Mortality and other outcome measures in osteoarthritis

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Chapter 1

General introduction

INTRODUCTION

Osteoarthritis (OA) is a common and heterogeneous disease, which can involve various movable joints. The hand, knee and hip joints are most commonly involved. OA is considered to be initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first at molecular level (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic abnormalities (characterized by cartilage degradation, osteophyte formation and bone remodelling, joint inflammation and loss of function), that can culminate in illness.[1] Pathologic abnormalities of soft tissue structures such as synovium, periarticular muscles, ligaments, meniscus may also occur.

Epidemiology

The prevalence of OA may differ depending on the definition that is used. Radiographic OA occurs more often than symptomatic OA. In the Netherlands, the prevalence of OA for patients visiting the general physician has been estimated to be 53.8 per 1 000 men and 88.5 per 1 000 women in 2011, resulting in a total estimate of well over one million patients in the whole country.[2] Knee OA has been reported to be the most prevalent, followed by hip OA and peripheral OA.
OA is a multifactorial disease and despite the discovery of many mechanical and systemic risk factors such as injury, mechanical stress and genetic factors, its precise pathogenesis has remained elusive.[3] What is, however, well recognised, is that age, sex and obesity are among the most well known risk factors.[4-6]

Osteoarthritis: clinical presentation

OA has a major impact on morbidity. The WHO Global Burden of Disease Study reported in their 2013 update that knee OA is the 13th cause of global years lived with disability (YLD).[7] In the Dutch population OA ranked sixth as contributor to disability with 122 400 YLDs.[8] YLDs equated disability adjusted life-years. Whether OA has an impact on mortality is less clear. In 2011 Nuesch et al published a study that suggested an association of OA with mortality.[9] In this population based cohort study using survey data from general practices in England, patients with radiographic OA were at higher risk of death than those in the general population. In addition, it was shown that a history of diabetes, cancer, or cardiovascular disease and the presence of walking disability were major risk factors.
Symptoms due to OA may be highly variable, since they depend upon factors such as the affected joint, the severity of OA and the number of affected joints.[4,10] Important clinical symptoms are pain, stiffness and disability. For an optimal evaluation of the outcome in OA, all domains of interest to patients should

be assessed. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) has recently developed a new preliminary set of domains for hand OA, taking patient perspectives into account. The OMERACT has indicated that other factors such as hand strength, hand mobility and aesthetic damage should also be taken into account.[11]

OA as a biopsychosocial model

Two patients with the exact same diagnosis and similar objective clinical features may describe in a completely different way how the disorder impact their lives. Leventhal's Common Sense Model (CSM) offers a possible explanation for this phenomenon. In this model, situational stimuli as disease processes may influence the representation of the health threat or emotion as illness perceptions, which in turn may involve coping responses in the process and ultimately lead to appraisal of the clinical outcome**.** Feedback loops also interlink the different components in this self regulation model (Figure 1).[12] The CSM is supported by cross-sectional studies in which illness perceptions of OA patients were associated with limitations in daily activities and quality of life,[13-15] while longitudinal studies reported an association between changes in illness perceptions with changes in outcomes.[16,17] The role of coping in this model in OA has, however, not been studied well.

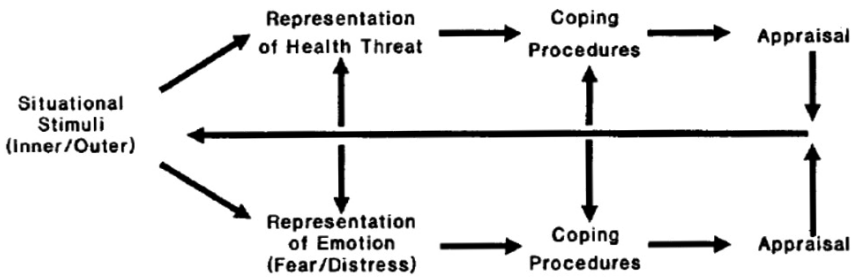

Figure 1. Leventhal's Common Sense Model (Leventhal 1992)

Imaging

Radiographs can be used to support the diagnosis of OA and to monitor the progression of the disease. Structural abnormalities of osteoarthritic joints, visualized as osteophytes and joint space narrowing on radiographs, are associated with hand pain, although this association is weak.[18,19]

Studies using ultrasonography have demonstrated that soft tissue abnormalities such as synovial thickening with positive Power Doppler signal is often present in the joint. Moreover, inflammatory ultrasound features have been shown to be associated with pain and radiographic damage, which support their potential

role in the disease process in hand OA. However, a difference remains between ultrasonography and clinical findings.[20,21]
Magnetic resonance (MR) imaging is a modern imaging method, which can visualize both hard and soft tissue abnormalities. In addition, abnormalities in subchondral bone, such as bone marrow lesions (BML), can be visualised (Figure 2). Studies have shown that BMLs are often present in knee OA and seem to play a role in pain[22], while in hand OA this abnormality has been rarely studied.

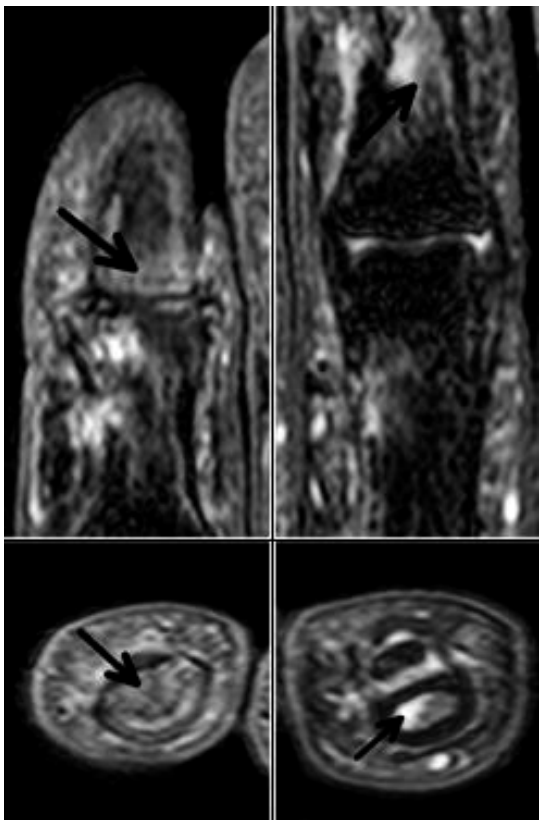

Figure 2. Magnetic Resonance Imaging: bone marrow lesions (arrow) were present in the second distal interphalangeal joint (A) and third proximal interphalangeal joint (B)

A MR imaging scoring method has been developed by Haugen et al as the first available scoring tool to assess OA abnormalities in the interphalangeal joints. This method incorporates important hand OA abnormalities such as synovitis, flexor tenosynovitis and BMLs and studies are now emerging for validation of this tool.[23,24] The use of MR imaging can improve our understanding of hand OA and the assessment of the burden of disease.

Aim of thesis

The aim of this thesis is:

1. To gain insights into the determinants of outcome in hand osteoarthritis
2. To investigate mortality in osteoarthritis

The HOSTAS study

Several of the studies presented in this thesis made use of the HOSTAS study. The Hand OSTeoArthritis in Secondary care (HOSTAS) study is an ongoing observational cohort study which has enrolled patients with hand OA consecutively since 2009. The study aims to investigate determinants of outcome in hand OA patients. Inclusion occurred when patients consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center for hand complaints and these hand complaints were diagnosed as primary hand OA. To reach a diagnosis, history, physical and radiographic examinations were used. Patients with secondary OA or hand complaints due to other disease causes were excluded. In total, over 500 patients are enrolled. Their OA status and its determinants are evaluated bi-annually during a visit to the LUMC and annually via questionnaires.

OUTLINE OF THE THESIS

In **part I** we investigate which determinants play a role in the clinical outcomes pain, disability, aesthetic damage and structural damage in hand OA, using the CSM model as a guide. **Chapter 2** we examine the role of joint-specific factors and coping styles on disability in hand OA patients. In **chapter 3** we describe the prevalence of aesthetic dissatisfaction in hand OA patients, its impact on daily life and their determinants such as osteoarthritic joint abnormalities, illness perceptions, anxiety and depression. In **chapter 4** we evaluate the presence of synovitis, tendon involvement and BMLs in hand OA, and their association with hand pain. **Chapter 5** concerns the association between BMLs and synovitis and radiographic progression of hand OA over 2 years.

Part II evaluates the association between OA and mortality. In **chapter 6** we investigate the mortality rates in patients with OA from two cohorts, the "Genetics ARthrosis and Progression"(GARP) cohort, including patients with primary familial OA at multiple sites, and the "Osteoarthritis Care Clinic", including patients with primary OA from the rheumatology outpatient clinic, in comparison to the general population. We also investigate specifically cardiovascular mortality. Many studies have investigated the association between OA and mortality with different conclusions. Therefore, we have performed a systematic literature review to summarise and determine the association between OA and mortality in **chapter 7**.

Finally, we provide a summary of the study results in the thesis and present a general discussion and future perspectives in **chapter 8**.

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PART I

Disease course and its determinants of outcome in hand osteoarthritis in secondary care

2

Chapter 2

Coping styles and disability in patients with hand osteoarthritis

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ABSTRACT

OBJECTIVE

Coping responses have been shown to determine health outcomes in chronic diseases. We examined the role of joint-specific factors and coping styles on disability in patients with hand osteoarthritis (OA).

METHODS

Primary hand OA patients who consulted secondary care, underwent physical examination to assess number of joints with bony joint enlargements, pain upon palpation, soft tissue swelling, deformities and limitations in motion. Coping styles were assessed with Coping with Rheumatic Stressors (CORS). Disability (score ≥5) was assessed by Functional Index for Hand OA (possible score 0-30) cross-sectionally and after 1 year.

With multivariate logistic regression, joint-specific variables and coping styles were associated with disability cross-sectionally and after 1 year, adjusted for age, sex, and BMI.

RESULTS

314 patients (88% women, mean age 61.4yrs) were included in the cross-sectional analyses, 68% were considered as disabled. Longitudinal data after 1 year were available in 173 patients (71% disabled). In multivariate analysis including all joint-specific factors, only painful joints and joints with limitations in motion were associated with disability.

Disadvantageous scores for the coping scales "comforting cognitions", "decreasing activity" and "pacing" were positively associated with disability cross-sectionally. Disability after 1 year was only associated with the coping scales "decreasing activity" and "pacing". Joint-specific factors were also associated with disability, independently of coping styles.

CONCLUSION

In patients with hand OA, joint-specific factors and coping styles 'decreasing activity' and 'pacing' were both associated with disability. Our results suggest that interventions should aim at joint-specific complaints as well as changing coping styles to improve functional outcome.

INTRODUCTION

Hand osteoarthritis (OA) is a common disorder, characterized by nodes and deformities of typically the distal interphalangeal (DIP), proximal interphalangeal (PIP), and the first carpometacarpal (CMC-1) joints.[1,2] Clinical burden of hand OA consists of pain and impaired functional ability.[3] It is unclear which factors contribute to these functional limitations, but earlier studies in OA, especially in patients with knee OA, showed that not only disease specific factors but also psychosocial factors are of importance.[4-6]

According to Leventhal's common sense model (CSM), illness perceptions (cognitive and emotional) and coping responses are both determinants of health outcomes. Stimuli in the form of symptoms serve as a starting point in the CSM model, which are interpreted and elaborated upon to form representations or illness perceptions and subsequently act as a guide to coping responses, which finally leads to appraisal of outcomes.[7] As coping can be modified, it is interesting to further elucidate this hypothesis.[8]

Studies investigating coping strategies of OA patients have been sparse [9-13] while even fewer studies focused on hand OA in particular.[10,14]

According to a semi-structured interview study by Hill et al, a variety of coping strategies are used by hand OA patients, particularly problem based coping, whereby patients adapt and find a different way of doing things. [14] However, from this study it remains unclear how these coping mechanisms may in turn influence clinical outcome.

