping and radiographic characteristics were measured. Lifestyle factors: BMI, smoking, physical activity and alcohol use were obtained by self-report. Smoking was categorized as smoker or non-smoker, the latter included ex-smokers. Presence of physical activity was defined as a minimum of 3 times a week at least half-an-hour of moderately intense physical activity. Pain coping characteristics were measured with the Pain Coping Inventory, which analyses 3 active pain coping strategies (transformation, distraction, reducing demands) and 3 passive pain coping strategies (retreating, worrying, resting).[6] Items in the strategies are rated according to a 4-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.

Comorbidity was assessed with a self-reported health module of the Central Bureau of Statistics (CBS) in the Netherlands with encompasses 24 chronic diseases.[14] Individual comorbidities were scored and the total number of comorbidities was calculated per participant ('comorbidity count').

To assess radiographic OA features of the knee posterior-anterior weight bearing radiographs of both tibio-femoral joints were obtained. All radiographs were scored blinded for pain status, at the same time knowing the sequence, according to Kellgren & Lawrence (K&L).[15] These radiographs were scored by four readers who were trained by a radiologist and an experienced reader for grading of radiographic OA. Inter-observer variability was tested during the scoring of the entire cohort in a subset of 38 participants scored by all five observers yielding moderate to substantial inter-observer agreement (average kappa 0.58 for presence of K&L 0 versus K&L 1- 2 - 3 in the knees).[16] For each knee the radiographic K&L change from baseline to 5 years of follow-up was measured and the greatest radiographic K&L change in one of the knees was used in the analyses. Severity of radiographic OA at baseline was defined by the knee with the highest K&L grade.[17]

Radiographs were also analysed for more detailed quantitative parameters by use of KIDA (Knee Images Digital Analysis), which is a reliable method to quantify the individual radiographic parameters of knee OA with small inter-observer variations in KIDA measurements.[18] The KIDA parameters: minimum joint space width (JSW in mm) and osteophyte area (in mm^2) were measured without knowing the sequence of the radiographs. Also for each knee the change from baseline to follow-up in JSW and osteophyte area was calculated and the greatest change in one of the knees was used in the analyses. All radiographs were scored blinded to pain status.

Statistical analyses

To define homogenous subgroups of trajectories based on the individual development over time (=growth curves), Latent Class Growth Analysis (LCGA) was used. The assumption in this method is that the data encompass one or more subgroups of individuals with similar trajectories. The goal is therefore to capture this population heterogeneity

with a (latent) categorical variable denoting the number of subgroups. In LCGA the classification is performed based on the intercept and slope for the individual growth curve parameters.[19] LCGA estimates a mean growth curve for each class, but no individual variation around the mean growth is permitted.[20]

The decision which of the models with *k* number of subgroups is the best, is determined by a combination of factors: fit indices, the research question, parsimony, -size of classes and interpretability. The model fit indices with corresponding criteria used in the analyses: -the smallest Bayesian information criteria (BIC) value, high entropy value (near 1.0) , a significant Vuong- Lo- Mendell-Rubin LRT (VLMR LRT) and bootstrap likelihood ratio test (BLRT). Both LRT tests provide a p-value, which indicates whether the minus 1 *k* model is rejected in favor of the *k* class model.[21]

To explain the differences between the identified trajectories, baseline characteristics were described and analyzed with multinomial logistic regression. The multinomial logistic regression is the logistic regression, which could be used when the categorical dependent outcome (in our study, the trajectories) has more than 2 levels. For our study, the identified trajectory with the best outcome is chosen as a reference group. First, univariate multinomial logistic analyses of single independent baseline variables were performed. When the p-value of the univariate regression was ≤ 0.1, and after a check for collinearity, the independent baseline variable was included into the multivariate multinomial logistic analysis.[22] In the following multivariate analyses we used a backward selection method (p-removal 0.05). Furthermore, Hosmer- Lemeshow goodness-off-fit test and Nagelkerke Pseudo R^2 statistics were calculated.[23] Apart from variables that might already be present at baseline, changes in radiographic OA features from baseline to 5 year follow-up were also evaluated. To evaluate whether the changes of radiographic features can explain differences between the trajectories a multinomial logistic regression was performed. Again, first the changes in radiographic features were analyzed in an univariate multinomial regression model and secondly added in the multivariate model as described above. This multivariate model was adjusted for baseline variables which were found to be significant in model A.

Mplus version 6.1 was used for LCGA ; all other analyses were performed using SPSS version 20.

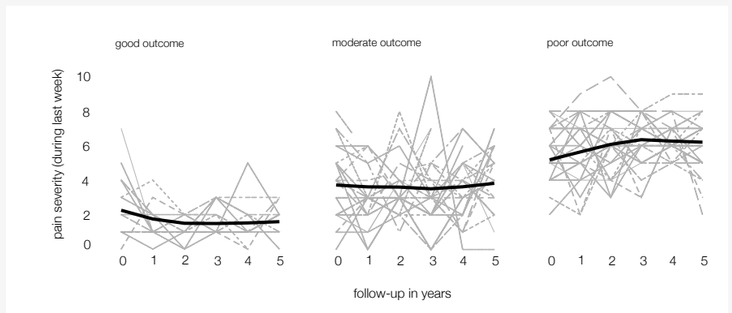

FIGURE 1 | The three pain trajectories. Per trajectory a 10% random selection of the observed pain scores during follow-up of participants is shown. The bold line is the mean of the trajectory of the pain scores during follow-up.

RESULTS

Identified outcome trajectories

Longitudinal data of 5 years follow-up of participants with knee pain at baseline and with available data of at least 3 follow-up visits was analyzed. Of 705 participants 81% were female, mean age of 56 years, at baseline the mean pain severity (NRS) was almost 4 on a scale of maximum 10 points, and 52% of participants had apart from knee pain also hip pain *(table 1)*. The model with three classes is determined as the best compared to a model with 4 classes, based on the combinations of fit indices, size of classes (smallest classes n= 189 compared to n= 71 in model with 4 classes) and interpretability. Three pain trajectories were designated as good, moderate and poor based on their outcome over time *(figure 1)*. Participants with good outcome trajectory (n=222) had a slight decrease in pain severity over time and ended up with lower pain severity. Participants with moderate outcome trajectory (n=294) had a variable course over time with moderate pain. The poor outcome trajectory participants (n=189) had an increase of pain severity over time. Baseline characteristics of participants in the three pain trajectories are given in *table 1.*

Differences between outcome trajectories based on baseline characteristics.

In *table 2* univariate odds ratios (OR) of the independent baseline variables in the multinomial logistic regression model as well as the included variables in the final multinomial logistic regression are presented. Presence of hip pain increased the odds for the moderate outcome with 1.8 compared to good outcome and increased the odds for the poor outcome with 3.0 compared to good outcome. BMI above 25 increased the odds for the moderate outcome with 1.7 compared to good outcome and increased the odds for the poor outcome with 2.4 compared to a good outcome. Being a smoker had univariate a significant OR which disappeared when highest education level was included in the multivariate model. Primary or secondary school as highest education level increased the odds for a moderate outcome with 2 and for poor outcome with 2.7 compared to good outcome. An increase in passive coping strategy 'worrying' increased the odds for a moderate outcome 1.9 times compared to a good outcome. With regards to a poor outcome this was 2.9 compared to good outcome. An increase in 'resting' strategy increased the odds for a poor outcome with 2.0 compared to good outcome. The presence of at least 3 comorbidities at baseline increased the odds for the moderate outcome with 2, and the odds for the poor outcome with 2.4 compared to the good outcome. There were found no association between the radiographic features at baseline and the moderate and poor outcome.

Difference between outcome trajectories based on changes of radiographic features

Table 3 suggests that most radiological K&L score changes occur in participants in the poor outcome trajectory, as also is the case in most increase in osteophytes area. After 5 year of follow-up, there were more joint replacements in the poor outcome (12 total knee and 5 total hip replacements) and in moderate outcome (4 total knee and 9 total hip replacements) compared to good outcome (1 total knee and 1 total hip replacements), respectively χ^2 p-values 0.02 and 0.03.

In *table 4* the univariate odds ratios of the changes of radiographic features from baseline to 5 year follow-up are presented. In the multivariate K&L model B, K&L changes were included as well as the baseline K&L grades as well as all the baseline variables of multivariate model A *(table 2)*. In model B, a K&L change of at least 2 grades after 5 years, increased the odds of the moderate outcome with 2.9 compared the good outcome and odds of the poor outcome with 3.7 compared to the good outcome. In model C, the K&L change and osteophyte change are included in the multivariate model, which also is corrected for the baseline variables of multivariate regression model A *(table 2)*. The univariate association of K&L change disappeared if model B also was corrected for change in osteophyte area (= model C).

DISCUSSION

The present study is one of the first to use LCGA to identify different trajectories of pain severity in participants with early symptomatic OA. We identified: good, moderate and poor outcome trajectories with different baseline characteristics. Participants

TABLE 1 | Baseline characteristics of all subjects and baseline characteristics of the identified trajectories

	All subjects	Good outcome	Moderate outcome	Poor outcome
n	705	222	294	189
Age	56 (5.1)	56 (5.1)	56 (5.4)	56 (4.7)
Female	571 (81%)	179 (81%)	235 (80%)	157 (83%)
BMI	26.5 (4.3)	25.4 (3.8)	26.5 (3.9)	27.7 (5.0)
Education level				
Primary school and secondary school	515 (73%)	136 (64%)	226 (78%)	153 (84%)
Pain severity (0-10)	3.7 (2.1)	2.3 (1.6)	3.7 (1.8)	5.2 (0.1)
Hip pain presence	365 (52%)	87 (39%)	154 (52%)	124 (67%)
Unhealthy lifestyle ≥ 2 of 4	253 (36%)	65 (32%)	112 (43%)	76 (44%)
Unhealthy lifestyle factors				
BMI > 25	398 (57%)	100 (46%)	172 (59%)	126 (68%)
No / little physical activity (0-2 days)	323 (46%)	100 (47%)	134 (47%)	89 (48%)
Smoker	94 (13%)	20 (9%)	43 (15%)	31 (17%)
Weekday alcohol consumption ≥ 3 units	73 (10%)	25 (12%)	32 (12%)	16 (9%)
Coping				
Active pain Coping				
Transformation	2.2 (0.7)	2.0 (0.7)	2.2 (0.7)	2.3 (0.6)
Distraction	2.2 (0.6)	2.1 (0.6)	2.2 (0.6)	2.4 (0.6)
Reducing demands	2.0 (0.6)	1.9 (0.6)	2.0 (0.6)	2.2 (0.6)
Passive pain Coping				
Retreating	1.6 (0.5)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)
Worrying	1.6 (0.4)	1.4 (0.3)	1.6 (0.4)	1.7 (0.5)
Resting	1.8 (0.5)	1.7 (0.5)	1.8 (0.5)	2.0 (0.5)
Comorbidity count				
≥ 3 comorbidities	111 (16%)	15 (7%)	51 (18%)	45 (24%)
Radiographic characteristics of knee				
Kellgren & Lawrence Grade				
K&L Grade 0	53%	48%	51%	44%
K&L Grade 1	47%	52%	49%	56%
Ostophyte area (mm^2)	8.4 (7.5)	7.5 (5.6)	8.6 (7.7)	9.3 (8.9)
Minimal JSW (mm)	2.6 (1.2)	2.7 (1.1)	2.6 (1.2)	2.6 (1.3)

Continuous variables are given as mean values, standard deviation between brackets and categorical variables as number, percentages between brackets. Unhealthy lifestyle ≥ 2 of 4: at least 2 of 4 lifestyle factors were unhealthy. BMI | body mass index, K&L | Kellgren and Lawrence grade, JSW | joint space width.