The Coping with Rheumatic Stressors (CORS) is a reliable and validated arthritis specific questionnaire, which measures coping strategies directed at the most prominent chronic stressors of rheumatoid arthritis: pain, limitations, and dependency.[15] The questionnaire has also been used to investigate coping strategies in patients with other rheumatic diseases, such as ankylosing spondylitis, but has not been used in OA before.[16]

The aim of the present study was to examine the role of joint-specific factors and coping styles on disability in patients with hand OA.

METHODS

Study design

The present study is part of the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing prospective follow-up study which has enrolled patients with hand OA consecutively since 2009. The HOSTAS aims to investigate determinants of outcome in patients with hand OA. Patients were included when they consulted

a rheumatologist at the outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and when the treating rheumatologist diagnosed these hand complaints as primary hand OA. History, physical and radiographic examination were used to make the diagnosis. Patients with hand complaints due to other disease causes or secondary OA due to other rheumatic diseases were excluded. Written informed consent was obtained from all participants according to the declaration of Helsinki. The study was approved by the LUMC medical ethical committee.
In the present study, patients have been included that had filled in a coping questionnaire (henceforth referred to as 'baseline'). In the follow-up study, patients have been included of whom 1-year follow-up data were available.

Demographics and clinical characteristics

Standardized questionnaires, which are filled in every year, were used to collect demographics and clinical characteristics, which included age, sex, body mass index (BMI) and symptom duration.
At inclusion and once every two years thereafter, participants underwent standardized physical examination of their hands by a trained research nurse. The DIP joints, PIP joints, interphalangeal thumb (IP-1) joints, metacarpophalangeal (MCP) joints and CMC-1 joints were evaluated for the number of joints with bony joint enlargements (0-30), pain upon palpation (total range score 0-90, range 0-3 for each joint, higher score=more pain) and soft tissue swelling (0-30). Joints with deformities (0-22) and limitations in motion (total range 0-66, range 0-3 for each joints, higher score=more limitations) were also assessed in the DIP, PIP, IP-1, MCP-1 and CMC-1 joints.

Radiographs

At inclusion and once every two years thereafter conventional radiographs of the hands (dorso-volar) were obtained. The DIP joints, PIP joints, IP-1 joints, MCP joints and CMC-1 joints were scored by WD using the Kellgren-Lawrence grading scale 0-4 (maximum score 120). WD was blinded for clinical and demographic data. Intra-reader reproducibility was assessed on a randomly selected sample (n=31) of radiographs and was high (ICC 0.95, 95% confidence intervals (CI) 0.89-0.97).

Disability

Since January 2011, disability was assessed at inclusion and at annual follow-up visits by the Functional Index for Hand OA (FIHOA), a 10 item questionnaire with items rated in terms of difficulty on a four point Likert scale (0 = possible without difficulty and 3 = impossible).[17] The scale ranges from 0 to 30. A FIHOA score of ≥5 was considered as disability.[18]

Coping

Coping was assessed with the Coping with Rheumatic Stressors (CORS), which measures eight coping strategies that are associated with pain (3 strategies), limitations (3 strategies) and dependence (2 strategies). Three scales measure strategies of coping with pain: comforting cognitions (9 items), decreasing activities (8 items) and diverting attention (8 items). Three coping scales refer to limitations: optimism (5 items), pacing (10 items) and creative solution seeking (8 items). Two scales measure dependency: making effort to accept one's dependence (6 items) and showing consideration (7 items). For each item the patients report how often they made use of that particular coping mechanism (range 1-4, higher score=more usage). Its metric properties for reliability are good (Cronbach's alfa 0.73-0.88, test-retest reliability 0.79-0.91 for all scales). Its correlation with variables such as sex, age, education and symptom duration was low.[15]

The assessment of the CORS occurred after January 2011 in all patients at the inclusion in the study and at biannual follow-up visits. In the current study the first CORS that was filled in was used.

For the analyses the CORS scales were divided into tertiles. The lowest tertile represented the most beneficial scores [19] and was used as reference category.

Data analysis

To investigate the determinants of the disability, odds ratio (OR) with 95% confidence intervals (CI) were calculated using multivariate logistic regression as measures of relative risk, while adjusting for age, sex and BMI. In addition, multivariate analyses were performed adjusting for joint-specific variables when appropriate. In individual patients data from questionnaires, physical examination and radiographs were acquired or assessed at the same time point.

Multivariate analyses were also performed for reporting disability after 1 year, adjusting for age, sex, BMI, joint-specific variables and baseline FIHOA.

For the CORS missing data were imputed according to the user manuals. Imputation for the missing data in the FIHOA was performed if 2 or fewer items were unanswered, by replacing missing data by the mean of answered items. If more than 3 items were missing the FIHOA was considered as missing.

All analyses were done using SPSS version 20 (SPSS Inc, Chicago, IL)

RESULTS

Study population

Between May 2009 and April 2013, 354 patients were included in the HOSTAS study. 91% of the patients met the ACR criteria for hand OA. The FIHOA and

CORS were completed by 315 patients, of which one patient was excluded due to incomplete CORS data. Therefore 314 (89%) patients were included in the present study; of these 197 patients participated in the HOSTAS study from 2011 and 117 patients started participation between 2009 and 2011 (Figure 1). A standardized physical examination and radiographs of their hands were available at the time point that the questionnaire was filled in 303 and 301 patients, respectively.
Longitudinal FIHOA data with 1 year follow-up were then obtained (range 0.8-1.6 years). Thirty-eight patients declined participation. The FIHOA was completed by 173 of the 211 (82%) patients eligible (follow-up after first available FIHOA was at least 1 year).
The patients' characteristics of those included in the cross-sectional study and of the subpopulation included in the longitudinal study are shown in Table 1.

Table 1. Baseline characteristics of 314 patients with clinical hand osteoarthritis (OA) consulting a Rheumatology outpatient clinic, of which 173 patients were followed prospectively

	Total population n=314	**Population with follow-up n=173**
Women, n (%)	275 (87.6)	149 (86.1)
Age, mean (SD), years	61.4 (8.9)	61.3 (8.6)
BMI, kg/m^2	26.4 (17.6-48.4)	26.4 (17.6-39.0)
Hand OA according to ACR criteria, no. (%)	91.1	92.5
Kellgren-Lawrence score (range 0-120)	21 (0-75)	21 (0-75)
Symptom duration, years	5.7 (0.1-58.7)	5.2 (0.1-58.7)
Time since diagnosis, years	2.0 (0.0-35.2)	2.0 (0.0-31.7)
FIHOA (range 0-30)	8 (0-24)	8 (0-24)
Patients with diability, no. (%)	212 (68)	118 (68)
CORS scales		
Pain-comforting cognitions (range 9-36)	27 (9-36)	26 (9-36)
Pain-decreasing activity (range 8-32)	17 (8-28)	17 (8-28)
Pain-diverting attention (range 8-32)	19 (8-32)	19 (8-31)
Limitations-optimism (range 5-20)	16 (7-20)	16 (7-20)
Limitations-pacing (range 10-40)	25 (10-40)	25 (10-40)
Limitations-creative solutions (range 8-32)	20 (8-32)	20 (8-32)
Dependency-accepting (range 6-24)	13 (6-24)	13 (6-24)
Dependency-consideration (range 7-28)	20 (7-28)	20 (7-28)

Median (range), unless otherwise stated

BMI= body mass index; FIHOA= Functional Index for Hand Osteoarthritis; CORS = Coping with Rheumatic Stressors; ACR=American College of Rheumatology

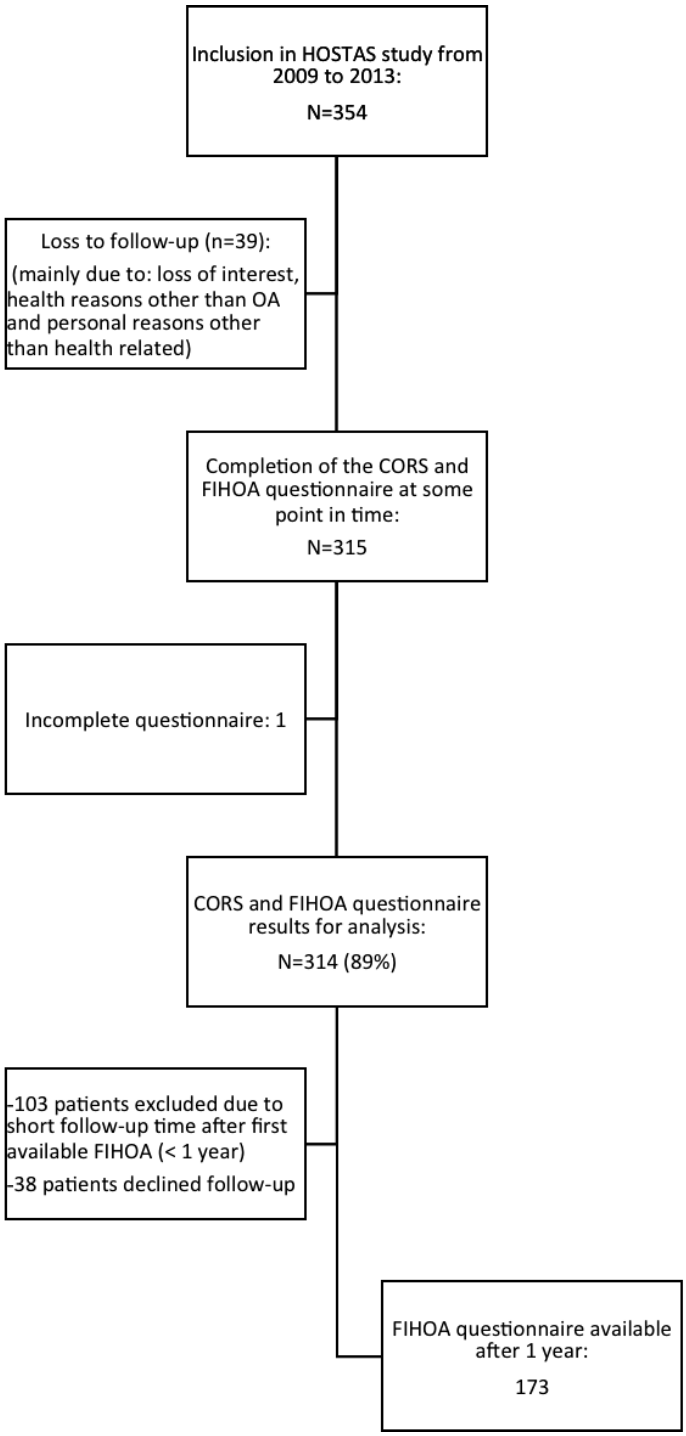
Inclusion in HOSTAS study from 2009 to 2013:
N=354
Loss to follow-up (n=39):
(mainly due to: loss of interest, health reasons other than OA and personal reasons other than health related)
Completion of the CORS and FIHOA questionnaire at some point in time:
N=315
Incomplete questionnaire: 1
CORS and FIHOA questionnaire results for analysis:
N=314 (89%)
-103 patients excluded due to short follow-up time after first available FIHOA (< 1 year)
-38 patients declined follow-up
FIHOA questionnaire available after 1 year:
173

Figure 1.