TABLE 2 | Multinomial logistic regression for univariate and multivariate association of baseline variables with moderate and poor outcome trajectory of pain (good outcome trajectory is used as reference group)

	Moderate outcome versus good outcome		Poor outcome versus good outcome	
	OR univariate	OR multivariate Model A	OR univariate	OR multivariate Model A
Female versus male (referent)	1.0 (0.6 – 1.5)		1.2 (0.7 – 2.0)	
Age	1.0 (0.9 – 1.0)		1.0 (0.9 – 1.0)*	
Hip pain presence versus no hip pain (referent)	1.7 (1.2 – 1.4)**	1.8 (1.2 – 2.7)**	3.0 (2.0 – 4.4)**	3.0 (1.8 – 4.9)**
Primary, secondary school versus high prof. education, university (referent)	2.0 (1.3 – 3.0)**	2.0 (1.3 – 3.1)**	2.9 (1.8 – 4.7)**	2.7 (1.6 – 4.7)**
BMI > 25 versus BMI ≤ 25 (referent)	1.7 (1.2 – 2.4)**	1.7 (1.1 – 2.5)**	2.5 (1.6 – 3.7)**	2.4 (1.5 – 3.9)**
No or little physical activity versus physical active (referent)	1.0 (0.7 – 1.4)		1.0 (0.7 – 1.5)	
Smoker versus non-smoker (referent)	1.7 (1.0 – 3.0)**		2.0 (1.1 – 3.6)**	
Weekday alcohol ≥ 3 units versus < 3 units (referent)	1.0 (0.6 – 1.7)		0.7 (0.4 – 1.4)	
Coping				
Active pain coping				
Transformation	1.3 (1.0 – 1.7)**		1.9 (1.4 – 2.6)**	
Distraction	1.2 (0.9 – 1.6)		1.8 (1.3 – 2.5)**	
Reducing demands	1.1 (0.8 – 1.5)		1.8 (1.3 – 2.5)**	
Passive pain coping				
Retreating	0.9 (0.6 – 1.3)		1.3 (0.8 – 1.9)	
Worrying	2.5 (1.5 – 4.1)**	1.9 (1.1 – 3.4)**	6.1 (3.5 – 10.5)**	3.0 (1.6 – 5.7)**
Resting	1.4 (1.0 – 2.1)**	1.2 (0.8 – 1.8)	3.2 (2.1 – 4.8)**	2.0 (1.2 – 3.2)**
Presence of comorbidity ≥ 3 versus comorbidity < 3 (referent)	2.8 (1.6 – 5.2)**	2.0 (1.0 – 3.9)**	4.3 (2.3 – 8.0)**	2.4 (1.2 – 4.9)**
Radiographic features				
K&L grade 0 or 1	0.9 (0.6 – 1.3)		1.1 (0.8 – 1.7)	
Osteophyte area (mm^2)	1.0 (1.0 – 1.1)*	1.0 (1.0 – 1.1)	1.0 (1.0 – 1.1)**	1.0 (1.0 – 1.1)**
Minimal JSW (mm)	0.9 (0.8 – 1.0)*		0.9 (0.7 – 1.0)*	
Hosmer-Lemeshow Goodness-of-Fit Test		0.315		0.315
Pseudo R^2 Nagelkerke		0.199		0.199

Odds ratios (OR) are given for univariate and mulitvariate association, between brackets confidence interval. BMI | body mass index, K&L | Kellgren & Lawrence grade, JSW | joint space width, * p-value ≤0.1 (cut-off point in univariate regression) ** p-value ≤ 0.05.

at baseline with a BMI above 25, who were lower educated, have at least 3 comorbidities, having additional hip pain, and apply the coping strategies 'worrying' and 'resting' were more likely to have a poor outcome compared to a good outcome. Besides these baseline variables, the poor outcome trajectory can be explained by a radiographic K&L change of at least 2 points in 5 year follow-up.

The results in this report are consistent with the heterogeneity of the evolution of pain over time, however most work in this area has focused on pain at the cohort level. In a previous study pain, on average, worsened over 7 years, but 35% and 27 % of those initially reporting hip and knee pain respectively had improved.[24] There are a few studies that have used a group-based modeling approach to identify trajectories in OA and identified different pattern of trajectories. Two studies showed that some subjects remained stable over time and others fluctuate or progressed.[25,26] A study with data of the Osteoarthritis Initiative (OAI) showed trajectories without these fluctuations over time.[27] The difference in pattern of trajectories can be explained by differences of included subjects; in the study of subjects with more severe baseline symptoms it was able to identify trajectories by increasing or decreasing pain over time. The pattern of trajectories in our study most closely resemble the identified trajectories of the OAI. However they identified 5 trajectories: two trajectories with mild pain, two trajectories with moderate pain, and a trajectory with severe pain.[27] This severe trajectory showed in contrast to our poor trajectory no small increase, which can be clarified by the less severe pain symptoms of the OAI participants in comparison to CHECK participants.[10]

TABLE 3 | Radiographic changes from baseline to 5 years of follow-up in the good, moderate and poor outcome trajectories

	All Subjects	Good outcome	Moderate outcome	Poor outcome
n	705	222	294	189
K&L change				
Δ0 (n)	50% (306)	56% (111)	48% (118)	49% (77)
Δ1 (n)	40% (239)	37% (74)	42% (105)	38% (60)
Δ2 + Δ3 (n)	10% (60)	7% (14)	10% (25)	13% (21)
Osteophyte area change (mm^2), mean	3.9 (7.8)	3.0 (6.0)	3.7 (7.5)	5.2 (9.9)
minJSW change (mm), mean	0.6 (1.1)	0.7 (1.1)	0.5 (1.1)	0.7 (1.1)

Changes in categorical variables are given in percentages, between brackets numbers. Changes in continues variables are given as mean values, standard deviation between brackets. K&L change | greatest radiographic change from baseline to follow-up in one of the knees. Osteophyte area change: greatest osteophyte change from baseline to 5 years follow-up in one of the knees. MinJSW change | greatest change in minimal Joint Space Width from baseline to follow-up in one of the knees.

The effect of high BMI is consistent with the literature.[28] With regard to smoking the results vary in the literature from a moderate protective effect in case-control studies to no effect OA when restricting the analysis to cohort studies.[28] One other study examined the effect of smoking on pain trajectories and concluded that current smokers had overall greater knee pain.[29] A recent meta- analysis of progression of OA showed no association between smoking and progression of OA. Smoking may be seen as a wider proxy marker of a person's social demographics, lifestyle, weight, which may be involved in the different pathways of progression of OA.[30] Besides, several OA studies reported that a low education level was associated with more self- reported pain,[31,32] which is in accordance with our results. In our study it seemed that smoking is a confounder in the relation between the trajectories and highest education level. Education is one measure of socioeconomic status (SES), which is often used in studies investigating the effectors of SES.[30,33]

The results on coping strategies used in our study differ from others that found no relation of active and passive coping strategies with pain intensity,[34] or demonstrated that active coping strategy predicted a high level of pain intensity.[35] Our findings support other findings on trajectories: obesity, comorbidities and lower education were associated with trajectories characterized by greater pain.[27]

Conflicting results have been reported on the association of pain and radiological damage.[8,36,37]

Worsening of disease, or OA progression, can occur at different rates. It has been suggested that individuals with slow progression may have more opportunity to adapt to the changes in physiology and therefore experience less pain.[11] This is confirmed in the CHECK and OAI cohort, where worsening of pain and function after 5 years of follow-up is related to rapid radiological progression (radiological change of K&L grade ≥2).[10] Besides progression of K&L in our study, a greater osteophyte area at baseline is also one of the variables which explains the poor outcome trajectory. The absence of a significant association of K&L change with the trajectories, when adjusted for 'osteophyte area change' could be explained by the fact that K&L scale is an osteophyte driven scale. A radiological change of K&L ≥2 is achieved mainly by change in osteophyte: from normal (grade 0) to definite OF (grade 2); or from possible OF (grade 1) to moderate OF (grade 3).

Our study has several strengths but also some limitations. The CHECK study is a prospective, observational cohort study with 10 year follow-up. The study is centrally coordinated to guarantee high-quality data (e.g. dropout after 8 years follow-up is less than 10%). CHECK subjects are characterized in three main OA domains through-out follow-up: clinical, radiographic, and biochemical.

There are also notable limitations. Since hip pain was more present in the poor outcome trajectory, it could be that this pain trajectory represents individuals with more generalized OA. Besides it would be interesting to know whether individuals of the poor outcome trajectory have characteristics of neuropathic pain. Unfortunately, this information on generalized OA and neuropathic pain was not measured. Although LCGA seems to be preferable above the more simple methods for identifying homogeneous subgroups, there is still an on-going discussion about model fit parameters for choosing the optimal number of classes.[20] The BIC is the most used model fit parameter and was used in this analysis.[19] We made an association model based on baseline variables and progression variables which could explain the difference between the trajectories. Very likely other variables, which we did not include, like generalized OA and neuropathic pain, could also play a role. Next step is to develop a prediction model in which also other clinical variables (e.g. range of motion, palpable warmth, crepitus) are included which can be measured by the general practitioner.

We conclude that different trajectories of pain exist, which can be explained by different clinical features, coping strategies and lifestyle factors. The pain evolution of participants in the poor outcome trajectory can be explained by increase in radiological damage (change of K&L grade ≥2) and greater osteophyte size at baseline. Participants with a BMI >25, secondary school as highest education level, having at least 3 comorbidities, additional hip pain, who worrying and avoid activity to cope their pain are more likely to develop a poor outcome trajectory. Distinguishing these baseline characteristics and different pain trajectories in the follow up could have implications for the treatment. Treating symptomatic OA should also be based on modifiable factors, comorbidities and behavior. —

TABLE 4 | Multinomial logistic regression for univariate and multivariate association of changes of radiographic features from baseline to follow-up with moderate and poor outcome trajectory of pain (good outcome trajectory is used as reference group)

	Moderate outcome versus good outcome			Poor outcome versus good outcome		
	OR univariate	OR multivariate K&L model B	OR multivariate OP model C	OR univariate	OR multivariate K&L model B	OR multivariate OP model C
K&L change						
Δ0	Referent	Referent		Referent	Referent	
Δ1	1.3 (0.9 – 2.0)	1.4 (0.9 – 2.2)		1.2 (0.7 – 1.8)	1.1 (0.6 – 1.9)	
Δ2 + Δ3	1.7 (0.8 – 3.4)*	2.9 (1.2 – 7.2)**		2.2 (1.0 – 4.5)**	3.7 (1.2 – 9.9)**	
Osteophyte area change	1.0 (1.0 – 1.0)		1.0 (1.0 – 1.1)	1.0 (1.0 – 1.1)**		1.0 (1.0 – 1.1)**
minJSW change	0.9 (0.8 – 1.1)			1.0 (0.8 – 1.2)		
Hosmer- Lemeshow Goodness-of-Fit Test	0.331		0.230		0.331	0.230
Pseudo R^2 Nagelkerke	0.238		0.246		0.238	0.246

Odds ratios (OR) are given for univariate and mulitvariate association, between brackets confidence interval. *p-value ≤0.1 (cut-off point in univariate regression), **p-value ≤ 0.05, K&L change | greatest radiographic change from baseline to follow-up in one of the knees. Osteophyte area change | greatest osteophyte change from baseline to 5 years follow-up in one of the knees. MinJSW change | greatest Joint Space Width from baseline to follow-up in one of the knees. Multivariate K&L model B | model corrected for baseline variables (BMI, education, hip pain, worrying, resting, comorbidity, osteophyte size) and K&L change. Multivariate OP (osteophyte) model C | model corrected for baseline variables (BMI, education, hip pain, worrying, resting, comorbidity, osteophyte size) and K&L change, change of osteophyte size.

REFERENCES

1. Yusuf E, Bijsterbosch J, Slagboom PE, Kroon HM, Rosendaal FR, Huizinga TW, et al. Association between several clinical and radiological determinants with long-term clinical progression and good prognosis of lower limb osteoarthritis. PLoS One 2011; 6:e25426.

2. Paradowski PT, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. Health Qual Life Outcomes 2005 ;3:59.

3. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip & Cohort Knee) study. Rheumatology (Oxford) 2013; 52:180-8.

4. Benyon K, Hill S, Zadurian N, Mallen C. Coping strategies and self-efficacy as predictors of outcome in osteoarthritis: a systematic review. Musculoskeletal Care 2010; 8:224-36.

5. Brown GK, Nicassio PM. Development of a questionnaire for the assessment of active and passive coping strategies in chronic pain patients. Pain 1987; 31:53-64.

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

7. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 2000; 87:325-34.

8. Kidd B. Mechanisms of pain in osteoarthritis. HSS J 2012; 8:26-8.

9. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt MC. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2013; 72:924-9

10. Wesseling J, Bierma-Zeinstra SM, Kloppenburg M, Meijer R, Bijlsma JW. Worsening of pain and function over 5 years in individuals with 'early' OA is related to structural damage: data from the Osteoarthritis Initiative and CHECK (Cohort Hip & Cohort Knee) study. Ann Rheum Dis 2013. [Epub ahead of publication].

11. White DK, Zhang Y, Niu J, Keysor JJ, Nevitt MC, Lewis CE, et al. Do worsening knee radiographs mean greater chances of severe functional limitation? Arthritis Care Res (Hoboken) 2010; 62:1433-9.

12. Wesseling J, Dekker J, van den Berg wb, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip & Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68:1413-9.

13. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (nrs Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (sf-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240-S252.

14. Botterweck A, Frenken F, Janssen S, Rozendaal L, Vree Md, Otten F. [Plausibility new measurements general health and lifestyles.] Plausibiltiet nieuwe metingen algemene gezondheid en leefstijlen. Centraal Bureau voor de Statistiek; 2001.

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

16. Damen J, Schiphof D, ten Wolde S, Cats HA, Bierma-Zeinstra SM, Oei EH. Inter-observer reliability for radiographic assessment of early osteoarthritis features: the CHECK (Cohort Hip & Cohort Knee) study. Osteoarthritis Cartilage 2014;22:969-74.

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

18. Marijnissen AC, Vincken KL, Vos PA, Saris DB, Viergever MA, Bijlsma JW, et al. Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis Cartilage 2008; 16:234-43.

19. Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol 2012; 65:1078-87.

20. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Soc Pers Psychol Compass 2008; 2/1:302-17.

21. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo simulation study. Struct Equation Modeling 2007; 14:535-69.

22. Twisk J.W.R. [Introduction in applied Biostatistics] Inleiding in de toegepaste biostatistiek. Maarssen: Elsevier Gezondheidszorg; 2007.

23. Pallant J. SPSS survival manual (3rd ed.). Open University Press; 2007.

24. Peters TJ, Sanders C, Dieppe P, Donovan J. Factors associated with change in pain and disability over time: a community-based prospective observational study of hip and knee osteoarthritis. Br J Gen Pract 2005; 55:205-11.

25. Leffondre K, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. J Clin Epidemiol 2004; 57:1049-62.

26. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71:1517-23.

27. Collins JE, Katz JN, Dervan EE, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2014; 22:622-30.

28. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010; 18:24-33.

29. Amin S, Niu J, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis 2007; 66:18-22.

30. Pearce F, Hui M, Ding C, Doherty M, Zhang W. Does smoking reduce the progression of osteoarthritis? Meta-analysis of observational studies. Arthritis Care Res (Hoboken) 2013; 65:1026-33.

31. Knight JB, Callahan LF, Luong ML, Shreffler J, Schoster B, Renner JB, et al. The association of disability and pain with individual and community socioeconomic status in people with hip osteoarthritis. Open Rheumatol J 2011; 5:51-8.

32. Leigh JP, Fries JF. Correlations between education and arthritis in the 1971-1975 NHANES I. Soc Sci Med 1994; 38:575-83.

33. Cleveland RJ, Luong ML, Knight JB, Schoster B, Renner JB, Jordan JM, et al. Independent associations of socioeconomic factors with disability and pain in adults with knee osteoarthritis. BMC Musculoskelet Disord 2013; 14:297.

34. Perrot S, Poiraudeau S, Kabir M, Bertin P, Sichere P, Serrie A, et al. Active or passive pain coping strategies in hip and knee osteoarthritis? Results of a national survey of 4,719 patients in a primary care setting. Arthritis Rheum 2008 15; 59:1555-62.

35. Steultjens MP, Dekker J, Bijlsma JW. Coping, pain, and disability in osteoarthritis: a longitudinal study. J Rheumatol 2001; 28:1068-72.

36. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol 1999; 26:1785-92.

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

In longitudinal pain data
3 trajectories of pain
severity were identified.

Participants with a BMI > 25,
hip pain, low education,
worrying and avoiding are more
likely to develop more pain.

Model G-40

7

IDENTIFYING TRAJECTORIES IN KNEE OSTEOPHYTE FORMATION IN EARLY OSTEOARTHRITIS; RESULTS OF 5 YEAR FOLLOW-UP IN CHECK (COHORT HIP & COHORT KNEE)

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ABSTRACT

Objective

OA can be characterised by structural changes and by clinical symptoms and signs. This study focuses on the heterogenic expression of osteophyte formation and aims to identify subgroups of participants with homogeneous patterns of osteophyte formation over time (trajectories), and to describe the prognostic factors of the different subgroups.

Methods

Longitudinal data of quantitative osteophyte formation, calculated as total area of mm^2 , over a period of five years follow-up of the early OA cohort CHECK (Cohort Hip & Cohort Knee) was used. Latent Class Growth Analysis identified homogenous subgroups with distinct trajectories of osteophyte formation. Multinomial regression analysis was used to examine the prognostic factors of the different subgroups.

Results

In data of 5 years follow-up of 929 participants, three subgroups were identified: an 'osteophyte increase' subgroup (n=32) with an increase in osteophyte formation, 'mild osteophyte' subgroup (n=181) with minimal increase, and 'no osteophyte' subgroup (n=716) without increase in osteophyte formation. Being older, a BMI above 25, the existence of local clinical signs at baseline (crepitus, warmth, bony tenderness, enlargement and effusion), and radiographic characteristics (initial osteophyte formation, narrowing of JSW) suggested a higher probability of a (mild) increase in osteophyte formation.

Conclusions

In participants with early symptomatic OA the common course of osteophyte formation over a period of 5 years is relatively flat. However, in a small subpopulation there was a remarkable increase in osteophyte formation. Identifying which patients will develop structural changes may in the future lead to specific treatment of these patients.

OSTEOARTHRITIS (OA) CAN BE MANIFESTED IN STRUCTURAL CHANGES OCCURRING AT THE JOINT LEVEL, LIKE JOINT SPACE NARROWING AND OSTEOPHYTE FORMATION, AND CAN BE DEFINED AS 'DISEASE OA'. Besides or together with structural changes, OA can be manifested by patients' reported symptoms, defined as 'illness OA'. As is well known, there is limited overlap between the disease OA and the illness OA.[1] Preliminary findings of the Osteoarthritis Initiative after 10 years suggest possibly different mechanisms in structural changes for joint space narrowing (JSN) and osteophyte formation.[2] These different mechanisms may result in different expression of disease between patients over time. It has been proposed that ideally these two different features of radiographic OA should not be integrated as a single Kellgren & Lawrence (K&L) grade, but looked at individually.[3] JSN is thought to be a feature of already advanced OA, therefore, revealing little about the early disease.[4,5] It is suggested that formation of osteophytes should be considered as an early feature of OA.[6] Furthermore, a previous study showed that osteophytes performed better as a primary diagnostic feature than JSN.[7] Osteophytes appear to be a central radiographic feature of the disease and are often shared across compartments of the joint.[8] It has been suggested that laxity and malalignment of the knee joint are causal biomechanical factors in the formation of osteophytes, but these biomechanical factors are also supposed to be results of the disease and therefore are involved in a vicious circle.[9,10] Besides, it has been suggested that activation of the synovial layer (synovitis) can finally results in formation of osteophytes. A suggested mechanism is that the inflammatory milieu stimulates the production of Transforming Growth factor-beta. Observations confirm that Transforming Growth factor-beta playes a role in osteophyte development.[11] CHECK (Cohort Hip & Cohort Knee) is an inception cohort of patients with early symptomatic OA of the hip and/or knee and therefore suitable to study the osteophyte formation over time.

In longitudinal studies on the evolution of pain in individual subjects, the patterns (or trajectories) of pain evolution were heterogeneous with some subjects experiencing worsening and others improvement.[12] Studies of structural changes also suggest that persons with knee OA may have diverse disease trajectories over time. It has been suggested that once structural changes of knees occur, they are far more likely to progress.[13] Identifying distinct trajectories of osteophyte formation would offer important insight into prognosis and would help selecting treatment modalities. Therefore, the present study focuses on the expression of osteophyte formation and aims to identify trajectories in persons with homogeneous patterns of osteophyte formation over time and to describe the different trajectories by prognostic factors. By describing clinical and radiographic characteristics of participants within distinctive trajectories, additional information can be obtained about the association of these prognostic variables with the course of the disease.[14] Therefore, the osteophyte trajectories are compared to the recently identified pain trajectories.[15]

METHODS

Study population

From October 2002 till September 2005 a multicentre cohort was formed of 1,002 participants with pain and/ or stiffness of knee and/ or hip. Individuals were eligible if they had pain or stiffness of knee or hip, were aged 45-65 years, and had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry. Individuals with clearly defined other reasons for knee or hip symptoms than OA were excluded. The study was approved by the medical ethics committees of all participating centres, and all participants gave their written informed consent before entering the study. A complete description of the CHECK study has been reported.[16,17] For the analyses in this study, CHECK participants with a follow-up period of at least 5 years with available radiographic data of at least 2 follow-up visits were included.

Identifying trajectories of osteophyte formation

At baseline and after 2 and 5 years, posterior-anterior weight- bearing radiographs of both knees were obtained to assess radiographic OA features of the tibiofemoral joints.[18] Knee Images Digital Analysis (KIDA) was used to analyse osteophyte area (in mm^2) as a continuous variable in lateral and medial femur, and lateral and medial tibia, to identify distinct trajectories of osteophyte formation. It has been reported that KIDA is more sensitive to measure differences over time than the qualitative grading system.[19] The KIDA parameters were measured by one experienced observer without knowing the sequence of the radiographs and blinded to patient characteristics. The osteophyte area was measured as the total osteophyte area (in mm^2) of both the osteophyte areas of left knee (sum of 4 locations) and the osteophyte areas of right knee (sum of 4 locations). Participants with available osteophyte area data of at least 2 follow-up visits were included in the analyses; in case left or right subtotal osteophyte area of a visit was missing, due to drop-out of the participant, total knee arthroplasty, or quality problems of the radiograph the total osteophyte area of that visit was coded as missing.

Radiographic characteristics

KIDA was also used to measure minimum joint space width (mJSW, in mm) in order to describe the identified trajectories of osteophyte formation. For each knee the mJSW was measured as the smallest distance between femur and tibia, and the smallest JSW of the left or right knee was used in analyses. Also for each knee change from baseline to 5 year follow-up in mJSW was measured and the greatest change in one of the knees was used in analyses.

To measure overall radiographic severity of OA, radiographs were also scored according to Kellgren & Lawrence (K&L),[20] on a 0-4 scale. Readers scored all consecutive radiographs at the same time knowing the sequence (baseline, 2 year and 5 year) but blinded to clinical data. Inter-observer variability was tested in a subset of 38 participants scored by all observers yielding moderate to substantial inter-observer agreement (kappa 0.60 for presence of K&L 0 versus K&L1- 2 - 3 in the knees, mean kappa's over three measurements: T0- T2- T5). Severity of radiographic OA at baseline was defined as the worst knee, based on the highest K&L grade.[21]

Clinical characteristics

Baseline demographic and clinical variables collected in the CHECK study were used in the analysis. Pain, stiffness and physical functioning were assessed with the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire, which is a disease specific self- reported questionnaire.[22,23] The five point Likert version of the WOMAC was used; item responses range from 'none' to 'extreme' and are summed to produce subscales (pain 0-20, stiffness 0- 8, functioning 0-68) with higher scores indicating worse health. CHECK participants were asked to complete WOMAC for knee and hip complaints together. Pain severity (during last week) was measured with the Numeric Rating Scale (NRS) rating from 0-10, with a higher score indicating more pain, also measuring the severity of knee and hip pain together. The NRS for pain is a one dimensional single-item scale that provides an estimate of patients' pain intensity.[24] Comorbidity was assessed with a self-reported health module of the Central Bureau of Statistics (CBS) in the Netherlands which encompasses 24 chronic diseases.[25] Individual comorbidities were scored and the total number of comorbidities was calculated per participant ('comorbidity count'). Clinical features of the knees

were assessed by a standardized protocol including palpable warmth, refill test to assess effusion, bony tenderness, bony enlargements and crepitus.

Biochemical markers
C-terminal telopeptide of type II collagen (CTX II) and cartilage oligomeric matrix protein (COMP), markers of cartilage and bone metabolism, were assessed at baseline.

Previous identified pain trajectories
Recently, three pain trajectories were identified in the CHECK population based on pain intensity during 5 years follow-up: 'poor outcome', 'moderate outcome' and 'good outcome'.[15] Participants with knee pain at baseline and with recorded pain data of at least 3 follow-up visits were included in the analyses of pain trajectories. Participants with 'good outcome' trajectory (n=222) had a slight decrease in pain severity over time and ended up with lower pain severity. Participants with 'moderate outcome' trajectory (n=294) had a variable course over time with moderate pain. The 'poor outcome' trajectory participants (n=189) had an increase of pain severity over time. These three trajectories could be explained by different clinical features, coping strategies and lifestyle factors.[15]

STATISTICAL ANALYSES

To define homogenous subgroups of participants with distinct trajectories of osteophyte formation as measured by KIDA, Latent Class Growth Analysis (LCGA) was used. The assumption in this method is that data encompass one or more trajectories of individuals with similar patterns. The goal is therefore to capture this population heterogeneity with a (latent) categorical variable denoting the number of trajectories. In LCGA the classification is performed based on the intercept and slope for the individual growth curve parameters.[26] LCGA estimates a mean growth curve for each class, but no individual variation around the mean growth is permitted.[27]

The decision which of the models with *k* number of trajectories is the best, is determined by a combination of factors: fit indices, the research question, parsimony, size of classes and interpretability. The model fit indices with corresponding criteria used in our analyses: the smallest Bayesian Information Criteria value, high entropy value (near 1.0), a significant Vuong- Lo- Mendell-Rubin Likelihood Ratio Test and Bootstrap Likelihood Ratio Test. Both Likelihood Ratio Tests provide a p-value, which indicates whether the minus 1 *k* model is rejected in favor of the *k* class model.[28]

Finally, multinomial logistic regression analyses were used to examine differences in baseline clinical and radiographic characteristics between the identified osteophyte trajectories. This regression was also used to evaluate the association between the identified osteophyte subgroups and the pain trajectories. As one of the identified trajectories is small, we only performed univariate multinomial logistic regression. Mplus version 6.1 was used for LCGA; all other analyses were performed using SPSS version 20.

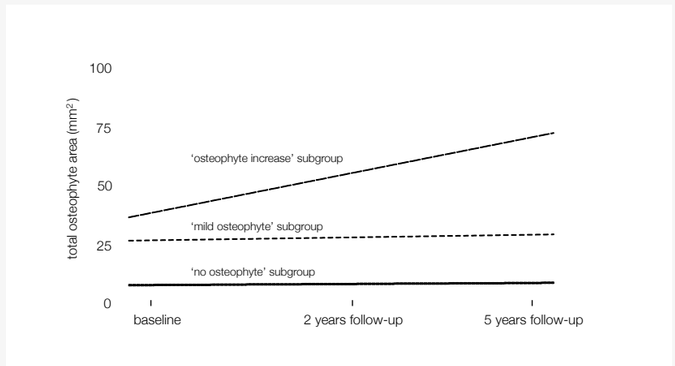


FIGURE 1 | Trajectories of osteophyte formation during 5 years follow-up

RESULTS

Study population
Longitudinal data of 5 years follow-up of participants with at least 2 follow-up visits was analyzed (n=929). A total of 73(/1,002) subjects had only one total osteophyte measurement and were excluded from the analysis. Baseline characteristics of the included participants were analyzed: 79% were female, mean age 56 years (with SD of 5), 55% had a BMI greater than 25 kg/m², 83% had knee pain of which 42% had also hip pain, 17% had hip pain only and the mean pain severity (NRS) was 3 on a scale of maximum 10 points.