The patients' characteristics of the subpopulation are similar to the characteristics of the total population.

The median FIHOA score was 8 (range 0-24) at baseline and 9 (range 0-28) at follow-up. At baseline, 68% of the patients could be considered as disabled as defined by a FIHOA score of ≥5. After 1 year, 71% (122 of 173) of the patients had disability due to their hand OA.

Disease specific determinants and disability

We hypothesized that disease specific features of hand OA could play a role in disability. Multivariate analyses on cross-sectional data were used to investigate the association of these features with disability (Table 2). These analyses demonstrated that joints painful upon palpation, joints with deformity and limited in motion were independently positively associated with disability. The objective features joints with bony joint enlargement and soft tissue swelling were not associated with disability. KL score was also associated with disability, as was the elapsed time since diagnosis. In multivariate analysis including all joint-specific factors, only painful joints and joints with limitations in motion remained associated.

Table 2. Univariate and multivariate analyses for disease specific determinants of disability in hand osteoarthritis (OA) patients (n=314)

	Prevalence	Crude OR	Adjusted OR*	Adjusted OR[&]
Symptom duration	5.7 (0.1-58.7)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	0.98 (0.94-1.02)
Time since diagnosis	2.0 (0.0-35.2)	1.11 (1.03-1.19)	1.11 (1.03-1.20)	1.08 (0.99-1.18)
Kellgren-Lawrence score (range 0-120)	21 (0-75)	1.02 (1.003-1.04)	1.02 (1.003-1.04)	1.00 (0.98-1.03)
Joints with bony enlargements, no. (range 0-30)	11 (0-24)	1.01 (0.96-1.05)	1.01 (0.96-1.06)	
Joints painful upon palpation, no. (range 0-90)	3 (0-53)	1.12 (1.06-1.18)	1.11 (1.05-1.18)	1.14 (1.06-1.23)
Joints with soft tissue swelling, no. (range 0-30)	0 (0-17)	1.08 (0.95-1.23)	1.09 (0.96-1.23)	
Deformed joints, no. (range 0-22)	5 (0-17)	1.09 (1.01-1.17)	1.10 (1.02-1.19)	1.00 (0.90-1.11)
Joints limited in motion, no. (range 0-22)	7 (0-48)	1.07 (1.04-1.11)	1.08 (1.04-1.11)	1.06 (1.01-1.11)

*Adjusted for sex, age, BMI

[&]Multivariate analyses with sex, age, BMI, symptom duration, time since diagnosis, Kellgren-Lawrence score, painful joints upon palpation, deformed joints and joints limited in motion

BMI= body mass index

In further analyses on the association between coping strategies and disability, we adjusted for the determinants joints painful upon palpation and limited in motion. The joint-specific factors were also associated with disability, independently of coping styles.

Coping strategies and disability

Of the 'coping with pain' strategies, the strategy 'comforting cognitions' with a median of 27 (range 9-36) was the most frequently used strategy. The other pain strategies were employed less often. 'Optimism' was the most often used 'coping with limitations strategy', with a median of 16 (range 7-20). Patients used 'consideration' more as a 'coping with dependency' strategy than 'accepting' (Table 1).

Coping with pain' strategies and disability

Cross-sectional multivariate analyses investigating the association between coping styles and disability are shown in Table 3. The lowest tertiles represented the most beneficial scores.

In cross-sectional analysis, the highest tertiles for the coping with pain scales 'comforting cognitions' and 'decreasing activity' were positively associated with disability. Lower scores on the 'comforting cognitions' scale were more disadvantageous and associated with more disability. A positive dose-response association between the CORS pain coping strategy 'decreasing activity' and disability was also found (Table 3). The strategy 'diverting attention' was not associated with disability.

Longitudinal analyses showed that the strategy 'comforting cognitions' was not associated with disability, while a significant dose-response relation still existed between the coping with pain strategy 'decreasing activity' and disability after 1 year (Table 4).

'Coping with limitations' strategies and disability

The coping with limitations strategy 'optimism' was not associated with disability either cross-sectionally or longitudinally. 'Pacing' as a strategy of coping with limitations showed a dose-response relation with disability in both the cross-sectional and longitudinal analyses. Cross-sectional and longitudinal analyses showed that 'creative solutions' was also not associated with disability.

Table 3. Association between disability, defined as FIHOA ≥ 5,and tertiles of coping strategies in hand OA patients (n=314)

CORS strategies tertiles*	No disability	Disability	Adjusted OR (95%CI)**
Pain-comforting cognitions			
>28	44	67	1.0
25-28	35	69	1.32 (0.71-2.43)
9-24	23	74	2.14 (1.08-4.22)
Pain-decreasing activity			
8-14	41	52	1.0
15-18	40	76	1.58 (0.85-2.95)
>18	21	83	2.59 (1.28-5.25)
Pain-diverting attention			
≥21	38	66	1.0
17-<21	32	80	1.57 (0.82-2.99)
8-16	32	64	1.38 (0.71-2.66)
Limitations-optimism			
>17	32	60	1.0
15-17	44	80	0.95 (0.51-1.79)
7-14	26	72	1.69 (0.86-3.36)
Limitations-pacing			
10-22	50	65	1.0
23-27	30	61	1.68 (0.88-3.21)
>27	22	86	3.07 (1.53-6.16)
Limitations-creative solutions			
>22	25	67	1.0
19-22	26	79	1.42 (0.70-2.88)
8-18	51	66	0.56 (0.29-1.06)
Dependency-accepting			
6-11	32	58	1.0
12-15	33	76	0.99 (0.51-1.90)
>15	33	78	1.10 (0.56-2.15)
Dependency-consideration			
>21	35	66	1.0
>18-21	24	69	1.93 (0.96-3.88)
7-18	39	76	1.16 (0.62-2.16)

#Adjusted for sex, age, body mass index, pain intensity score, joints limited in motion

*Lowest tertile represents the most helpful illness representation and serves as reference category

FIHOA= Functional Index for Hand Osteoarthritis

Table 4. Association between disability after 1 year, defined as Functional Index for Hand Osteoarthritis (FIHOA) ≥5, and tertiles of coping strategies at baseline in hand OA patients (n=173)

CORS strategies tertiles*	No disability	Disability	Adjusted OR (95%CI)*
Pain-comforting cognitions			
>28	17	42	1.0
25-28	18	43	0.57 (0.19-1.76)
9-24	16	36	0.39 (0.11-1.34)
Pain-decreasing activity			
8-14	21	31	1.0
15-18	21	40	1.19 (0.40-3.56)
>18	9	50	5.68 (1.52-21.19)
Pain-diverting attention			
≥21	17	44	1.0
17-<21	15	45	0.77 (0.24-2.42)
8-16	19	32	0.47 (0.15-1.44)
Limitations-optimism			
>17	18	40	1.0
15-17	18	42	0.85 (0.28-2.57)
7-14	15	40	0.60 (0.19-1.92)
Limitations-pacing			
10-22	28	35	1.0
23-27	12	37	4.40 (1.32-14.65)
>27	11	50	5.00 (1.45-17.30)
Limitations-creative solutions			
>22	9	44	1.0
19-22	18	38	0.25 (0.07-0.90)
8-18	24	40	0.43 (0.13-1.37)
Dependency-accepting			
6-11	15	32	1.0
12-15	18	51	0.91 (0.29-2.85)
>15	16	38	0.64 (0.19-2.11)
Dependency-consideration			
>21	14	45	1.0
>18-21	12	35	0.52 (0.14-1.88)
7-18	22	41	0.34 (0.11-1.08)

[&]Adjusted sex, age, BMI, pain palpation, limited in motion, FIHOA baseline

*Lowest tertile represents the most beneficial illness representation and serves as reference category

FIHOA= Functional Index for Hand Osteoarthritis

‘Coping with dependence’ strategies and disability

The coping with dependency was measured using two scales: making effort to accept one’s dependence and showing consideration. No association was seen between these coping strategies and disability in either cross-sectional or longitudinal analyses.

DISCUSSION

In the present study we investigated the association between coping strategies and disability in patients with hand OA using validated questionnaires and longitudinal data. We found that patients who cope with pain by employing the strategy ‘comforting cognitions’ less often, experienced more disability. More employment of the strategy ‘decreasing activity’ led to more disability. Patients who cope with the limitations due to their hand OA by ‘pacing’ also experience more disability. Disability after 1 year was only associated with the coping scales ‘decreasing activity’ and ‘pacing’, and provided further proof for a causal relationship between these factors and disability; these associations were independent from joint-specific factors. The joint-specific factors painful joints and joints with limitations in motion were also associated with disability, independently of coping styles.

‘Comforting cognitions’ was associated with disability in our cross-sectional data, but no longer associated after a year. This suggests that ‘comforting cognitions’ does not cause patients to experience disability. It is rather more likely that disability causes the use of this strategy.

‘Decreasing activity’ as a way of coping with pain and ‘pacing’ as a way of coping with limitations were both associated with disability, both in cross-sectional and longitudinal data, suggesting a causal relationship. We considered these coping scales to be passive coping scales. The results are in line with our expectations. Limitation of activity may result in deterioration of muscular strength and endurance.[20] It is thus likely that patients using ‘limiting activity’ as a way of coping with pain are at more risk of developing disability independent of disease status.

Though studies investigating coping strategies in hand OA have been rare, studies have been conducted in diseases such as rheumatoid arthritis (RA). Previous studies with RA patients reported that ‘decreasing activity’ was associated with psychological distress, a negative disease impact and decrease in dexterity, which is in line with our results. [21,22]

However, in RA 'pacing' was not related to changes in dexterity, while we did find an association between 'pacing' and disability in our study. It is possible that differences in underlying disease mechanisms of RA and OA may explain this difference in results. Also in a study which investigated coping in knee and hip OA, the coping scores were different when comparing to patients with RA and other chronic painful conditions.[9]

In contrast to our findings, another cross-sectional study did not find an association between coping with pain strategies and disability in hand OA patients.[10] In the study by Stukstette et al, the Pain Coping Inventory (PCI) questionnaire was used, which measured a patient's strategies for dealing with pain. Though the PCI is able to investigate an association between coping with pain strategies and daily activities, it does not measure a patient's strategies for dealing with limitations or dependency and our results could not be compared to theirs for these dimensions of coping. In their study, an univariate association was found between coping with pain strategies and limitations in daily activities, but no longer in the multivariate model which also included OA disease specific factors such as pain and joint stiffness. Whether these coping with pain strategies were also not associated with limitations in daily activities over time is unknown, due to a lack of longitudinal data. Aside from these differences in the measuring instrument, our findings may differ due to differences in patient inclusion criteria and subsequent differences in patient characteristics.
In Stukstette's study patients were only included if they scored at least 9 on the Australian Canadian Osteoarthritis Hand Index (AUSCAN) (range 0-36) and fulfilled the ACR hand OA criteria, while the HOSTAS included all patients who sought care in the LUMC. This suggest that though coping with pain strategies may independently be associated with joint-specific factors, though differences may still exist in the coping styles of more severely OA affected individuals versus the less severely affected patients.

Though studies in hand OA may be sparse, there have been studies investigating coping strategies and disability in OA located elsewhere. A study investigating the relationship between coping with pain strategies and functional impairment in knee and hip OA found a good correlation for passive pain coping dimensions and function, with more impaired patients using more passive coping.[9] In another study investigating the use of various coping styles at baseline and pain and disability at follow-up in knee and hip OA patients, the passive coping style of 'resting' predicted a higher level of disability, supporting our own findings that passive coping strategies were associated with more disability.[23]

If passive coping strategies are associated with more disability, one would hypothesize that active coping strategies are associated with less disability. However, as we have seen previously in a clinical study, active coping strategies are not associated with less disability.[24] It is therefore not surprising that we were also unable to find an association between active coping strategies such as creative solutions with less disability in our study. We suspect that the employment of creative solutions may be a result rather than a cause of disability. However, more research will be necessary to confirm this hypothesis.