Subgroups based on osteophyte trajectories
The optimal number of trajectories identified through LCGA was three (*table 1*). Identifying three trajectories in this population resulted in a trajectory with initial osteophyte formation and an increase in osteophyte formation ('osteophyte increase' subgroup; n= 32), a trajectory with initial osteophyte formation and minimal increase ('mild osteophyte' subgroup; n=181) and a trajectory without initial osteophyte formation and without increase ('no' osteophyte' subgroup; n=716) (*figure 1*). In 77% of the participants no change in osteophyte formation was observed, representing the most common osteophyte pattern.

Differences between subgroups based on baseline characteristics
Baseline demographics of participants, grouped according to identified trajectories are given in *table 2*. The local clinical signs, knee pain, morning stiffness, crepitus, warmth, bony tenderness, bony enlargement and effusion were most frequently present in the osteophyte increase subgroup, and lowest frequency was observed in the 'no osteophyte' subgroup. As compared to participants of subgroup 'no osteophyte', participants of the subgroup 'increase of osteophyte' and subgroup 'mild osteophyte', were more likely to be older, and to have a BMI above 25, higher pain intensity, positive clinical sign of a warm knee, bony tenderness, and effusion of the

TABLE 1 | Fit indices, entropy and posterior probabilities across models.

N° of trajectories	Bayesion information criteria (BIC)	Entropy	Vuong-LMR-LRT p-value	Bootstrap LRT p-value	Trajectories sub-group	n	posterior probability
2	19597,064	0.959	0.0972	< 0.0001	1	850	0.99
					2	79	0.95
3	19162,425	0.902	0.0316	< 0.0001	1	32	0.98
					2	716	0.97
					3	181	0.89
4	18999,979	0.906	0.2197	< 0.0001	1	194	0.89
					2	684	0.96
					3	41	0.94
					4	10	0.97
5	18914,140	0.898	0.3347	< 0.0001	1	200	0.87
					2	660	0.95
					3	27	0.82
					4	10	0.96
					5	32	0.95

Lowest BIC indicates best fitting model
Significant p- value (p< 0.05: model with k number of trajectories has a better fit compared to model with k-1 trajectories). Entropy and posterior probability close to 1 indicate good classification.
Vuong- LMR-LRT | Vuong-Lo-Mendell-Rubin likelyhood ratio test, Bootstrap LRT | Bootstrap likelihood ratio test

TABLE 2 | Baseline demographic and disease characteristics

Subgroup	'Osteophyte increase'	'Mild osteophyte'	'No osteophyte'
n	32	181	716
Age in years	58 (3.9)	57 (4.9)	55 (5.3)
Gender, female	84%	66%	82%
BMI > 25 kg/m^2	69%	66%	51%
Clinical signs			
Knee pain	97%	89%	81%
Pain intensity (0-10)	4 (2.1)	3 (2.2)	3 (2.0)
Morning stiffness knee	81%	53%	51%
Crepitus knee	63%	48%	44%
Warmth	16%	9%	4%
Bony tenderness	69%	49%	41%
Bony enlargement	13%	5%	4%
Effusion knee	19%	15%	6%
Radiographic feature of knee			
K&L Grade 0	10%	35%	55%
K&L Grade 1	90%	65%	45%
Ostophyte area (mm^2)	40 (18.1)	25 (9.9)	8 (5.8)
Minimal JSW (mm)	1.7 (1.7)	2.6 (1.3)	2.7 (1.2)
WOMAC subscales			
Pain (range 0-20)	7 (3.1)	6 (3.6)	5 (3.3)
Stiffness (range 0-8)	3 (1.3)	3 (1.6)	3 (1.7)
Physical function (range 0-68)	23 (9.5)	18 (12.1)	15 (11.3)
Comorbidity count			
≥ 3 comorbidities	16%	19%	22%
Biomarkers			
CTX II (ng/mmol)	374.2 (206.4)	251.2 (139.4)	207.0 (110.7)
COMP (µg/ml)	9.7 (2.4)	8.5 (2.4)	8.5 (2.3)

Mean values, standard deviation between brackets and categorical variables as percentages (%) are given. BMI | body mass index, K&L | Kellgren and Lawrence grade, WOMAC | Western Ontario and McMaster Universities OA index with higher scores indicating worst health

TABLE 3 | Multinomial regression analysis for univariate variables at baseline for each trajectory ('no osteophyte' subgroup is used as the reference group)

Subgroup	'Osteophyte increase' versus 'no osteophyte'	'Mild osteophyte' versus 'no osteophyte'
	OR Univariate Beta (p-value)	OR Univariate Beta (p-value)
Female versus male (referent)	0.9 (0.80)	2.4 (< 0.001)
Age	1.1 (0.02)	1.1 (< 0.001)
BMI > 25 versus BMI ≤ 25 (referent)	2.3 (0.04)	1.9 (< 0.001)
Clinical signs		
Pain intensity	1.2 (0.05)	1.1 (0.01)
Crepitus knee	2.1 (0.04)	1.2 (0.33)
Warmth	4.5 (0.004)	2.4 (0.007)
Bony tenderness	3.1 (0.003)	1.4 (0.05)
Bone enlargement	3.6 (0.02)	1.2 (0.66)
Effusion knee	3.4 (0.01)	2.7 (< 0.001)
Radiographic feature of knee		
K&L Grade 0 versus grade 1	10.9 (< 0.001)	2.3 (< 0.001)
Total Ostophyte area (mm^2)	1.5 (< 0.001)	1.4 (0.001)
Minimal JSW (mm)	0.5 (< 0.001)	0.9 (< 0.001)
Presence of comorbidity ≥ 3 versus comorbidity < 3 (referent)	0.9 (0.49)	1.1 (0.37)
Biomarkers		
CTX II (ng/mmol)	1.0 (< 0.001)	1.0 (< 0.001)
COMP (µg/ml)	1.2 (< 0.001)	1.2 (< 0.001)

BMI | body mass index, K&L | Kellgren & Lawrence, JSW | joint space width, CTX II | C-terminal telopeptide of type II collagen, COMP | cartilage oligomeric matrix protein

knee, a greater initial osteophyte area, a smaller JSW and higher CTX II and COMP levels (*table 3*). A positive clinical sign of knee crepitus and bony enlargement was more likely to be present in the 'osteophyte increase' subgroup compared to the 'no osteophyte' subgroup, than to be present in the 'mild osteophyte' subgroup. Participants in the 'mild osteophyte' subgroup were more likely to be male compared to participants in the 'no osteophyte' subgroup.

Overlap between osteophyte subgroups and pain trajectories

Table 4 compares the identified osteophyte subgroups with the previously identified pain trajectories. In the 'osteophyte increase' subgroup 15 (of 31) participants were part of the 'poor outcome' trajectory, which was 48% of the participants of ' increase osteophyte' subgroup. In the 'mild osteophyte' subgroup 63 (of 140) participants were part of the 'moderate outcome' trajectories, which was 45% of the 'mild osteophyte' subgroup. One hundred seventy two participants (of 511) of the 'no osteophyte' subgroup were part of the 'good outcome' trajectory, which was 34% of the participants 'no osteophyte' subgroup. There were 247 participants ('osteophyte increase' subgroup n=1; 'mild osteophyte' subgroup n=41; 'no osteophyte' subgroup n=205) excluded in the analysis of pain trajectories who entered the present study. Sixteen participants who were included in analysis of pain trajectories were excluded in the analysis of osteophyte subgroups. In *table 5* the univariate associations of the pain trajectories with the osteophyte subgroups are presented. The 'poor outcome' pain trajectory increased the odds of the ' osteophyte increase' subgroup with 6.6 compared to the 'good outcome' pain trajectory. The moderate outcome' pain trajectory increased the odds of the 'osteophyte increase' subgroup with 3.6 compared to the 'good outcome' pain trajectory. There were no associations found between the different pain trajectories and the 'mild osteophyte' subgroup.

Discussion

The present study evaluated changes in osteophyte formation over 5 years in individuals with symptomatic OA and classified 929 participants in 3 trajectories using LCGA. In most participants the osteophyte formation did not change over 5 years. In one trajectory with only 32 participants (3%) there was a remarkable increase in osteophyte formation: an average slope of the osteophyte area increase of 17.4 mm^2 over 5 years. The minimal increase subgroup included 20% of the sample, with an average slope of 1.3 mm^2 over 5 years. Since the average probability score of the trajectory classification for each

TABLE 4 | Participants according to the identified pain trajectories and osteophyte subgroups

Subgroup	'Osteophyte increase'	'Mild osteophyte'	'No osteophyte'	Not included in osteophyte analyses (n)
'Poor outcome' trajectory	48% (15)	26% (37)	25% (130)	7
'Moderate outcome' trajectory	42% (13)	45% (63)	41% (209)	9
'Good outcome' trajectory	10% (3)	29% (40)	34% (172)	7
Not included in pain analyses (n)	1	41	205	

TABLE 5 | Multinomial regression analysis for univariate variables at baseline for each trajectory ('no osteophyte' subgroup is used as the reference group)

Subgroup	'Osteophyte increase' versus 'no osteophyte'	'Mild osteophyte' versus 'no osteophyte'
	OR Univariate Beta (p-value)	OR Univariate Beta (p-value)
Pain trajectories		
Good outcome	Referent	Referent
Moderate outcome	3.6 (0.05)	1.3 (0.3)
Poor outcome	6.6 (0.003)	1.2 (0.4)

estimated trajectory was at least 89% participants are considered to be correctly classified into the estimated trajectories. Overall, participants with minimal and remarkable increase compared to 'no osteophyte' formation, were more likely to be older, obese, to have positive clinical signs of an osteoarthritic knee joint and to have higher baseline levels of cartilage degradation marker (COMP) and higher levels of bone metabolism marker (CTX-II). Characteristics of the baseline radiograph itself were prognostic factors for the formation of subsequent osteophytes.

Results of this study add to the growing body of evidence that only in a small percentage of patients with early OA radiographic disease progression occurs over the first five years. Changes in formation of osteophytes can be classified in three different trajectories. In another study identifying trajectories of joint space narrowing in subjects with symptomatic OA, the same patterns were seen; JSW of 70% of subjects remained unchanged over 2 years and JSW decreased in only a small sample.[29]

Studies on the formation of osteophytes over time are scarce. Studies on radiologic development of OA mainly focus on the global K&L score and report that knees that are progressing are far more likely to continue to progress than knees which have been stable in terms of structural deterioration.[13] Our results confirm this state of inertia.

In this study we could only assess univariate associations between baseline clinical factors and the identified trajectories due to the small number (3%) of participants in the 'increase osteophyte subgroup'. Higher probability of an increase in osteophyte formation is expected if the participant is older, obese, has an initial osteophyte and narrowing of the JSW. This corresponds with elsewhere reported predictors of progression in the identified trajectories of JSN; those progressors tended to be older, heavier and had an initial existence of the radiographic feature (less JSW). The presence of local clinical signs (crepitus, warmth, bony tenderness, enlargement and effusion) in our study suggested a higher probability of an (mild) increase in osteophyte formation. These local signs correspond with the typical OA findings on examination.

Comparing the identified subgroups of osteophyte formation and trajectories of pain evolution, there seems to be some overlap in participants belonging to worst trajectory in osteophyte formation and worst pain trajectory. Of course there was also disagreement between trajectories regarding pain and osteophytes, which is in line with the concept that there is limited overlap between the disease OA and the illness OA.[1] The 'poor' and 'moderate' outcome pain trajectories suggested a higher probability of an 'osteophyte increase' subgroup, however a 'moderate' outcome pain trajectory did not suggested a probability of a 'mild osteophyte' subgroup. Less than half of the participants of a osteophyte subgroup corresponded with a relevant pain trajectory. A limitation in this evaluation is the reported missing data.

The strength of this study is the longitudinal design with 3 measurements over a period of 5 year follow-up. Additional strengths are the use of LCGA to capture the consistence of one or more trajectories of individuals with similar developmental trajectories; the use of more sensitive quantitative measurements of osteophyte formation and a relatively complete data set.

There are also limitations to this study. Although LCGA seems to be preferable above the more simple methods for identifying homogeneous trajectories, there is still an on-going discussion about model fit parameters for choosing the optimal number of classes.[26,27] Focusing on only one radiographic feature leads to an oversimplification of the osteoarthritic process. We are aware that knee OA is a complex disease affecting multiple features in multiple compartments.[8] Another limitation is a technical one: the quantitative measurement of osteophyte formation, since an osteophyte can appear to change in an image with only small changes in rotation.[13]

In conclusion, in persons with symptomatic OA the common course of osteophyte formation over a period of 5 years is relatively flat, showing no increase in most patients. However, in a small subpopulation there was a remarkable increase in osteophyte formation. Based on the formation of osteophytes and the identified pain trajectories in largely the same population, we can better understand that in every person with OA the evolution of illness and disease of OA develops according to specific phenotypes or trajectories. There is limited overlap between these trajectories and phenotypes: the trajectory of more pain increases the odds of the trajectory with an increase in structural damage. Better insights in these different trajectories of illness and disease may ultimately lead to more targeted treatment of the patient. —

In most participants the osteophyte formation did not change over 5 years.

In a small subpopulation there was a remarkable increase in osteophyte formation.

REFERENCES

1. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011;19:478-82.