Our study results also have their limitations. The HOSTAS study is an observational study which included both patients with recent diagnosis of OA and those who were diagnosed many years go with also a wide variation in symptom duration. As patients did not all enter at the time when OA symptoms first began or when the diagnosis was made, we hypothesized that this may influence our results. Fortunately, our analyses showed that the duration of symptoms is not a determinant of disability. While the association between the elapsed time since diagnosis and disability may show a trend in multivariate analyses, its influence seemed to be very limited.

We have observed both a dose response relationship and a temporal relationship in longitudinal analyses, for the association between the coping strategies 'decreasing activity' and 'pacing' and disability. Causality is always difficult to investigate in an epidemiological study, but since these associations fulfill Hill's criteria for causality, it is likely that a causal relationship between these passive coping mechanisms and disability exists.[25] Therefore these negative coping skills could serve as a target for therapy.
In previous research it has been demonstrated that education on OA can improve clinical outcomes.[26,27] Evidence for the efficacy of psychological interventions such as pain coping strategies skills training in OA patients is also growing.[8,28,29]
By better understanding which coping strategies may influence physical limitations, psychological interventions such as psychoeducation and cognitive restructuring can be employed to improve clinical outcome by addressing coping strategies.[8,28,29]
Since coping mechanisms are considered to be influenced by illness perceptions, as suggested by the CSM, further research to elucidate their relationship is warranted.

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3

Chapter 3

Aesthetic dissatisfaction in patients with hand osteoarthritis and its impact on daily life

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ABSTRACT

OBJECTIVE

To evaluate nature and extent of aesthetic dissatisfaction in patients with hand osteoarthritis (OA), and to investigate its impact on daily life and their determinants.

METHODS

Patients with primary hand OA, consulting secondary care, underwent physical examination for number of joints with bony joint enlargements, soft tissue swelling and deformities, and radiographs. Questionnaires were filled in to measure pain and function(Functional Index for Hand Osteoarthritis), dissatisfaction with the appearance of the hands and its impact(aesthetic scales from Michigan Hand Outcomes Questionnaire), anxiety and depression(Hospital Anxiety and Depression Scale) and illness perceptions (Illness Perception Questionnaire – Revised). Odds Ratio (OR) with 95% confidence intervals (CI) were calculated using multivariate logistic regression as measures of relative risk for dissatisfaction with appearance or its impact, adjusted for age, sex, BMI and joint-specific abnormalities (bony joint enlargements, deformities or radiographic severity), self-reported pain and function.

RESULTS

Of 247 patients (mean age 61.6 years, 88% women), 63 patients (26%) were aesthetically dissatisfied and 33 patients (13%) reported impact on daily life due to dissatisfaction.

Patients with joint-specific abnormalities were at higher risk for reporting dissatisfaction. Patients who reported impact, also reported more depression and negative illness perceptions, independently from joint-specific abnormalities.

CONCLUSION

Hand OA patients report aesthetic dissatisfaction with their hands regularly, especially in those with joint abnormalities. This dissatisfaction has negative impact in a small group of patients who also reported more depression and negative illness perceptions. These results indicate the influence of psychosocial factors on outcome measures in patients with hand OA.

INTRODUCTION

To evaluate the outcome of hand osteoarthritis(OA), all domains of interest should be assessed. Recently, hand OA patients have reported aesthetic damage as a domain of importance.[1,2]

Aesthetic damage in hand OA has been described previously,[2-4] though impact of dissatisfaction with hand appearance on daily life remains unclear. Michigan Hand Outcomes Questionnaire(MHQ), a reliable and validated questionnaire, includes a scale assessing aesthetics of the hands, evaluating both dissatisfaction and impact of dissatisfaction.[5,6]

Aesthetic dissatisfaction can be considered as part of clinical outcome, which in turn result from disease processes and factors like illness perceptions and coping responses. Illness perceptions are determinants of outcomes, according to Leventhal's Common Sense Model(CSM). Illness perceptions in OA were previously associated with limitations in daily activities and quality of life, while changes in illness perceptions of OA patients were associated with changes in outcomes.[7-10]

We evaluated the prevalence of aesthetic dissatisfaction in hand OA patients, its impact on daily life and their determinants.

METHODS

Study design

Cross-sectional data were used of HOSTAS(Hand OSTeoArthritis in Secondary care), an ongoing study which has enrolled hand OA patients consecutively since 2009. Inclusion occurred when patients consulted the Rheumatology outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and primary hand OA was diagnosed by the rheumatologist. Informed consent was obtained. Study was approved by LUMC's medical ethical committee.

Demographics and clinical characteristics

Standardized questionnaires collected demographics and clinical characteristics.
At inclusion and once every two years thereafter, participants underwent standardized physical examination. Distal interphalangeal(DIP) joints, proximal interphalangeal(PIP) joints, interphalangeal thumb(IP-1) joints, meta-carpophalangeal(MCP) joints and first carpometacarpal(CMC-1) joints were

evaluated for absence or presence of bony joint enlargements and soft tissue swelling. 'Deformities' was assessed in DIP, PIP, IP-1, MCP-1 and CMC-1 joints.

Radiographs

DIP, PIP, IP-1, MCP and CMC-1 joints were scored by WD using Kellgren-Lawrence (KL) grading scale (maximum=120). Intrareader reproducibility was high (ICC 0.95(0.89-0.97).[11]

Pain and aesthetics

Since January 2011, pain and aesthetics were measured at inclusion and biannually by the corresponding MHQ subscales and calculated by summing 5-point Likert scale responses. Pain was normalized to 0-100 (100=maximum pain). Normalization was not applied to aesthetics (higher scores=better hand performance), which contained one question measuring satisfaction (range 1-5, lower scores=more dissatisfaction) with appearance of the hands and 3 questions concerning its impact, namely discomfort in public, depression and/or interference with normal social activities (range 1-5 for each question, lower scores=more impact).[6] A <3 score was considered as dissatisfaction and a score of <3 for either one of the questions concerning impact was considered as experiencing impact.

Left and right hand scores were averaged, when no statistical differences were seen(Wilcoxon signed-rank test).

Disability

The functional index for hand OA (FIHOA) rates disability on a 10-item questionnaire, all on a four-point Likert scale (0-30).[12]

Anxiety and depression

Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) (item range 0-3, 3=worst). Subscale scores, ranging from 0-21(higher scores=higher anxiety or depression),[13] were divided into 3 ranges.[14]

Illness perceptions

The Illness Perception Questionnaire-Revised(IPQ-R) measures both patients' cognitive and emotional representations of their illness.[15,16]
IPQ-R assesses the following subscales: 1)'identity' measures whether 14 common symptoms are related to their OA according to participants, 2)'acute/chronic timeline'(higher score=more beliefs on chronicity) represents the likely chronic duration of their illness, 3)'consequences'(higher score=more consequences) reflects the consequences of their illness, 4)'personal control'(higher score=higher

perceived control) represents personal control, 5)'treatment control'(higher score=higher perceived efficacy of medical treatment) represents the effect of the treatment of their disease, 6)'illness coherence'(higher score=higher coherence) reflects the patient's perceived understanding of OA, 7)'cyclical timeline'(higher score=stronger belief in cyclical nature of OA) represents the likely variability of their disease, and 8)'emotional representations'(higher score=more negative emotions) reflects negative emotions experienced due to OA.

Data analysis

To investigate determinants of dissatisfaction with appearance and its impact, odds ratio (OR) with 95% CI were calculated using multivariate logistic regression as measures of relative risk, while adjusting for age, sex and BMI.
Additionally, multivariate analyses were performed adjusting for joint-specific variables or radiographic severity when appropriate.
All analyses used SPSS v20 (SPSS Inc, Chicago,IL)

RESULTS

Study population

Between May 2009 and July 13th 2012, 293 patients were included in the HOSTAS study and 253 patients completed the aesthetic scale of MHQ. Six patients were excluded later, when diagnosis changed. For this analysis, 247 patients were included, using the first available MHQ (Table 1).
Ninety-one percent of patients met ACR's criteria for hand OA and 193 patients (of 210 available radiographs) had at least one DIP or PIP joint with Kellgren-Lawrence (KL) scoring ≥2,

Aesthetic dissatisfaction and its determinants

Sixty-three(26%) of all patients reported dissatisfaction with aesthetics of their hands(median score=4.0, range 1-5, Supplementary Appendix 1). Five male and 58 female patients reported aesthetic dissatisfaction.
We hypothesized that visible abnormalities of the hands and clinical symptoms, i.e. bony enlargements, soft tissue swellings, deformities and self-reported pain, could play a role in aesthetic dissatisfaction. Deformities were independently associated with dissatisfaction. Bony enlargements were associated with dissatisfaction, but no longer after adjustments (Table 2). Like deformities and bony enlargements, radiographic damage also belongs to the domain structural damage and was associated with dissatisfaction (Supplementary Appendix 2).

Anxiety, depression and IPQ-R scales were not associated with aesthetic dissatisfaction, with the exception of emotional representations.

Table 1. Characteristics of 247 patients with hand OA in HOSTAS, diagnosed at the rheumatology outpatient clinic

Baseline characteristics	**Patients (n = 247)**
Women (n (%))	217 (88)
Age (mean (SD))	61.6 (8.7)
BMI (kg/m^2)	26.5 (17.6-47.7)
Kellgren-Lawrence score (range 0-120)	21 (0-75)
Number of joints affected* (n (%) (0-30)	5 (0-21)
Number of erosive joints# (n (%) (0-18)	0 (0-13)
Duration of symptoms (years)	5.6 (0.1-58.7)
Joints with bony enlargements (mean (SD)) (0-30)	11.4 (5.4)
Deformed joints (0-22)	5.0 (0-17)
Joints with soft tissue swelling (0-30)	0 (0-17)
MHQ pain (mean (SD)) (0-100)	43.2 (19.1)
FIHOA (0-30)	8.0 (0-24)
HADS anxiety (0-21)	4.0 (0-18)
HADS depression (0-21)	2.0 (0-17)
IPQ-R dimensions	
Identity (0-14)	5.0 (0-13)
Timeline acute/ chronic (6-30)	26.4 (12-30)
Consequences (6-30)	16.0 (6-30)
Personal control (6-30)	19.0 (6-29)
Treatment control (5-25)	14.0 (5-22)
Illness coherence (5-25)	19.0 (7-25)
Timeline cyclical (4-20)	14.0 (5-20)
Emotional representation (6-30)	13.5 (6-30)

Values are medians plus range unless stated otherwise.
OA= osteoarthritis; BMI= body mass index; MHQ= Michigan Hand Outcomes Questionnaire; FIHOA= Functional Index for Hand Osteoarthritis; HADS= Hospital Anxiety and Depression; IPQ-R= Illness Perception Questionnaire-Revised.
*Number of joints at Kellgren-Lawrence ≥2
#At least 1 interphalangeal joint

Table 2. Multivariate analyses for the determinants of aesthetic dissatisfaction and impact due to aesthetic dissatisfaction

	Aesthetic dissatisfaction		**Impact due to aesthetic dissatisfaction**	
	Adjusted OR (95% CI)*	**Adjusted OR (95% CI)****	**Adjusted OR (95% CI)***	**Adjusted OR (95% CI)****
Age	1. 02 (0. 99 - 1. 06)	0. 99 (0. 95 - 1. 03)	1. 02 (0. 98 - 1. 07)	0. 98 (0. 92 - 1. 03)
Sex	1. 92 (0. 69 - 5. 36)	1. 12 (0. 36 - 3. 53)	5. 48 (0. 71 - 42. 33)	1. 71 (0. 19 - 15. 03)
BMI	0. 97 (0. 91 - 1. 04)	1. 00 (0. 93 - 1. 08)	1. 02 (0. 94 - 1. 10)	1. 04 (0. 94 - 1. 14)
Bony joint enlargements tertiles				
0-8	1. 0	1. 0	1. 0	1. 0
9-14	1. 76 (0. 73 - 4. 23)	1. 14 (0. 44 - 2. 93)	3. 00 (0. 85 - 10. 56)	2. 99 (0. 75 - 11. 86)
≥15	3. 12 (1. 29 - 7. 56) #	1. 95 (0. 76 - 5. 01)	4. 12 (1. 15 - 14. 84) #	3. 59 (0. 86 - 15. 00)
Deformed joints tertiles				
0-4	1. 0	1. 0	1. 0	1. 0
5-6	2. 66 (1. 05 - 6. 71)	2. 37 (0. 92 - 6. 10)	2. 39 (0. 72 - 7. 97)	1. 76 (0. 49 - 6. 31)
≥7	6. 21 (2. 55 - 15. 13) #	5. 23 (2. 05 - 13. 36) #	4. 39 (1. 38 - 13. 94) #	2. 72 (0. 78 - 9. 54)
Swollen joints hands	1. 07 (0. 95 - 1. 20)		1. 10 (0. 94 - 1. 28)	
MHQ pain scale tertiles				
0-34	1. 0	1. 0	1. 0	1. 0
35-51	1. 71 (0. 79 - 3. 70)	1. 35 (0. 58 - 3. 12)	3. 95 (0. 82 - 19. 11)	2. 65 (0. 52 - 13. 60)
52-100	1. 94 (0. 89 - 4. 24)	1. 38 (0. 58 - 3. 27)	12. 60 (2. 82 - 56. 41) #	10. 30 (2. 20 - 48. 14) #

*Adjusted for age, sex, BMI.

**Multivariate model with age, sex, BMI, bony joint enlargements, deformed joints, self-reported pain

#p Value < 0.05

BMI= body mass index; MHQ= Michigan Hand Outcomes Questionnaire

Impact due to dissatisfaction and its determinants

Thirty-three(13%) patients reported impact due to dissatisfaction. Median scores for each of the 3 separate items were 5(range 1-5, lower scores=more discomfort, depression and interference, supplementary Appendix 1). One male and 32 female patients reported impact.

Bony enlargements, deformities and self-reported pain were associated with impact due to dissatisfaction of hand appearance (Table 2). Self-reported disability was associated as well (See supplementary Appendix 3). After further adjustments for joint-specific factors, only self-reported pain and radiographic damage remained.

After adjustments, depression remained associated (Table 3) with impact.

Higher scores for consequences and emotional representation and lower scores of illness coherence were associated with impact (Table 3).

Additional analyses including radiographic damage showed the same results. Analyses investigating disability instead of self-reported pain, showed similar results (data not shown).

Table 3. Multivariate analyses for personal determinants of impact due to aesthetic dissatisfaction

	Adjusted OR (95% CI)*	**Adjusted OR (95% CI)****
HADS anxiety range		
0-7	1. 0	1. 0
8-10	1. 50 (0. 47 - 4. 81)	1. 09 (0. 31 - 3. 91)
11-21	6. 08 (2. 15 - 17. 18) #	2. 34 (0. 68 - 8. 09)
HADS depression range		
0-7	1. 0	1. 0
8-10	3. 49 (1. 11 - 10. 96) #	2. 37 (0. 64 - 8. 82)
11-21	16. 38 (4. 34 - 61. 89) #	10. 54 (1. 97 - 56. 29) #
IPQ-R subscales		
Identity	1. 27 (1. 10 - 1. 48) #	1. 18 (0. 99 - 1. 40)
Timeline chronic	1. 06 (0. 95 - 1. 20)	1. 02 (0. 90 - 1. 17)
Consequences	1. 24 (1. 12 - 1. 38) #	1. 19 (1. 06 - 1. 34) #
Personal control	1. 07 (0. 95 - 1. 20)	1. 03 (0. 92 - 1. 17)
Treatment control	0. 88 (0. 76 - 1. 03)	0. 87 (0. 73 - 1. 03)
Illness coherence	0. 81 (0. 73 - 0. 90) #	0. 84 (0. 75 - 0. 94) #
Timeline cyclical	0. 94 (0. 83 - 1. 08)	0. 95 (0. 83 - 1. 09)
Emotional representation	1. 19 (1. 10 - 1. 30) #	1. 14 (1. 05 - 1. 25) #

*Adjusted for age, sex, BMI

**Adjusted for age, sex, BMI, bony joint enlargements, deformed joints and self-reported pain.

#p Value < 0.05

HADS= Hospital Anxiety and Depression Scale, IPQ-R= Illness Perception Questionnaire-Revised.

DISCUSSION

This is the first study to investigate impact on certain aspects of daily life due to aesthetic dissatisfaction in hand OA patients using validated questionnaires. We found that although hand OA patients experience dissatisfaction with the appearance of their hands regularly, impact due to this dissatisfaction is reported by a small group only. Patients with joint-specific determinants were at higher risk for reporting dissatisfaction. Patients who reported impact, also reported more depression and negative illness perceptions. Personal factors were mainly associated with impact and not with simply aesthetic dissatisfaction. These results indicate the influence of personal factors on outcome measures in hand OA patients.

Deformed joints were only associated with aesthetic dissatisfaction. After adjustments, only a trend remains between bony enlargements and either aesthetic dissatisfaction or impact. This loss of association may be due to a lack of power, since bony enlargements were associated with high aesthetic concern in the first in-depth study on this domain.[2] Self reported pain, disability (by the FIHOA) and radiographic damage remain associated with impact due to dissatisfaction.

In contrast to the previous study,[2] a relatively small group of our patients experienced impact due to dissatisfaction. This difference in findings may be due to differences in methods. Previously,[2] assessment occurred by posing one standardized question to indicate the aesthetic impact of hand OA (scale of 0-100, 100=maximal aesthetic discomfort). Participants could interpret this as assessment of aesthetic impact of hand OA or just aesthetic dissatisfaction; the group experiencing impact could be smaller. In HOSTAS, this was measured separately.
However, their group of hand OA patients experiencing impact could indeed be larger, perhaps due to cultural differences.

In line with our expectations and previous study, depression was associated with impact, but not aesthetic dissatisfaction.[2]

IPQ-R subscales were only associated with impact, with the exception of emotional representations. We expected that aesthetic dissatisfaction especially depends upon joint-specific determinants and less on personal determinants. In contrast, patients with negative illness perceptions experienced more impact.
Our study had its limitations. For this study, MHQ was assessed in 247 patients, whose data were subsequently used for all analyses. Unfortunately, we were

limited by missing data. Although clinical examination and questionnaires were available in the far majority of patients, but not in all.
We were interested in factors associated with aesthetic dissatisfaction, so neutral satisfaction was grouped with satisfaction. If the neutral group was excluded, we may have found stronger associations.
MHQ's aesthetic scale is designed to yield one score. For a better understanding of not only the item aesthetic dissatisfaction but also of the impact that aesthetic dissatisfaction may lead to, we separated the scores and grouped patients who scored low on either one of the three aesthetic questions concerning impact. This was necessary to discern between presence of just aesthetic dissatisfaction and impact due to aesthetic dissatisfaction.

Programs teaching self-management skills can improve clinical outcomes in people with OA.[17] Our results have shown that patients who experienced more impact from hand OA, also reported having negative perceptions. We hypothesize that patients with negative perceptions, particularly those who report having a lower degree of understanding of their OA, may benefit especially from self-management training. The incorporation of self-management as a part of the treatment in hand OA patients should be considered in clinical practice. Future research on aesthetics of hand OA will be necessary to further our understanding and to confirm or not our hypotheses.

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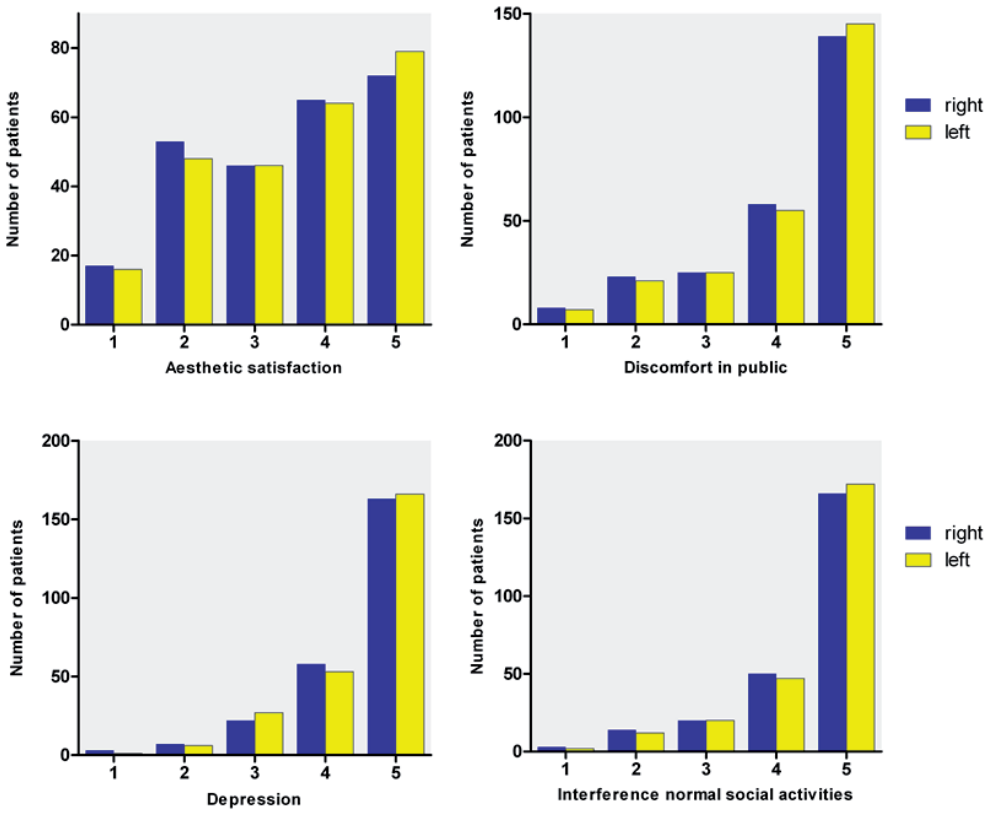
SUPPLEMENTARY APPENDIX 1.