2. Eckstein F, Kwoh CK, Link TM. Imaging research results from the Osteoarthritis Initiative (oai): a review and lessons learned 10 years after start of enrolment. Ann Rheum Dis 2014; 73:1289-300

3. Kraus VB. Osteoarthritis year 2010 in review: biochemical markers. Osteoarthritis Cartilage 2011;19:346-53.

4. Buckland-Wright JC, Lynch JA, Dave B. Early radiographic features in patients with anterior cruciate ligament rupture. Ann Rheum Dis 2000; 59:641-6.

5. Kumm J, Tamm A, Lintrop M, Tamm A. The prevalence and progression of radiographic knee osteoarthritis over 6 years in a population-based cohort of middle-aged subjects. Rheumatol Int 2012; 32:3545-50.

6. Hart DJ, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee--doubtful or definite? Osteoarthritis Cartilage 2003; 11:149-50.

7. Spector TD, Hart DJ, Byrne J, Harris pa, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. Ann Rheum Dis 1993; 52:790-4.

8. van der Esch M, Knol DL, Schaffers IC, Reiding DJ, van Schaardenburg D, Knoop J, et al. Osteoarthritis of the knee: multicompartmental or compartmental disease? Rheumatology (Oxford) 2014; 53:540-6.

9. Felson DT, Gale DR, Elon GM, Niu J, Hunter DJ, Goggins J, et al. Osteophytes and progression of knee osteoarthritis. Rheumatology (Oxford) 2005; 44:100-4.

10. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis 2010; 69:1940-5.

11. van der Kraan PM, van den Berg WB. Osteophytes: relevance and biology. Osteoarthritis Cartilage 2007; 15:237-44.

12. Peters TJ, Sanders C, Dieppe P, Donovan J. Factors associated with change in pain and disability over time: a community-based prospective observational study of hip and knee osteoarthritis. Br J Gen Pract 2005 ;55:205-11.

13. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt mc. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2013; 72:924-9.

14. Fletcher RH, Fletcher SW. Clinical epidemiology: The essentials. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2005.

15. Wesseling J, Bastick AL, ten Wolde S, Kloppenburg M, Lafeber FP, Bierma-Zeinstra S, et al. Good, moderate and poor outcome trajectories of pain severity in early symptomatic knee OA; 5 year follow-up of CHECK (Cohort Hip & Cohort Knee). Submitted 2014.

16. Wesseling J, Dekker J, van den Berg wb, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip & Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009 ; 68:1413-9.

17. Wesseling J, Boers M, Viergever MA, Hilberdink WK, Lafeber FP, Dekker J, et al. Cohort profile: Cohort Hip & Cohort Knee (CHECK) study. Int J Epidemiol 2014. [Epub ahead of print]

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

19. Kinds MB, Marijnissen AC, Vincken KL, Viergever MA, Drossaers-Bakker KW, Bijlsma JW, et al. Evaluation of separate quantitative radiographic features adds to the prediction of incident radiographic osteoarthritis in individuals with recent onset of knee pain: 5-year follow-up in the CHECK cohort. Osteoarthritis Cartilage 2012; 20:548-56.

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

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

22. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at omeract III. J Rheumatol 1997; 24:799-802.

23. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. Satisfactory cross cultural equivalence of the Dutch womac in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63:36-42.

24. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (sf-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240-S252.

25. Botterweck A, Frenken F, Janssen S, Rozendaal L, Vree Md, Otten F.[Plausibility new measurements general health and lifestyles] Plausibiliteit nieuwe metingen algemene gezondheid en leefstijlen. Heerlen: Centraal Bureau voor de Statistiek; 2001.

26. Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol 2012; 65:1078-87.

27. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Soc Pers Psychol Compass 2008; 2::302-17.

28. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo simulation study. Struct Equation Modeling 2007;14:535-69.

29. Bartlett SJ, Ling SM, Mayo NE, Scott SC, Bingham CO, III. Identifying common trajectories of joint space narrowing over two years in knee osteoarthritis. Arthritis Care Res (Hoboken) 2011; 63:1722-8.

8

SUMMARY & DISCUSSION

THE OVERALL AIM OF THE CHECK STUDY IS TO GAIN MORE KNOWLEDGE ON THE COURSE, PROGNOSIS AND UNDERLYING MECHANISMS OF EARLY SYMPTOMATIC OA IN HIP OR KNEE, WITH A FOCUS ON CLINICAL, RADIOGRAPHIC AND BIOCHEMICAL VARIABLES. These variables assess consequences of osteoarthritis regarding body functions and structures, activities and participation as well as environmental and personal factors of a person with OA. For this purpose a longitudinal (10 years follow-up) cohort study was started with 1,000 persons with signs and symptoms of early osteoarthritis of hip and/or knee.

OUTLINE AND SCOPE OF THIS THESIS

The research described in this thesis is part of the CHECK study. The overall aim is to analyze disease characteristics (pain, physical functioning) of early symptomatic OA and to examine the evolution of structural damage in relation with disease characteristics. As an introduction we provide up-to-date details of CHECK, also to enable researchers worldwide to start collaborations and to maximize use of the available data and resources (*chapter 2*).

In *part I* of the thesis similarities within and differences between the two most well-known cohorts of persons with early osteoarthritis are described. Parallel to CHECK, an observational study on OA was initiated by the NIH (National Institute of Health, United States of America): the Osteoarthritis Initiative (OAI). This 4-year follow-up study also has the objective to study the natural history of, and risk factors for, the onset and progression of early OA. In fact both initiatives, CHECK and the OAI, search answers to similar questions in somewhat different populations. We evaluated whether CHECK and -on comparable inclusion criteria selected- study populations of the OAI are similar and what we might learn from combining information from both cohorts (*chapter 3*). Baseline data from both cohorts were analyzed, and more differences than expected were observed. This led us to formulate a hypothesis on the relation between complaints of early disease and pain on one side and damage on the other side. To test this hypothesis we compared longitudinal data of both cohorts by observing differences in the development of joint damage and evolution of pain and physical functioning (*chapter 4*). Signs and symptoms in both cohorts remained rather stable over 4-5 years, and also the differences between both cohorts persisted.

In *part II* we focus on differences in evolution of disease characteristics within the CHECK-participants. It is known that patients with symptomatic OA have a high number of comorbidities, significantly more than non-OA patients. First we evaluated the relationship between comorbidity (absolute number as well as the presence of specific comorbidities) and pain, physical functioning and mental health status of participants with early symptomatic OA (*chapter 5*). We confirmed that, also in early symptomatic OA, comorbidity plays an important role in the expression of signs and symptoms of OA. The level and course of the main clinical symptom pain can differ a lot between individual patients over time. With Latent Class Growth Analysis we identified homogeneous subgroups of pain trajectories in patients with symptomatic knee OA, and tried to predict these different pain trajectories by disease characteristics at baseline (*chapter 6*). An obvious next question is whether such homogenous subgroups also exist with regard to structural damage. With Latent Class Growth Analysis we also identified homogeneous subgroups of osteophyte formation over time (trajectories) in CHECK-participants and identified prognostic factors for these trajectories (*chapter 7*).

The specific questions discussed in this thesis are only a small part of the large amount of research within the CHECK cohort that has already been done or can be done in the future. Therefore we will place these specific findings into perspective and will give some suggestions for future research.

FIRST FINDINGS OF CHECK (HIGHLIGHTS)

CHECK, initiated by the Dutch Arthritis Association, was devised in 1999/2000 by a multi-disciplinary group of researchers from different fields and specialties. From the start the following disciplines have been involved: rheumatology, general practice, orthopedics, rehabilitation, medical imaging, epidemiology and physiotherapy. CHECK is a multicenter 10-year follow-up study of 1,002 persons with early osteoarthritis of hip and/or knee. The first participant was included in November 2002, the last participant will be out in December 2015. Data on the first five years have been consolidated in 2011 and will soon become freely available for researchers worldwide. The study provides a valuable data set to answer many longitudinal research questions regarding a broad range of aspects of OA of the hip or knee. Some already published findings include:

Clinical variables

OA is not one disease and worldwide researchers are trying to dissect OA based on e.g. the patterns of clinical signs and its course, on development of separate radiographic features and on patterns of

biochemical markers.[1,2] Based on 5 years follow-up data of activity limitations in the knee OA population three homogeneous subgroups were identified: a 'good outcome' subgroup that develops or displays slight activity limitations over time; a 'moderate outcome' that develops or displays moderate activity limitations over time; and a 'poor outcome' subgroup that develops or displays severe activity limitations over time.[1] Prognostic factors for activity limitations include clinical (e.g. ≥ 3 comorbidities, muscle weakness, bony tenderness), radiographic (osteophytes), metabolic (higher BMI) and psychological factors (low vitality, avoidance of activities).[3] A combined psychological and neuromuscular model was proposed that partially explains the development of activity limitations.[4,5] According to this model, pain and low vitality lead to subsequent avoidance of activities and thereby to muscle weakness and activity limitations.[6-8] Besides the course of activity limitations, also the course of work participation was analysed. Remarkably, two-year course of work participation was similar to that of the general Dutch population; after two years sustained work participation was predicted by lower age, but not by OA related factors.[9]

Radiographic variables

A newly developed method to analyse knees radiographically, Knee Images Digital Analysis (KIDA), is sensitive to detect early progression of radiographic knee damage, especially through measurement of separate quantitative features of knee OA.[10] Based on KIDA features (joint space width (minimum, medial, lateral), varus angle, osteophyte area, eminence height, and bone density) 5 phenotypes of radiographic progression could be identified. These represent the level of disease progression (Severe or No progression), the phase of progression (Early or Late) and the prominent involvement of Bone density.[2]

Statistical Shape Modelling (SSM) can assess the radiographic shape of the hip, and is used to test whether the morphology of the hip joint can be a risk factor for OA. Evaluation of hip radiographs of CHECK participants showed that the SSM-modelled shape of the hip can predict total hip replacement, but variation in shape cannot predict clinical symptoms of OA.[11] In addition, individuals with severe cam-type deformity (hip incongruity by non-spherical head) and reduced internal rotation were at high risk of fast progression to end stage OA.[12] Finally, pincer deformity (acetabulum over-coverage) did not lead to OA of the hip, but acetabulum under-coverage did.[13]

Biochemical markers

In CHECK 14 markers of cartilage, bone and synovial metabolism were assessed at baseline to improve understanding of pathophysiology and as potential prognostic factors. None of these markers proved sufficiently discriminating to predict diagnosis or prognosis of OA. Two reflected a broader spectrum than originally expected. The cartilage degradation marker, CTX-II, showed striking similarities with markers of bone metabolism, suggesting that CTX-II also originates from bone. The cartilage degradation marker COMP (Cartilage Oligomeric Matrix Protein) may also originate from (inflamed) synovial tissue in early-stage OA.[14,15]

MAIN FINDINGS FROM THIS THESIS

Are participants of CHECK and -on comparable inclusion criteria selected- study populations of the OAI similar and what might we learn from combining information from both cohorts?

Both cohorts study early osteoarthritis, but report differences in complaints and structural damage at inclusion. Radiographic knee OA was present in a significant smaller number of the CHECK participants compared with the OAI-participants. In contrast, participants in CHECK had more pain, more stiffness, more limitations in activities, and a worse health status (*chapter 3*). These observed differences between both cohorts could not be explained by baseline characteristics such as drug use, body mass index or gender. Based on the milder radiological findings we hypothesized that CHECK was started in an earlier phase of the disease than OAI.[16] This hypothesis served as a basis for evaluation of the longitudinal data in *chapter 4*. How is the relation of joint damage with evolution of pain and physical functioning in these two cohorts? In both cohorts (CHECK n= 714; OAI n=930) we concluded that rapid joint damage (change of ≥2 grades of K&L in 4 - 5 years) is related to worsening of pain and function. In participants with slow progression (radiological change of 1 grade or less of K&L), pain and physical function remained fairly stable over 4 to 5 year.[17] Remarkably, in both cohorts the level of pain and physical function remained basically the same, and also the differences between the OAI and CHECK participants remained the same in the pursuing 4-5 years. These data do not support our original hypothesis that CHECK had started at an early stage of the disease compared to OAI. Interestingly, it was recently reported that participants of the OAI cohort have a higher self-reported health status compared to a nationally representative survey of USW persons with OA.[18] As possible explanation for the observed differences the rather strict exclusion criteria for OAI have been suggested. These OAI exclusion criteria, such as inability to undergo MRI, severe joint space narrowing in both knees and comorbid conditions that could interfere with participation, may have created a relatively healthy OA cohort.[19] This could also partially explain the observed differences in complaints between the CHECK and OAI cohorts. It cannot be ruled out that existing social, cultural, and health care system differences between the US and the Netherlands influence these observed differences as well. Besides, as a methodological explanation, many variables that are related to evolution of pain and functional problems are not or not identically measured in CHECK and OAI, such as measurement of comorbidities, reporting of constant or intermittent pain and pain related behavior.