SUPPLEMENTARY APPENDIX 2. Multivariate analyses for the determinants of aesthetic dissatisfaction and impact due to aesthetic dissatisfaction

	Aesthetic dissatisfaction		**Impact due to aesthetic dissatisfaction**	
	Adjusted OR (95% CI)*	**Adjusted OR (95% CI)****	**Adjusted OR (95% CI)***	**Adjusted OR (95% CI)****
Age	1. 02 (0. 99 - 1. 06)	0. 98 (0. 94 - 1. 03)	1. 02 (0. 98 - 1. 07)	0. 99 (0. 93 - 1. 04)
Sex	1. 92 (0. 69 - 5. 36)	1. 81 (0. 60 - 5. 44)	5. 48 (0. 71 - 42. 33)	3. 91 (0. 47 - 32. 33)
BMI	0. 97 (0. 91 - 1. 04)	0. 96 (0. 89 - 1. 03)	1. 02 (0. 94 - 1. 10)	0. 99 (0. 91 - 1. 09)
Kellgren-Lawrence score				
0-13	1. 0	1. 0	1. 0	1. 0
14-27	1. 25 (0. 50 - 3. 15)	1. 18 (0. 47 - 2. 99)	1. 43 (0. 44 - 4. 58)	1. 24 (0. 37 - 4. 18)
≥ 28	5. 72 (2. 29 - 14. 34) #	5. 49 (2. 19 - 13. 76) #	3. 42 (1. 07 - 10. 90) #	3. 42 (1. 03 - 11. 33) #
MHQ pain scale tertiles				
0-34	1. 0	1. 0	1. 0	1. 0
35-51	1. 71 (0. 79 - 3. 70)	1. 57 (0. 67 - 3. 65)	3. 95 (0. 82 - 19. 11)	3. 00 (0. 59 - 15. 34)
52-100	1. 94 (0. 89 - 4. 24)	1. 80 (0. 76 - 4. 26)	12. 60 (2. 82 - 56. 41) #	11. 63 (2. 50 - 54. 06) #

*Adjusted for age, sex, BMI.

**Multivariate model with age, sex, BMI, self-reported pain and Kellgren-Lawrence score

#p Value < 0.05

BMI= body mass index; MHQ= Michigan Hand Outcomes Questionnaire

SUPPLEMENTARY APPENDIX 3. Multivariate analyses for the determinants of aesthetic dissatisfaction and impact due to aesthetic dissatisfaction

	Aesthetic dissatisfaction		**Impact due to aesthetic dissatisfaction**	
	Adjusted OR (95% CI)*	**Adjusted OR (95% CI)****	**Adjusted OR (95% CI)***	**Adjusted OR (95% CI)****
Age	1. 02 (0. 99 - 1. 06)	0. 99 (0. 95 - 1. 03)	1. 02 (0. 98 - 1. 07)	0. 97 (0. 91 - 1. 02)
Sex	1. 92 (0. 69 - 5. 36)	1. 16 (0. 37 - 3. 67)	5. 48 (0. 71 - 42. 33)	2. 82 (0. 32 - 24. 82)
BMI	0. 97 (0. 91 - 1. 04)	1. 00 (0. 93 - 1. 08)	1. 02 (0. 94 - 1. 10)	1. 03 (0. 93 - 1. 14)
Bony joint enlargements tertiles				
0-8	1. 0	1. 0	1. 0	1. 0
9-14	1. 76 (0. 73 - 4. 23)	1. 10 (0. 43 - 2. 80)	3. 00 (0. 85 - 10. 56)	1. 98 (0. 50 - 7. 89)
≥15	3. 12 (1. 29 - 7. 56) #	1. 87 (0. 72 - 4. 85)	4. 12 (1. 15 - 14. 84) #	2. 47 (0. 59 - 10. 35)
Deformed joints tertiles				
0-4	1. 0	1. 0	1. 0	1. 0
5-6	2. 66 (1. 05 - 6. 71)	2. 33 (0. 91 - 5. 98)	2. 39 (0. 72 - 7. 97)	1. 81 (0. 50 - 6. 58)
≥7	6. 21 (2. 55 - 15. 13) #	5. 12 (2. 01 - 13. 09) #	4. 39 (1. 38 - 13. 94) #	2. 44 (0. 70 - 8. 53)
FIHOA				
0-10	1. 0	1. 0	1. 0	1. 0
11-20	2. 28 (1. 23 - 4. 23)	1. 66 (0. 83 - 3. 29)	12. 03 (4. 33 - 33. 37) #	10. 66 (3. 40 - 33. 46) #
≥21	1. 01 (0. 20 – 5. 05)	0. 84 (0. 14 – 5. 14)	11. 21 (2. 21 – 56. 78) #	15. 35 (2. 38 – 99. 22) #

*Adjusted for age, sex, BMI.

**Multivariate model with age, sex, BMI, bony joint enlargements, deformed joints and FIHOA

#p Value < 0.05

BMI= body mass index; FIHOA= functional index for hand osteoarthritis

Chapter 4

Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis

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ABSTRACT

OBJECTIVE

To determine the association between bone marrow lesions (BMLs) and (teno) synovitis as assessed on magnetic resonance (MR) imaging in patients with pain in hand osteoarthritis (OA).

METHODS

In 105 consecutive primary hand OA patients (83% women, mean age 59 years), who were diagnosed by rheumatologists and included in the HOSTAS (Hand OSTeoArthritis in Secondary care) cohort, contrast-enhanced MR imaging of right distal and proximal interphalangeal joints were obtained. In 92 patients joint site specific pain upon palpation was assessed within 3 weeks of MRI examination.
MR features were scored (0-3) following the Oslo hand OA score: BMLs, synovitis, cysts, flexor tenosynovitis (FTS). Additionally, extensor tendon inflammation (ETI)(0-3) was scored. Odds ratios (OR, 95% CI) were calculated using generalised estimating equations for MR features with joint pain, adjusted for putative confounders. Stratified analyses were performed to investigate interaction.

RESULTS

BMLs, synovitis, cysts, FTS and ETI were demonstrated in 56%, 90%, 22%, 16% and 30% of patients, respectively. BMLs (grade 2/3 vs 0: 3.5 (1.6-7.7)) and synovitis (3 vs 0: OR 3.6 (95%CI 1.9-6.6)) were severity-dependent associated with joint pain, but FTS and ETI were not. Stratified analyses showed that BMLs did not associate with pain in the absence of synovitis, whereas synovitis was associated with pain in the absence of BMLs. Interaction was seen between BMLs and synovitis grade 2 or 3.

CONCLUSION

In hand OA patients severe synovitis is associated with joint pain, which is worsened when BMLs co-occur, suggesting synovitis as primary target of treatment.

INTRODUCTION

Hand osteoarthritis (OA) can result in a high clinical burden. Especially hand pain can lead to a decreased quality of life.[1] Knowledge of the underlying pain mechanisms in hand OA enables optimal treatment of hand pain. Many ultrasonography studies in hand OA patients demonstrated that synovial inflammation is present in hand OA and plays a role in the presence of hand pain. Tenosynovitis of the flexor tendon is also present in hand OA and associated with hand pain,[2,3] but the involvement of the extensor tendon is unknown.

MR studies have indicated that in the subchondral bone of osteoarthritic joints ill-defined areas of high signal intensity can be visualized on fat-suppressed T2 weighted or short tau inversion recovery (STIR) sequences, so-called bone marrow lesions (BML).[4] Histologically BMLs represent mainly areas of fibrosis, necrosis and trabecular bone abnormalities.[5] In knee OA these BMLs have been widely investigated and play a role in knee pain.[6] BMLs in hand OA have been rarely studied. In two studies of late stage hand OA patients the presence of BMLs has been demonstrated.[2,3] Haugen et al showed an association between BMLs and hand pain, both cross-sectionally and longitudinally.[2,3,7]

Since no data of BMLs in patients in earlier stages of hand OA are available, we set-up a study to determine their prevalence in patients presenting themselves to our Rheumatology outpatient clinic. It is unclear how BMLs relate to synovitis in osteoarthritic hand joints and therefore we do not know whether synovitis or BMLs are crucial in hand pain. Hence we investigated their co-occurrence and interaction with respect to pain, to be able to determine which target is most promising to alleviate pain. This is also important, since imaging synovitis is difficult due to the need for contrast enhanced MR imaging, which adds cost, complexity and risk to the MR imaging protocol. We also investigated whether extensor tendon involvement plays a role in hand OA.

METHODS

Study design

Cross-sectional data were used of the HOSTAS (Hand OSTeoArthritis in Secondary care) study, an ongoing cohort. This cohort enrolled consecutively diagnosed patients with hand OA since 2009 to investigate determinants of outcome in hand OA. Patients were included when they consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and these hand complaints were diagnosed as primary hand OA.

Exclusion criteria include any other pathological condition that could explain existing symptoms, secondary OA and routine MRI-contraindications.
For the present analysis, only patients were included who received a contrast enhanced MRI (CE-MRI).
Written informed consent was obtained from all participants. The study was approved by the LUMC medical ethical committee.

Demographics and clinical characteristics

Standardized questionnaires were used to collect demographics and clinical characteristics. Participants underwent standardized physical examination of their hands by a trained research nurse. All distal interphalangeal (DIP), proximal interphalangeal (PIP) joints, metacarpal phalangeal (MCP) joints, 1st interphalangeal (IP) joints and 1st carpometacarpal (CMC) joints were evaluated for site specific pain upon palpation (0-30, additive scale).[8]

Self-reported pain

Pain intensity in the right hand was measured by a pain visual analogue scale (VAS). Furthermore, the Michigan Hand Outcomes Questionnaire (MHQ) pain subscale was filled in (5-point Likert scale and normalization to 0–100, higher scores = greater pain).[9] Also the pain subscale of the Australian Canadian Hand OA Index (AUSCAN) in its Likert format was acquired.[10] Both MHQ and AUSCAN assess hand pain in both hands simultaneously.

Mental health

Subscales of the 36-item Short Form Health Survey (SF-36) were measured to calculate the mental health component score. This component score was standardized using data based on the norms from the Dutch population.[11,12]

MR Imaging

From March 2011 to October 2012, MR imaging was performed as part of the baseline examination of the patients included in HOSTAS, using an ONI-MSK-Extreme 1.5 Tesla (T) extremity MR imaging scanner (GE, Wisconsin, USA), with a dedicated 100 mm coil. The right hand PIP and DIP joints (n=8) of each patient were examined, regardless of clinical features or dominance.
The following sequences were used: coronal T1-weighted (T1-w) fast spin echo (FSE) images (repetition time (TR)/echo time (TE) 575/11 milliseconds (ms), acquisition matrix (AM) 388×288, echo train length (ETL) 2, minimum TE), axial T1-w FSE images (TR/TE 500/10.2 ms, AM 340×288, ETL 2, minimum TE), coronal T2-w FSE images with frequency-selective fat-saturation (FSFS) (TR/TE 3000/61.8 ms, AM 300×224, ETL 7) and axial T2-w FSE images with FSFS (TR/TE 3000/57 ms, AM

336×192, ETL 7) before contrast injection, and coronal T1-w FSE images with FSFS (TR/TE 600/10.4 ms, AM 364×224, ETL 2, minimum TE) and axial T1-w FSE images with FSFS (TR/TE 650/7.7ms, AM 320×192, ETL 2, minimum TE) after intravenous injection of Gadolinium-chelate (Gd) (gadoteric acid, Guerbet, standard dose 0.1 mmol/kg).
Coronal images had a field of view of 120 mm and 18 slices with a slice thickness of 2 mm and a slice gap of 0.2 mm. Axial images had a field of view of 100 mm and 24 slices with a slice thickness of 3 mm and a slice gap of 0.3 mm. Total acquisition time was 30 minutes.
MR imaging scoring was performed by one dedicated well-trained reader (RL) (supervised by radiologist MR with more than 20 years experience) using a modified version of the Oslo hand OA MR imaging scoring system (Figure 1).[13] Scoring was performed blinded for demographic and clinical data.
Synovitis was defined as an area in the synovial membrane that showed post-Gd enhancement of a thickness greater than the width of normal synovium (>1 mm)[13] on T1-w images and seen on at least 2 consecutive slices. Scoring was based using thirds of the maximum potential volume of enhanced synovial tissue (0= normal, 1= mild, 2= moderate and 3= severe).