Apart from analyzing observed differences between the two OA cohorts, it is also relevant to study possible differences in evolution of disease characteristics within CHECK. First we evaluated the relationship between comorbidity (absolute number as well as the presence of specific comorbidities) and pain, physical functioning and mental health status of participants with early symptomatic OA of hip or knee (*chapter 5*). We noted that especially additional problems in musculoskeletal system and obesity have a negative effect on pain and physical health status. But also mental status is affected in early symptomatic OA by the presence of specific comorbidities.[20] An explanation could be the avoidance model, the association between pain, avoidance of activities, muscle strength and activity limitations in participants with early OA; this mechanism could be reinforced by painful comorbidities.[6] Another explanation could be central pain sensitization, suggesting that more than just the receptor area for the painful joint is involved in nociception.[21] Pain may arise from nociceptive fibers and/ or mechanoreceptors in the different tissues of the joint, by effusion and intra-articular tension. In addition to peripheral sensitization central sensitization also has its effect on pain in patients with OA.[22] Others have also reported that knee-specific pain and disability, as measured with the WOMAC, can be worse in presence of pain elsewhere in the musculoskeletal system.[23]

Since comorbidity in CHECK and OAI was evaluated with different questionnaires, we could not adjust for comorbidity in analyzing differences in pain and physical functioning between both cohorts. The association of comorbidity reported in CHECK with pain and physical function might further explain reported differences between CHECK and OAI, since in OAI comorbidities were an exclusion, but not in CHECK. This underscores the importance of international consensus on measuring the same items, in the same way and at the same time points in prospective cohorts of patients with chronic diseases.

Possible differences in evolution of disease characteristics within CHECK were studied in two relevant areas: the clinical hallmark pain and the radiological hallmark osteophytes. In *chapter 4* it was concluded that on group level the evolution of pain remains fairly stable, but a considerable individual variation was found. In order to identify homogeneous subgroups of pain trajectories in patients with early symptomatic OA the Latent Class Growth Analysis (LCGA) was applied (*chapter 6*). The latent class growth analysis is a method to identify homogeneous subgroups within a large heterogeneous population and to identify meaningful groups or classes of individuals. It seems to be the most appropriate method for fully capturing information about inter-individual differences in intra-individual change taking into account unobserved heterogeneity (different groups or trajectories) within a larger population.[24] The same method was used to identify homogeneous subgroups regarding the formation of osteophytes (*chapter 7*).

Three homogeneous subgroups of pain trajectories in

patients with symptomatic knee OA were identified: participants with good outcome trajectory (n=222) had a slight decrease in pain severity over time and ended up with lower pain severity. Participants with moderate outcome trajectory (n=294) had a variable course over time with moderate pain. The poor outcome trajectory participants (n=189) had an increase of pain severity over time. These trajectories of pain could be characterized by different clinical features, coping strategies and lifestyle factors. Participants that had at baseline a BMI above 25, and/or who had a lower education, had 3 or more comorbidities, had additional hip pain, and/or used the coping strategies 'worrying' and 'resting' were more likely to have a poor outcome. Apart from these baseline characteristics the poor outcome trajectory was also associated with rapid joint damage (radiographic K&L change of at least 2 points in 4-5 year follow-up). These findings are in line with the findings of *chapter 4*, where it was suggested that individuals with slow radiographic progression may have more opportunity to adapt to the changes in physiology and therefore experience less pain.[25] Of course, these findings need to be validated in another early OA population.

In the introduction of this thesis, we emphasized that one should make a distinction between the disease process, structural joint changes ('the disease'), and complaints associated with osteoarthritis ('the illness'). In previous chapters the complaints or consequences of OA were the variables of interest. In *chapter 7* structural joint damage, the formation of osteophytes, is the subject of more detailed evaluation. Could we identify subgroups of participants with homogeneous patterns of osteophyte formation over time (trajectories), and examine the prognostic factors for these different trajectories? Three homogeneous subgroups of osteophyte formation could be identified, but the mean course of osteophyte formation over a period of 5 years is relatively flat, showing no increase of osteophytes in most patients. We suggest that an increase in osteophyte formation is more probable if the participant is older, obese, has already an initial osteophyte and narrowing of the JSW, and has local clinical osteoarthritic signs, such as crepitus, warmth, bony tenderness, enlargement and effusion. To better identify prognostic factors for the formation of osteophytes, we will need to analyse data of a more prolonged period of time in persons with early OA.

Of course it is interesting to compare the identified trajectories of evolution of pain (*chapter 6*) with the subgroups of evolution of osteophyte formation (*chapter 7*). There is limited overlap between these trajectories: the trajectory of increase of pain does not correspond with a subgroup of increase in structural damage. Here too, further research, especially with a longer follow-up, for example 10 years, could give better insights in the different trajectories of illness and disease and may potentially lead to more specific treatment of the individual patient. Since in most persons with symptomatic OA there is a flat trajectory of osteophyte formation over a period of 5 years, OA can be characterised rather as a chronic disease than a progressive disease.[26]

CONSEQUENCES FOR A PERSON WITH OA, IMPLICATIONS FOR CLINICAL PRACTICE

Research in this thesis is primarily aimed at obtaining a better understanding of disease characteristics (pain, physical functioning) of early symptomatic OA and to examine evolution of clinical symptoms and structural damage in relation to disease characteristics. In addition, we aimed to get more insight in the overlap between the disease process (structural joint changes) and the illness (patients' complaints) in early symptomatic OA.

For a physician it is important to recognize, and inform the patient with knee OA about, the existence of subgroups (trajectories) in the evolution of pain, activity limitation and development of structural damage, all with different prognosis.[1,26,27] Overall, OA is generally been thought of as a progressive condition. However, this study suggest that this is not necessary the case of the disease process (structural joint damage) and the illness within 5 years. Only a small proportion of the people with OA will have serious increase in osteophyte formation and two points increase in K&L grade in 5 year time.[26] For a physician this finding is important, in order to reassure most patients with early OA that it is unlikely that they have a progressive joint disease. At the same time the physician has to inform the patient about the limited overlap between this chronic disease process (of structural joint damage) and the complaints of the patients (illness). More recently, the concept of OA as a disease as well as an illness has progressed, recognizing that OA interventions may have discordant effects on illness and disease.[28] In future evaluation of treatments for OA one should consider the effect of treatment on structural changes as separate from the effect on patient-reported symptoms.

In the management of early symptomatic OA attention should also be given to the limited but possible worsening of radiographic joint damage over time. The physician should not only take joint damage at that moment into account, but also changes over a period of time. This will give more insight in the disease process of the individual patient (trajectory); e.g. knees that have progressed are far more likely to continue to progress than knees which have been stable in structural damage. Worsening of pain and function and initial osteophytes are associated with a higher probability to progress in osteophyte formation.[17,26,29]

In the management of pain in early symptomatic OA attention should also be given to personal and environmental factors, that may worsen pain and also physical function. Participants with baseline BMI above 25, with lower education, with 3 or more comorbidities, with additional hip pain and/or using the coping strategies 'worrying' and 'resting' are more likely to have a poor outcome of pain.[27] The focus of the physician should not only be on OA itself, but also on a possible second disease, since comorbidity worsens pain and physical and mental health.[20]

Our results confirm the relevance of the framework of ICF, which emphasizes that an individual's health experience is the interaction between the health condition (biological dysfunction) and social, personal and environmental factors.[30] Pain itself has distressing features (its intensity, its quality and predictability), and the pain has impact on mobility, mood and sleep.[31] To clarify the relationship among pain, fatigue, mood, disability, and contextual factors (like coping and social support) several models have been developed.[6,32] One model describes that OA pain causes depressed mood through its effect on fatigue and disability; these effects may lead to worsening of pain and disability.[32] Another model suggests that pain and low vitality lead to subsequent avoidance of activities and thereby to muscle weakness and activity limitations.[6] These models support the need for improved OA pain management by including contextual factors (environmental and personal factors), to prevent or reduce the negative downstream effects of pain. In particular, when OA is characterized as a chronic disease, the cure should help the patient towards a good quality of life and to health and well-being, in spite of suffering from knee OA or hip OA.[33] Therefore, management in the early stage of OA should also target a careful assessment of the severity of the patient reported outcomes and of contextual factors.[30,34] Probably the best treatment should be established through tailored treatment which takes into account patients reported outcomes, personal and environmental factors (symptom modifying) and the most involved joint tissue (structure modifying to prevent the development of joint failure).

RECOMMENDATIONS FOR FUTURE RESEARCH

Based on the findings of our study, several recommendations for future research can be made. To understand the relevance of the identified subgroups (trajectories) in illness and disease process of early symptomatic OA, further research is needed on different trajectories and the factors that can predict it. Different trajectories identified need to be validated in another early OA cohort. The formation of osteophytes has to be studied over a more prolonged period of time in persons with early OA. Since structural damage in OA deteriorates slowly, more changes in the formation of osteophytes can be expected with a longer follow-up. In this thesis we only studied the trajectories of osteophyte formation, since this should be considered as an early feature of OA.[35] However, to characterize different phenotypes of structural changes in either cartilage, bone, or synovial tissue, more research has to be done.[36,37] The concept has to be proven, that there are different phenotypes depending on the most involved tissue at a given time. Besides, it is thought that clinical phenotypes may be change during the disease course.[38]

A next step in the CHECK study would be, to identify trajectories in persons with homogeneous patterns of joint space width on radiographs and to describe these different trajectories by baseline characteristics. Subsequently, to combine the results of the different trajectories of the structural changes with the different trajectories based on pain and activity limitation. This will give information whether indeed different tissue are dominating in the early stage of OA and if the clinical expression of a certain phenotype is associated with predominant involved joint tissue. Improved insights in the different trajectories of illness and disease may give the opportunity to more specific targeted treatment of the patient.[37,38]

Also, more research is required to elucidate pain mechanism in OA and to facilitate better characterization of the nature of pain.[28,34] There is evidence to suggest that people with chronic, painful OA may experience sensitization of the peripheral and/ or central pain pathway, which may lead to neuropathic pain.[34,39] Thus, OA patients may have pain that is predominantly nociceptive (resulting from joint tissue damage, predominantly neuropathic, or of mixed nociceptive/ neuropathic etiology.[28,34] To measure the quality or characteristics of pain and its impact on mobility, mood and sleep, a new hip/ knee OA pain measure was developed, the OARSI-OMERACT Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP).[40] In CHECK, there will be ICOAP data available from 5 year follow-up until 10 year that characterize the nature of pain. By using this data, perhaps we could stratify OA patients on the basis of the type of pain present.

Another point of attention in future research is to evaluate which aspects of the illness (e.g. pain, sleep quality, depressed mood) are most important to the patient and should be targeted in treatment.[28]

When continuing a cohort of patients during longer follow-up, it is important to involve patients in the working group of the study, with the aim to help implementing the study in the study side and to discuss progress. But it is also important to involve some patients in the preliminary stage of the study to discuss the wants and needs of the patient and thereby to increase the willingness of patients to continue to participate. Besides, at the start of a cohort study a special retention program has to be developed to optimize the compliance of the patients and to motivate health professionals involved in participating hospitals (physicians, researchers, X-ray technicians, research nurses). Activities can include: a personalized study scheme for patients to clarify all examinations over time, newsletters for patient and health professionals, websites for patients and health professionals, organizing symposia for both groups to present results and progress of the cohort.

In conclusion, better (or more specific) characterization of the patients' symptoms, contextual factors and of the damaged tissue is needed, to improve our ability to target the right treatment to the right patient, resulting in improved outcome. —

REFERENCES

1. Holla JF, van der Leeden M, Heymans MW, Roorda LD, Bierma-Zeinstra SM, Boers M, et al. Three trajectories of activity limitations in early symptomatic knee osteoarthritis: a 5-year follow-up study. Ann Rheum Dis 2013; 73:1369-75.

2. Kinds MB, Marijnissen AC, Viergever MA, Emans PJ, Lafeber FP, Welsing PM. Identifying Phenotypes of Knee Osteoarthritis by Separate Quantitative Radiographic Features May Improve Patient Selection for More Targeted Treatment. J Rheumatol 2013 ;40:891-902.

3. Holla JF, Steultjens MP, Roorda LD, Heymans MW, ten Wolde S, Dekker J. Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee. Arthritis Care Res (Hoboken) 2010; 62:1415-25.

4. Steultjens MP, Dekker J, Bijlsma JW. Avoidance of activity and disability in patients with osteoarthritis of the knee: the mediating role of muscle strength. Arthritis Rheum 2002; 46:1784-8.

5. Bot SD, Terwee CB, van der Windt DA, Feleus A, Bierma-Zeinstra SM, Knol DL, et al. Internal consistency and validity of a new physical workload questionnaire. Occup Environ Med 2004; 61:980-6.

6. Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF, et al. Avoidance of Activities in Early Symptomatic Knee Osteoarthritis: Results from the CHECK Cohort. Ann Behav Med 2012; 44:33-42.

7. Holla JF, van der Leeden M, Peter WF, Roorda LD, van der Esch M, Lems WF, et al. Proprioception, laxity, muscle strength and activity limitations in early symptomatic knee osteoarthritis: results from the CHECK cohort. J Rehabil Med 2012; 44:862-8.

8. van der Esch M, Holla JF, van der Leeden M, Knol DL, Lems WF, Roorda LD, et al. Decrease of muscle strength is associated with increase of activity limitations in early knee osteoarthritis: 3-year results from the Cohort Hip & Cohort Knee study. Arch Phys Med Rehabil 2014. [Epub ahead of print]

9. Bieleman HJ, Reneman MF, Drossaers-Bakker KW, Groothoff JW, Oosterveld FG. Prognostic factors for sustained work participation in early osteoarthritis: a follow-up study in the Cohort Hip & Cohort Knee (CHECK). J Occup Rehabil 2013; 23:74-81.

10. Kinds MB, Marijnissen AC, Vincken KL, Viergever MA, Drossaers-Bakker KW, Bijlsma JW, et al. Evaluation of separate quantitative radiographic features adds to the prediction of incident radiographic osteoarthritis in individuals with recent onset of knee pain: 5-year follow-up in the CHECK cohort. Osteoarthritis Cartilage 2012; 20:548-56.

11. Agricola R, Reijman M, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). Osteoarthritis Cartilage 2013; 21:559-64.

12. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis 2013; 72:918-23.

13. Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SM, Verhaar JA, et al. Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage 2013; 21:1514-21.

14. van Spil WE, Drossaers-Bakker KW, Lafeber FP. Associations of ctx-II with biochemical markers of bone turnover raise questions on its tissue origin: data from CHECK, a cohort study of early osteoarthritis. Ann Rheum Dis 2013; 72:29-36.

15. van Spil WE, Jansen NW, Bijlsma JW, Reijman M, DeGroot J, Welsing PM, et al. Clusters within a wide spectrum of biochemical markers for osteoarthritis: data from CHECK, a large cohort of individuals with very early symptomatic osteoarthritis. Osteoarthritis Cartilage 2012; 20:745-54.

16. Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SM, Boers M, Cats HA, et al. CHECK (Cohort Hip & Cohort Knee): similarities and differences with the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68:1413-9.

17. Wesseling J, Bierma-Zeinstra SM, Kloppenburg M, Meijer R, Bijlsma JW. Worsening of pain and function over 5 years in individuals with 'early'

OA is related to structural damage: data from the Osteoarthritis Initiative and CHECK (Cohort Hip & Cohort Knee) study. Ann Rheum Dis 2013; 2013. [Epub ahead of print]

18. Reichmann WM, Katz JN, Losina E. Differences in self-reported health in the Osteoarthritis Initiative (OAI) and Third National Health and Nutrition Examination Survey (NHANES-III). PLoS One 2011; 6:e17345.

19. Collins JE, Katz JN, Dervan EE, Losina E. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2014; 22:622-30.

20. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip & Cohort Knee) study. Rheumatology (Oxford) 2013; 52:180-8.

21. Kidd B. Mechanisms of pain in osteoarthritis. HSS J 2012; 8:26-8.

22. Geenen R, Bijlsma JW. Psychological management of osteoarthritic pain. Osteoarthritis Cartilage 2010;18:873-5.

23. Croft P, Jordan K, Jinks C. "Pain elsewhere" and the impact of knee pain in older people. Arthritis Rheum 2005; 52:2350-4.

24. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Soc Pers Psychol Compass 2/1;2008:302-17.

25. White DK, Zhang Y, Niu J, Keysor JJ, Nevitt mc, Lewis CE, et al. Do worsening knee radiographs mean greater chances of severe functional limitation? Arthritis Care Res (Hoboken) 2010; 62:1433-9.

26. Wesseling J, Kuchuk NO, Bierma-Zeinstra S, Marijnissen AC, Lafeber FP, Bijlsma JW. Identifying trajectories in knee osteophyte formation in early symptomatic osteoarthritis; results of 5 year follow-up in CHECK (Cohort Hip & Cohort Knee). Submitted 2014.

27. Wesseling J, Bastick AL, ten Wolde S, Kloppenburg M, Lafeber FP, Bierma-Zeinstra S, et al. Good, moderate and poor outcome trajectories of pain severity in early symptomatic knee OA; 5 year follow-up of CHECK (Cohort Hip & Cohort Knee). Submitted 2014.

28. Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage 2011; 19:478-82.

29. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt mc. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2013; 72:924-9.

30. Stucki G, Ewert T. How to assess the impact of arthritis on the individual patient: the WHO icf. Ann Rheum Dis 2005; 64:664-8.

31. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/omeract initiative. Osteoarthritis Cartilage 2008; 16:415-22.

32. Hawker GA, Gignac MA, Badley E, Davis AM, French MR, Li Y, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. Arthritis Care Res (Hoboken) 2011; 63:1382-90.

33. Dieppe P, Marsden D. Managing arthritis: the need to think about whole systems. Rheumatology (Oxford) 2013; 52:1345-6.

34. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005; 365:965-73.

35. Hart DJ, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee--doubtful or definite? Osteoarthritis Cartilage 2003; 11:149-50.

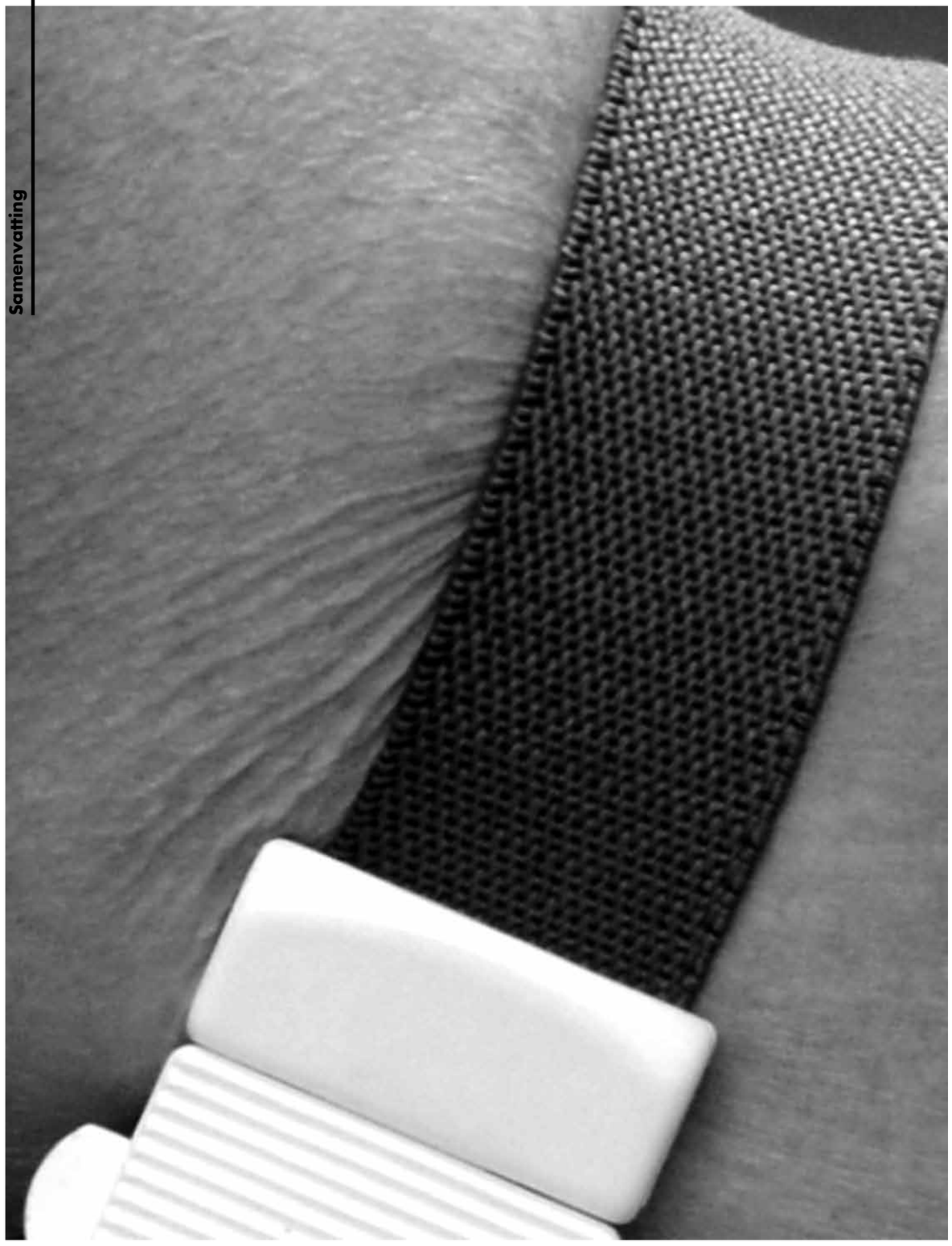
36. Eckstein F, Kwoh CK, Link TM. Imaging research results from the Osteoarthritis Initiative (OAI): a review and lessons learned 10 years after start of enrolment. Ann Rheum Dis 2014; 73:1289-300.

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

38. Castaneda S, Roman-Blas JA, Largo R, Herrero-Beaumont G. Osteoarthritis: a progressive disease with changing phenotypes. Rheumatology (Oxford) 2014; 53:1-3.

39. Hochman JR, French MR, Bermingham SL, Hawker GA. The nerve of osteoarthritis pain. Arthritis Care Res (Hoboken) 2010; 62:1019-23.

40. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (nrs Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11:S240-S252.



SAMENVATTING

TEGENWOORDIG KAN ARTROSE NIET LANGER GEZIEN WORDEN ALS EEN SIMPELE CONSEQUENTIE VAN HET OUDER WORDEN EN DEGENERATIE VAN HET KRAAKBEEN.

Hoofdstuk 1 beschrijft dat het belangrijk is voor het beter begrijpen van artrose om een onderscheid te maken tussen het ziekteproces als zodanig, dat leidt tot veranderingen in de verschillende weefsels in het gewricht, en de klachten van de patiënten door de artrose. Kenmerkende veranderingen in het gewrichtsweefsel, die ook op een röntgenfoto te zien zijn, zijn: schade aan en verlies van gewrichtskraakbeen, uitgroei aan de randen van het bot (osteofyten) en kwaliteitsverandering van het bot onder het kraakbeen (sclerose). Daarnaast kan er ook een gewrichtsontsteking ontstaan, kan de spierkracht verminderen en kunnen de gewrichtsbanden verzwakken. Kortom alle structuren van het gewricht kunnen meedoen. De voornaamste klachten van mensen met artrose zijn pijn, stijfheid en het minder kunnen uitvoeren van de activiteiten in het dagelijks leven (zoals lopen, opstaan en gaan zitten).

Het is nog niet duidelijk hoe de beginfase van artrose eruit ziet. We weten te weinig waarom bij de ene patiënt de klachten langzaam erger worden, terwijl bij de andere patiënt de klachten veel sneller verergeren. Ook weten we te weinig van de samenhang tussen de radiologische verandering in het gewricht en de klachten die gepaard gaan met artrose; er kunnen klachten zijn zonder zichtbare radiologische schade. Om meer te begrijpen van de aandoening en haar beloop, is een groot observationeel onderzoek nodig dat start in de beginfase van artrose.

Het Reumafonds heeft de aanzet gegeven tot een 10-jarig onderzoek naar het beloop van beginnende heup- en knieartrose om het natuurlijk beloop van de aandoening in kaart te brengen bij deelnemers met beginnende artrose klachten: CHECK (Cohort Heup En Cohort Knie). De algemene doelstelling van CHECK is het bestuderen van het beloop van de klachten en het analyseren van het mechanisme dat de klachten en gewrichtsschade veroorzaakt. Tevens beoogt CHECK markers voor de diagnose en het beloop van de gewrichtsschade te identificeren en prognostische factoren aan te tonen voor het voorspellen en verklaren van artrose.

De verwachting is dat we door de resultaten van het onderzoek, artrose eerder kunnen ontdekken bij patiënten en dat we daardoor beter kunnen behandelen. Ook hopen we dat we in de toekomst artrose beter kunnen voorkomen. Daarnaast heeft de CHECK studie als nevendoelstelling om een infrastructuur voor artrose onderzoek te creëren. De basis van de studie biedt namelijk de mogelijkheid om spin-off studies toe te voegen aan deze infrastructuur.

In *hoofdstuk 2* van dit proefschrift wordt gestart met het beschrijven van de opzet, de metingen en de eerste wetenschappelijk resultaten die in CHECK zijn gevonden. Het bijzondere van de CHECK studie is dat er gegevens verzameld worden over beginnende artrose op drie verschillende terreinen; we verzamelen informatie over de klinische, biochemische en radiologische variabelen. Met de beschrijving van *hoofdstuk 2* willen wij ook onderzoekers over de hele wereld in staat stellen samenwerkingen te starten, zodat er maximaal gebruik gemaakt kan worden van de beschikbare gegevens en de middelen.

De belangrijkste bevindingen, die door verschillende onderzoekers geconstateerd zijn binnen de CHECK studie, zijn:

Op klinisch gebied

Het beloop van beperkingen in activiteiten bij mensen met knie artrose varieert sterk tussen personen. Daarom is binnen de heterogene artrosepopulatie onderzocht of er subgroepen bestaan met een vergelijkbaar beloop van beperkingen in activiteiten. Drie verschillende subgroepen zijn geïdentificeerd. Deelnemers in subgroep 1 rapporteerden weinig of geen afname van beperkingen in activiteiten gedurende 5 jaar follow-up. Deelnemers in subgroep 2 rapporteerden matige beperkingen in activiteiten. Deelnemers in subgroep 3 rapporteerden veel of een toename in beperkingen in activiteiten gedurende 5 jaar follow-up. Deze subgroepen verschilden in socio-demografische, klinische en psychologische kenmerken.

Een gecombineerd psychologisch en neuromusculair model verklaart gedeeltelijk de ontwikkeling van de beperkingen in activiteit. Volgens dit model, leiden pijn en lage vitaliteit tot (verder) vermijden van activiteiten en daardoor tot spierzwakte en beperkingen van de activiteit.