Flexor tenosynovitis was defined as an area in the flexor tendon sheath that showed post-Gd enhancement of a thickness greater than the normal width of the tendon sheath (as shown in the Oslo atlas) on T1-w images, visible on at least 2 consecutive slices and involving the entire tendon sheath by being circumferential. Scoring occurred as follows: 0= normal, 1= <0.5 tendon thickness, 2= ≥0.5 and <1 tendon thickness, 3= ≥1 tendon thickness.
Extensor tendon inflammation was defined as an area in the extensor tendon that showed enhancement of a thickness greater than the normal width of the tendon, is visible on at least 2 consecutive slices and when opposite sides of the extensor were enhanced. Scoring was performed according to the same scoring method as the flexor tendon: 0= normal, 1= <0.5 tendon thickness, 2= ≥0.5 and <1 tendon thickness, 3= ≥1 tendon thickness.

BMLs at distal and proximal joint site were defined as lesions within the trabecular bone with signal characteristics consistent with increased water content and ill-defined margins on T2. The distal and proximal part of the joint was scored separately for the proportion of bone with BML: 0= no BML, 1= 1 - 33 % of bone with BML, 2= 34% - 66 % of bone with BML, 3= 67% - 100% of bone with BML. The highest score was taken as the BML score for the whole joint.
Cysts (0-1; absent or present) at distal and proximal joint site were defined as sharply marginated bone lesions with typical signal characteristics (Low signal

intensity on T1 pre-gadolinium and high signal intensity on T2), which is visible in two planes without a cortical break.
One of the authors (RL) re-scored 11 randomly selected MR scans after at least 3 weeks, and the intra-reader reliability for synovitis, flexor tenosynovitis, BML and cyst was high (ICC ≥0.97), while the ICC for extensor tendon inflammation was intermediate (ICC 0.76).

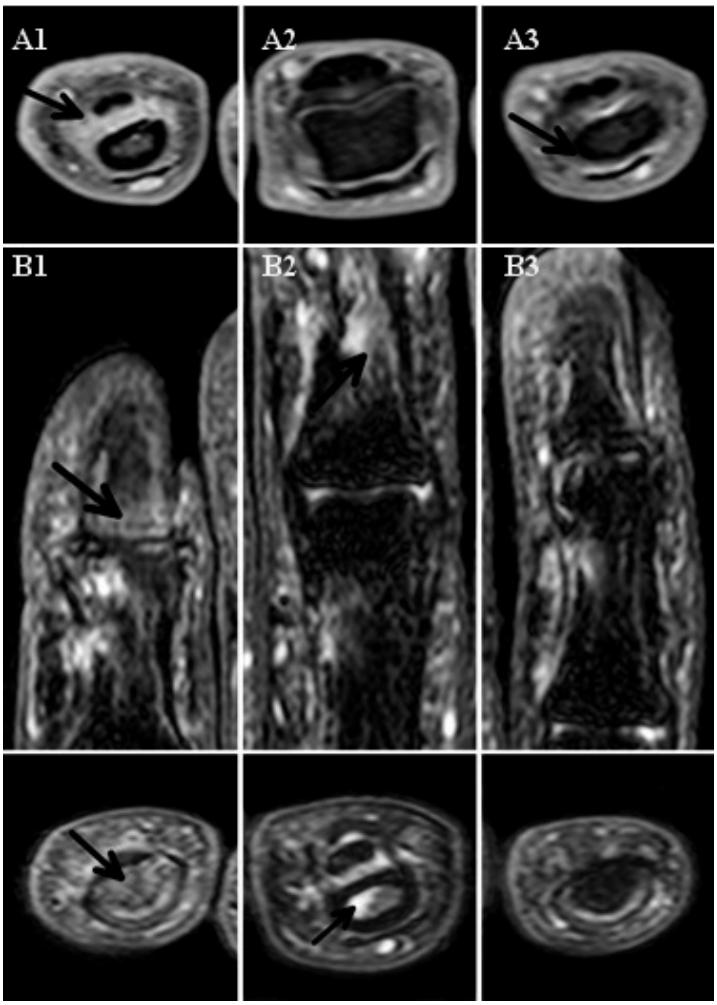

Figure 1. Axial (A) T1-weighted FSE images with frequency selective fat saturation post-gadolinium enhancement, axial (C) and coronal (B) T2-weighted FSE images with frequency selective fat saturation MR imaging of the same patient: Synovitis (A1) and bone marrow lesion (BML, B1, C1) were present in the painful second distal interphalangeal joint. A non-painful third proximal interphalangeal joint with BML (B2, C2) and no synovitis (A2). Synovitis (A3) without the presence of BML(B3, C3) in the painful fourth distal interphalangeal joint.

Radiographs

Conventional radiographs of the hands (dorso-volar) were obtained. The DIP joints, PIP joints, 1st IP joints, MCP joints and 1st CMC joints were scored by one of the authors (WD). The Kellgren-Lawrence (KL) grading scale (0-4, maximum score 120) was used for the scoring of structural osteoarthritic damage and the Verbruggen-Veys anatomical phase scoring was used for erosion (N-S-J-E-R depicted as 0-1-2-3-4, maximum score 120). Joints were considered erosive when they were in phase E (erosive) or R (remodeled). The dedicated well-trained scorer (WD) (supervised by MKL with more than 10 years experience in scoring hand radiographs) was blinded for clinical and demographic data. Intra-reader reproducibility, taking in account the severity of the score, depicted by the intraclass correlation coefficient (ICC) was assessed on a randomly selected sample (n= 31) of radiographs and was high (ICC for KL 0.91 and for Verbruggen-Veys 0.86).

Statistics

Odds Ratios (OR) with 95% confidence intervals (CI) were calculated using generalized estimating equations (GEE) to investigate the association between MR imaging features with site specific pain upon palpation in DIP and PIP joints, while adjusting for age, sex, BMI and patient effect. Additionally, ORs with 95% CIs were calculated with logistic regression for the association between summated MR imaging scores and self-reported pain, with adjustment for age, sex, BMI, mental health and KL score. The cut-off for the VAS pain, MHQ pain and AUSCAN pain was the median. Furthermore, a stratified analysis was performed to investigate BMLs and the effect of synovitis in site specific pain upon palpation.

If more than 3 weeks elapsed between the time of MR imaging and physical examination, the data were excluded from this analysis.

RESULTS

Study population

In 105 patients (83% women, median age 59.4 years, 91% fulfilled the American College of Rheumatology criteria for hand OA)[14].

MR imaging was obtained from 840 joints of the right hand (Table 1). In 8 DIP and PIP joints of the right hand, the median number of hand joints with a KL grade of at least 2 was 2 (0-8) and percentage of erosive hand OA was 23%. Due to technical problems, in 3 and 4 joints no BMLs or synovitis could be scored respectively. Other features such as cysts could be evaluated in all joints (n= 736).

In 92 patients physical examination was performed within 3 weeks of the MR imaging and the association between MR imaging features with hand pain was

analyzed. Patient and clinical characteristics from these 92 patients did not differ from the total population of 105 patients(data not shown).

Table 1. Baseline characteristics of 105 consecutive hand osteoarthritis (OA) patients diagnosed at an outpatient clinic of rheumatology

Variable*	**Hand OA patients (n=105)**
Age, yrs	59.4 (40.4-79.9)
Female sex, n (%)	87 (83)
BMI	26.9 (17.6-40.7)
Symptom duration, yrs	5.3 (0.33-36.8)
ACR criteria hand OA, n (%)	95 (91)
Radiographic hand OA**, n of patients (%)	92(88)
Assessment of 8 scanned joints	
Erosive hand OA, n of patients (%)#	24 (23)
Number of joints with KL≥2	2 (0-8)
Number of site specific painful joints upon palpation	1 (0-8)
Self-reported symptoms	
VAS pain right hand, mm	36 (0-83)
VAS pain left hand, mm	34 (0-83)
AUSCAN pain (0-20)	10 (0-20)
MHQ pain (0-100)	45 (0-95)

*Median (range) unless otherwise stated

**At least one joint with Kellgren-Lawrence score ≥ 2

At least one erosive IP joint in the right hand

8 joints: PIPJs, DIPJs right hand

BMI= body mass index; VAS= visual analogue scale; MHQ= Michigan Hand outcomes Questionnaire; ACR= American College of Rheumatology

Prevalence of BMLs, synovitis, tendon inflammation and cysts

BMLs were present in 56% of the 105 patients and synovitis in 90%. Abnormalities in tendons were found less often: flexor tenosynovitis in 16%, while extensor tendon inflammation was seen in 30%. Cysts was seen in 22% of the patients (Table 2). BMLs was preferentially seen in DIP 2, 3 and PIP 2, synovitis in DIP 2, 3 and PIP 2 through 5, flexor tenosynovitis in PIP 3 and extensor tendon inflammation in PIP 5 (Figure 2).

Table 2. Prevalence of MR imaging features in distal and proximal interphalangeal joints of the right hand in 105 patients with hand osteoarthritis.

MR imaging feature	Hand OA patients (n=105)
Joint	
Bone marrow lesion	
Patients, n (%)	59 (56)
Joints, median (range)	1 (0-6)
Synovitis	
Patient, n (%)	94 (90)
Joints, median (range)	3 (0-8)
Flexor tendon	
Tenosynovitis	
Patient, n (%)	17 (16)
Joints (range)	0 (0-4)
Extensor tendon	
Tendon inflammation	
Patient, n (%)	31 (30)
Joints, median (range)	0 (0-8)
Cyst	
Patients, n (%)	23 (22)
Joints, median (range)	0 (0-3)

Figure 2. Prevalence (percentage of patients) of MR imaging features in all proximal and distal interphalangeal joints of the right hand in 105 consecutive patients with hand osteoarthritis diagnosed at a rheumatology outpatient clinic.

Association between MR imaging features and site specific pain upon palpation in right DIP and PIP joints

736 joints in the 92 patients were available for the investigation of the association between MR imaging features and pain. After adjustment for age, sex, BMI and patient effect, BMLs and synovitis were associated with pain in the site specific joint upon palpation (Table 3).
Flexor tenosynovitis, extensor tendon inflammation and cyst in the tendons were not associated with pain upon palpation in the joint.
On conventional radiographs, structural osteoarthritic damage, as characterized by KL grade of at least 2, was also associated with pain (Table 3).

Additional analyses including BML and synovitis together in the multivariate analyses showed associations for BMLs (grade 2+3 versus 0: OR 3.5 (1.6-7.7)) and synovitis (grade 3 versus 0: OR 3.6 (95%CI 1.9-6.6)). The associations between BMLs or synovitis with pain remained after adjustment for structural damage in the joint. Structural damage was characterized by a KL score of at least 2. When KL score was added to the analyses, KL score was no longer statistical significantly associated after adjustment for BMLs and synovitis (Table 3).