Op radiologisch gebied

Er is een nieuwe methode ontwikkeld om knieën radiologisch te analyseren: Knee Images Digital Analyse (KIDA). Uit onderzoek is gebleken dat deze methode gevoelig is voor het meten van vroege progressie van radiologische schade. Op basis van KIDA zijn vijf fenotypes van radiologische progressie geïdentificeerd. Deze vertegenwoordigen de mate van progressie van de ziekte (ernstige of geen progressie), de fase van de progressie (vroeg of laat) en de prominente rol van de botdichtheid.

Statistische Shape Modelling (SSM) is een computer methode om de radiologische vorm van de heup te beoordelen. Deze methode wordt gebruikt om te testen of de vorm van het heupgewricht een risicofactor voor artrose kan zijn. Uit evaluatie van de heup röntgenfoto van CHECK deelnemers blijkt dat met behulp van deze SSM methode, de vorm van de heup een mogelijke heupprothese kan voorspellen.

Op biochemisch gebied

Er zijn 14 markers van kraakbeen, bot en synoviale metabolisme op baseline gemeten. Er is onderzocht of deze markers als een prognostische factor zouden kunnen dienen. Geen van deze markers zijn echter voldoende discriminerend voor diagnose van artrose of om de prognose van artrose over 5 jaar te voorspellen.

Het onderzoek dat beschreven is in dit proefschrift, is onderdeel van de CHECK studie. Het doel van dit proefschrift is om kennis te verkrijgen over het beloop

van de ziektekenmerken (pijn, fysiek functioneren) en de ontwikkeling van structurele schade bij beginnende symptomatische artrose. Met beginnende symptomatische artrose wordt het stadium van artrose bedoeld zonder herkenbare structurele gewrichtsschade maar wel met klachten die horen bij artrose.

Tegelijk met CHECK is er een studie over artrose opgestart in de US, het OsteoArthritis Initiative (OAI). Deze 4-jarige follow-up studie bestudeert het natuurlijk beloop van artrose, de risicofactoren voor het ontstaan en de progressie ervan. In feite zoeken beide studies, CHECK en OAI, antwoorden op dezelfde vragen in vergelijkbare populaties in totaal andere culturen. In *deel I* van dit proefschrift zijn deze twee cohorten met elkaar vergeleken, waarbij eerst de baseline gegevens van beide cohorten zijn vergeleken (*hoofdstuk 3*) en vervolgens is bekeken hoe deze gegevens zich ontwikkelden over 4 jaar (*hoofdstuk 4*). Er zijn opvallende verschillen tussen de twee cohorten ten aanzien van de radiologische schade en ervaren gezondheid. Er was bij start van de studies meer radiologische gewrichtsschade aanwezig in het OAI cohort in vergelijking met het CHECK cohort. Echter, bij de CHECK deelnemers was sprake van meer pijn, meer stijfheid en meer beperkingen in activiteiten en een slechtere gezondheid. Door het samenvoegen van gegevens uit beide cohorten hebben we geconstateerd dat een snelle verandering in gewrichtsschade gepaard gaat met een verergering van de pijn en fysiek functioneren. Opvallend is dat in beide cohorten zowel het niveau van deze klachten, als de verschillen tussen de OAI en CHECK deelnemers gedurende 4-5 jaar hetzelfde bleef. Onlangs is gemeld dat de deelnemers van het OAI cohort een betere zelf-gerapporteerde gezondheidstoestand hebben, in vergelijking met een landelijk representatieve populatie van artrose patiënten in de US. Dit zou een mogelijke verklaring kunnen zijn voor de waargenomen verschillen tussen beide cohorten. Een aantal variabelen die nauw samenhangen met de ontwikkeling van pijn en functionele problemen, zijn niet of niet identiek gemeten in beide cohorten. Dit geldt bijvoorbeeld voor het meten van comorbiditeiten, de soort pijn (constante of intermitterende pijn) en de copingstrategie. Daarom wordt ook benadrukt dat het belangrijk is om internationale consensus te hebben over het meten van dezelfde items, op dezelfde manier en op dezelfde tijdsmomenten in prospectieve cohorten van patiënten met chronische aandoeningen.

In *deel II* van dit proefschrift zijn we ons gaan focussen op de verschillen in ontwikkeling van de ziektekenmerken tussen de CHECK deelnemers. Eerst is de relatie tussen comorbiditeit (absoluut aantal andere aandoeningen dan artrose en de aanwezigheid van specifieke andere aandoeningen) en pijn, fysiek functioneren en mentale gezondheid van de deelnemers geëvalueerd (*hoofdstuk 5*). We constateerden dat vooral aanvullende aandoeningen in het houdings- en bewegingsapparaat en obesitas een negatief effect hebben op de pijn en de lichamelijke gezondheid. Maar ook de mentale gezondheidstoestand wordt in de beginfase van artrose beïnvloed door de aanwezigheid van andere aandoeningen. Een mogelijk mechanisme hierachter is het 'vermijdingsmodel'; de relatie tussen pijn, het vermijden van activiteiten en daardoor afname in spierkracht met als gevolg beperkingen in activiteiten. Dit mechanisme zou kunnen worden versterkt door pijnlijke andere aandoeningen.
Deze bevinding heeft een belangrijke implicatie voor de klinische praktijk van de arts in het behandelen van mensen met beginnende artrose. De focus van de arts moet niet alleen op artrose zelf zijn, maar ook op een mogelijke tweede aandoening bij de patiënt, omdat deze de pijn en de lichamelijke en geestelijke gezondheid ook verslechtert.

In *hoofdstuk 4* is geconcludeerd dat op groepsniveau de ontwikkeling van pijn gedurende 5 jaar redelijk stabiel blijft, maar dat er een aanzienlijke individuele variatie is. In *hoofdstuk 6* onderzochten we of er binnen deze heterogeniteit in beloop van pijn, subgroepen te identificeren zijn met een vergelijkbaar pijnbeloop. In dit hoofdstuk worden de drie gevonden subgroepen in het beloop van pijn beschreven. Bij de deelnemers in de ' goede prognose' subgroep trad na verloop van tijd een lichte daling op in de pijn en eindigde de deelnemers met weinig pijn. Deelnemers in de 'gematigde prognose' subgroep rapporteerden een wisselend beloop van pijn en in deze subgroep eindigde de pijn na verloop van tijd met milde pijn. Bij de deelnemers in de 'slechte prognose' nam de ernst van de pijn geleidelijk toe. Deze 3 verschillende subgroepen van pijn kunnen worden gekenmerkt door verschil in klinische kenmerken, coping strategieën, leefstijlfactoren en radiologische progressie van deelnemers. Deelnemers met een BMI (body mass index) boven de 25, of met een lagere opleiding, of met meerdere comorbiditeiten, of met ook pijn in de heup, of die de coping-strategieën 'zorgen maken' en 'rust nemen' vaak hanteren, hebben meer kans op een toename van pijn over de tijd. Afgezien van deze baselinekenmerken is het 'slechte pijn uitkomst' traject ook gerelateerd aan snelle verandering in gewrichtsschade. Deze bevinding komt overeen met de bevindingen van *hoofdstuk 4*, waarin is gesuggereerd dat mensen met een langzame radiologische verergering meer kans hebben zich aan te passen aan deze veranderingen in de fysiologie en daardoor minder pijn zouden kunnen krijgen. Uiteraard moeten deze bevindingen nog worden gevalideerd in een andere populatie met beginnende artrose.

In de inleiding van dit proefschrift is benadrukt dat het belangrijk is om een onderscheid te maken tussen het ziekteproces met structurele veranderingen in het gewricht, en klachten van de patiënt door artrose. In voorgaande hoofdstukken waren de klachten of de gevolgen van artrose het onderwerp van studie. In *hoofdstuk 7* is een specifiek onderdeel van de gewrichtsbeschadiging, namelijk de vorming van osteofyten, het onderwerp van nader onderzoek. Drie homogene subgroepen met verschillende trajecten van osteofyt vorming konden worden geïdentificeerd. Slechts bij een klein deel van de deelnemers was de osteofyt al bij aanvang aanwezig en nam hij in grootte toe. Bij het merendeel van de deelnemers was er nauwelijks verandering in deze röntgenschade waar te nemen. De analyses suggereerden verder dat een toename van de osteofyt vorming waarschijnlijker is als de deelnemer ouder is, zwaarlijvig is, reeds een eerste osteofyt heeft of een vernauwing van de gewrichtsspleet, of lokale klinische artrotische tekens heeft, zoals crepitus, warme gewrichten, pijngevoeligheid van het bot, of een gezwollen gewricht.
Om deze suggesties van prognostische factoren te bewijzen, zullen we de gegevens van osteofyt vorming over een langere tijdsperiode moeten analyseren.

In *hoofdstuk 8* worden de belangrijkste resultaten van het onderzoek besproken en geven we de mogelijke implicaties weer van deze bevindingen voor de arts, patiënt en wetenschap. Voor arts en patiënt is het belangrijk om kennis te hebben van het bestaan van subgroepen (trajecten) in de ontwikkeling van pijn, beperking van de activiteit en in de ontwikkeling van structurele schade. En te weten dat deze subgroepen verschillende prognostische en andere factoren hebben die het beloop van deze trajecten negatief kunnen beïnvloeden. Ook toont dit onderzoek aan dat slechts in een klein deel van de mensen met beginnende artrose ernstige toename in osteofyt vorming en radiologische ernst van de artrose zal optreden gedurende 5 jaar. Daarom zou de arts veel patiënten kunnen geruststellen dat het onwaarschijnlijk is dat hij/zij een progressieve beloop van de aandoening heeft in de eerste 5 jaar. Tegelijkertijd zou de arts de patiënt moeten informeren over het feit dat dit proces niet helemaal synchroon verloopt met het beloop van pijn. Het blijkt dat het beloop van pijn negatief beïnvloed kan worden door leefstijl, persoonlijke en psychische factoren. Ook hebben we aangetoond dat de arts voor het behandelen van de pijnlijke artrose oog moet hebben voor een tweede aandoening. Comorbiditeit en met name overige houdings- en bewegings- aandoeningen verslechteren de pijn en kwaliteit van leven. Bij de behandeling van beginnende symptomatische artrose dient ook aandacht te worden besteed aan verandering van de radiologische schade. Snelle radiologische verergering heeft een negatieve invloed op pijn, evenals persoonlijke, fysieke en sociale factoren (externe factoren). Kortom, de arts zou bij een patiënt met beginnende artrose het radiologisch proces, de klachten, de persoonlijke en externe factoren van de patiënt inzichtelijk moeten maken en zo nodig een gerichte behandeling voorstellen.

Het proefschrift bevestigt de gedachte dat we in artrose op zoek moeten gaan naar specifieke homogene fenotypes (subgroepen) van het artrose proces (radiologische schade) in het begin en in het beloop van klachten en symptomen van de patiënt. Een betere karakterisering van symptomen, schade aan het gewrichtsweefsel en externe factoren, kan uiteindelijk resulteren in het vinden van de juiste behandeling voor de juiste patiënt. —

CURRICULUM VITAE

Janna (Janet) Wesseling was born on May 26th 1972 in Assen, the Netherlands. In 1990 she graduated secondary school (VWO) at the Christelijke Scholengemeenschap Assen.

In September 1990 she started the study Human Movement Sciences at the University in Groningen with Rehabilitation as specialization, and obtained her Master of Science degree in 1994.

Subsequently, she started in the same year her study Physiotherapy at the Hogeschool in Utrecht. In 1997, she started as a physiotherapist in the Allied Health Care Center for Rheumatology and Rehabilitation in Groningen. In this primary care center she developed together with her colleagues a multidisciplinary treatment program for fibromyalgia and she treated in particular patients with a chronic disease.

In 2001 she started as a research coordinator of the Dutch Arthritis Foundation funded CHECK (Cohort Hip & Cohort Knee) study at the department of Rheumatology & Clinical Immunology, University Medical Center Utrecht. During her work she obtained the Master of Epidemiology at EPIDM (EMGO) of the VU Medical Center Amsterdam.

She was in the department also involved, as project manager, in different projects aiming to improve care and integration of outpatient care and science.

Currently, she is still working for CHECK, to finish this 10 year follow-up study and to make the data available, so it can be used by other researchers to allow optimal benefit. —

photo | Jeroen Dietz (detail)

DANK JULLIE WEL

‘Wordt het een spannend boek?’
‘En gaan veel mensen jouw boek dan ook lezen?’ vroegen mij kinderen toen ik hun uitlegde wat ik aan het doen was. Dit heeft mij aangemoedigd om er een boeiend boek van te maken. Een boek waarin de lezer geprikkeld wordt om de nieuwe wetenschappelijke inzichten te gaan lezen en waarin de lezer ook daadwerkelijk een beeld krijgt van CHECK het onderzoek.

Dit proefschrift was er niet geweest zonder de inzet van de 1,002 deelnemers die al (bijna) 10 jaar lang één keer per jaar naar het onderzoekscentrum komen voor de vragenlijst, het lichamelijk onderzoek, röntgenfoto’s en het bloed en urine onderzoek. Hartelijk dank aan alle deelnemers die zich hebben ingezet voor CHECK!

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‘Het leven is lang, de wereld is groot, het is een kwestie van lef… en geluk.’

Het is een prachtig vormgegeven boek geworden! Voor de vormgeving, lay-out en foto’s komt alle eer aan de grafisch ontwerper Astrid.
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En tot slot mijn ‘kleine’ inspiratie en energiebronnen; zoek je naam!
Mart, jouw naam hoort ook hier te staan.
Dankzij jou!

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