Interaction between BMLs and synovitis in their association with site specific pain upon palpation

BMLs and synovitis often co-occurred. This co-occurence could conceal their relative contribution in the association with site specific pain upon palpation. Therefore, a stratified analysis was performed to investigate BMLs and the sole effect of synovitis in site specific pain upon palpation and to elucidate potential interaction between BMLs and synovitis. Seven percent (n=54) of the hand joints were painful upon palpation in the absence of both BMLs and synovitis. In 231 hand joints, synovitis was present while BMLs were absent. When grade 3 synovitis was present without BMLs (n=20), 7 joints (35%) were painful upon palpation. BMLs, both small and moderate/severe lesions, were seldom present when synovitis was absent (33 joints of 416 joints without synovitis had a BML grade 1 and only one joint had a BML grade 2/3); BMLs did not have an effect on pain in the absence of synovitis. In joints where BMLs and moderate and severe synovitis (grade 2 or 3) co-occur (n=49), 26 (53%) of these joints were painful upon palpation. The associations between MR imaging features and pain in the different strata are depicted in Table 4 and examples are shown in Figure 1. In the joints with moderate synovitis (grade 2) the co-occurrence with BMLs resulted in an increased risk for site specific pain upon palpation when compared to joints without BMLs (5.1 (2.1-12.2) instead of 1.2 (0.4-3.2) (Table 4). While the basic risk for site specific pain upon palpation for sole BMLs or moderate synovitis is 1(background risk=1+ 0.2

(synovitis risk) – 0.2 (BML risk), whereas the risk for co-occurrence of synovitis grade 2 and BMLs is 5.1; therefore a clear interaction can be demonstrated. In joints with severe synovitis (grade 3) a comparable interaction is seen: the basic risk for site specific pain upon palpation for sole BMLs or severe synovitis is 2.1 (background risk= 1+ 1.3(synovitis risk) – 0.2 (BML risk) . Whereas the risk for site specific pain upon palpation for the co-occurrence of severe synovitis and BMLs is 6.9. Adjustment for KL grade did not change these interactions(data not shown).

Table 3. Association between MR imaging features and 736 distal and proximal interphalangeal joints assessed for site specific pain upon palpation in 92 patients with hand OA.

	Pain joint +/-	**Adjusted OR (95%CI)***	**Adjusted OR (95%CI)****	**Adjusted OR (95%CI)*****
Joint				
BML				
Grade 0	96/518	1.0	1.0	1.0
Grade 1	20/67	1.5 (0.9-2.5)	1.2 (0.7-2.2)	1.1 (0.6-2.0)
Grade 2+3	18/14	6.3 (2.9-13.8)	3.5 (1.6-7.7)	3.1 (1.4-7.1)
Synovitis				
Grade 0	59/357	1.0	1.0	1.0
Grade 1	36/178	1.2 (0.8-1.8)	1.1 (0.8-1.7)	1.1 (0.7-1.6)
Grade 2	18/40	2.6 (1.4-4.6)	1.9 (1.01-3.6)	1.8 (0.96-3.6)
Grade 3	20/24	5.4 (2.8-10.4)	3.6 (1.9-6.6)	3.2 (1.7-6.3)
Flexor tendon				
Tenosynovitis				
Grade 0	130/585	1.0		
Grade 1	3/14	0.7 (0.2-2.4)		
Extensor tendon				
Inflammation				
Grade 0	121/568	1.0		
Grade 1	12/31	1.3 (0.6-3.0)		
Cyst				
Grade 0	130/584	1.0		
Grade 1	4/18	1.0 (0.4-2.6)		
Structural damage				
Kellgren-Lawrence				
< 2	76/447	1.0		1.0
≥ 2	55/150	2.1 (1.4-3.0)		1.3 (0.9-2.0)

*Adjusted for age, sex, BMI and patient effect
**Multivariate model with age, sex, BMI, patient effect, synovitis, and BMLs
***Multivariate model with age, sex, BMI, patient effect, synovitis, BMLs and Kellgren-Lawrence score (<2 versus ≥ 2)
BMI= body mass index, BML= bone marrow lesion, NA= not applicable

Table 4. Odds ratio (with 95% confidence interval) of site specific pain upon palpation by synovitis status and the presence or absence of bone marrow lesions (BMLs) in 732 joints of 92 patients with hand osteoarthritis (OA).

	No synovitis N=416	**Synovitis**		
		Grade 1 N=214	**Grade 2 N=58**	**Grade 3 N=44**
BMLs absent	1 (background) N=382	1.2 (0.8-1.8) N=178	1.2 (0.4-3.2) N=33	2.3 (0.96-5.7) N=20
BMLs present	0.8 (0.2-2.8) N=34	1.3 (0.6-3.2) N=36	5.1 (2.1-12.2) N=25	6.9 (2.7-17.7) N=24

*Adjusted for age, sex and BMI

Association between MR imaging features and self-reported pain

No association was seen between the summated score of MR imaging features and self-reported VAS pain of the right hand, AUSCAN pain and MHQ pain (data not shown)

DISCUSSION

In 840 interphalangeal joints from 105 hand OA patients BMLs, (teno)synovitis, tendon inflammation and cysts were frequently seen. Both BMLs and synovitis were associated with site specific pain upon palpation. Novel in this study is that BMLs alone were not associated with pain, whereas severe synovitis alone was, and that a clear interaction between BMLs and synovitis was seen. In 53 % of joints with BMLs and moderate to severe synovitis, site specific pain upon palpation was observed, resulting in a nearly 7-fold increased risk for pain when compared to interphalangeal joint without BMLs or synovitis. This is an important finding, identifying synovitis as primary possible target in future therapeutic options.

Though previous MR Imaging studies in hand OA have been scarce, knee OA has been the topic of extensively research. Features such as BMLs and synovitis are often associated with pain in such studies. [6,15-17] It is possible that a similar interaction between the two features also exists in knee OA and may explain the inconsistency of the results. Unfortunately, further distinction between the two features and its possible interaction have not been investigated as we have done with our study.

Neither flexor tenosynovitis nor extensor tendon inflammation nor cysts were associated with pain. Flexor tenosynovitis was investigated previously and was associated with pain, when only corrected for age and sex.[3] We could not replicate these results. A possible explanation lies in a difference of study population and differences in the methods of the studies. The prevalence (median=1) of joints

with flexor tenosynovitis and the number of painful joints (median=4) in the other study was higher while patients were older (mean=68.8).[3] To our best knowledge, this is the first study to report on the presence of extensor tendon inflammation in hand OA. The anatomic absence of a tendon sheath and close relation with the joint made us question whether a direct relation between extensor tendon inflammation and joint pain would be present. This MR feature was found in a third of the patients. Though no association was found between extensor tendon inflammation and pain, it is possible that this feature is associated with other clinical properties, such as hand mobility. More studies will be needed to further investigate this feature.

Our study also has its limitations. We have employed a modified version of the hand OA MR imaging scoring system, a system developed in recent years. However we used a 1.5T MR systems, which would produce different images than the 1.0T systems used to develop the initial score. Based on previous studies in OA, we have incorporated additional features such as extensor tendon inflammation to further investigate our own understanding of the association between MR imaging features and clinical signs of OA.
Since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ between DIP and PIP joints, it could be useful to analyze these groups of joints separately. Due to low numbers this was not possible in our study. The reliability of the MRI scorings yielded mostly good results for the features investigated in our study. The ICC for extensor tendon inflammation was lower than the other features, but still performed better when compared to the ICC of flexor tenosynovitis in another MRI study.[13] Future studies will be necessary to investigate if extensor tendon inflammation is perhaps a more difficult feature to define or the definition needs further adaptation.

The study population consists of a relatively large proportion of women (83%). Hand OA occurs more often in women than in men.[18] This could explain the high female participation rate in both our study group and in a previous MR Imaging study for hand OA where 91% of the study population consisted of women.[3]

Our results illustrate the advantages of MR imaging over radiographs and ultrasonography. Features such as BMLs and synovitis offer better agreement with the clinical assessment of a patient. We have found that the presence of BMLs and synovitis on joint level are both independently associated with site specific pain upon palpation, when corrected for age, sex, BMI, KL-grade and patient effect. BMLs and synovitis are not associated with self-reported pain on the patient level, which may be explained by an inability to correct for the individual patient effect.

Pain is subjective and it will be challenging to discover which known and unknown variables will all contribute to the patient effect. We hypothesized that mental health may explain this patient effect, but this was not the case. The involvement of the carpometacarpal joint may be another one of such variables, as previous study has shown that this joint contributes more to pain than interphalangeal joints. Unfortunately, we could not further test our theories due to lack of information.[19]

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5

Chapter 5

Bone marrow lesions and synovitis on MRI associate with radiographic progression after two years in hand osteoarthritis

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ABSTRACT

OBJECTIVE

To study the association of magnetic resonance (MR) features with radiographic progression of hand osteoarthritis over two years.

METHODS

Of 87 primary hand osteoarthritis patients (82% women, mean age 59 years), baseline distal and proximal interphalangeal joint contrast-enhanced MR images were scored 0-3 for bone marrow lesions (BMLs) and synovitis following the Oslo score.

Baseline and two-year follow-up radiographs were scored following Kellgren-Lawrence (KL) (0-4) and OARSI scoring methods (0-3 osteophytes, joint space narrowing (JSN)). Increase ≥ 1 defined progression.

Associations between MR features and radiographic progression were explored on joint and on patient level, adjusting for age, sex, BMI, synovitis and BML. Joints in end-stage were excluded.

RESULTS

Of 696 analysed joints, 324 had baseline KL=0, 28 KL=4 and after two years 78 joints progressed. BML grade 2/3 was associated with KL progression (2/3 vs 0: adjusted RR (95%CI) 3.3 (2.1-5.3)) and with osteophyte or JSN progression, as was synovitis. Summated scores were associated with radiographic progression on patient level (RR crude BML 1.08 (1.01-1.2), synovitis 1.09 (1.04-1.1), adjusted synovitis 1.08 (1.03-1.1)).

CONCLUSION

BMLs, next to synovitis, show, already after two years, graded associations with radiographic progression, suggesting that both joint tissues could be important targets for therapy.

INTRODUCTION

The hand osteoarthritis (OA) disease process leads to joint destruction, visualised as radiographic damage.[1] With the need to develop effective therapies for hand OA, it is important to understand which processes are involved. By the time radiographic damage is visible, much of the disease process already took place.[2] Visualisation of the disease process in an earlier stages will facilitate identification of treatment targets and performance of clinical trials.

From ultrasonography studies in hand OA we know that synovial inflammation plays a role in radiographic progression.[3-5] MR has the advantage that subchondral bone can be visualized,[6] where bone marrow lesions (BMLs) are seen as increased water content in the trabecular bone, compatible with possible inflammation or bone fibrosis and remodelling.[7,8] In knee OA studies, BMLs were associated with structural progression.[2,9] In hand OA, one MR study (1.0 Tesla) showed that BMLs, next to synovitis, could predict radiographic progression after 5 years.[10] However, clinical trials in hand OA measure outcome after one or two years follow-up, warranting more data on MR imaging.[11]

As it is unclear whether underlying processes play the same role in onset (incident) and progression of radiographic osteoarthritic damage,[2] we studied both together and apart for their association with baseline MR features. Next to the joint level, with summated MR scores we investigated progression on patient level, the level most clinically relevant. This study used for the first time a midterm follow-up of two years.

METHODS

Study design

We used data of HandOSTeoArthritis in Secondary care (HOSTAS), an observational cohort of consecutive patients from our outpatient clinic (a secondary and tertiary referral center enabling inclusion of patients in all disease stages), who were included after the clinical diagnosis of primary hand OA was made by their treating rheumatologist. The present analysis concerns patients who received contrast-enhanced MR imaging, included March 2011 to October 2012.

Exclusion criteria were: any other pathological condition explaining the hand symptoms, secondary OA and routine MR contraindications. Written informed consent was obtained from all participants. The study was approved by the LUMC medical ethics committee.

For clinical assessment see supplement.

Radiographs

Baseline and two-year follow-up radiographs of distal interphalangeal (DIPJs), proximal interphalangeal (PIPJs), interphalangeal (IPJs), metacarpophalangeal (MCPJs) and 1st carpometacarpal joints of both hands (30 joints per patient) were scored 0-4 following Kellgren-Lawrence (KL) scoring and 0-3 (IPJs 0-1) for osteophytes and JSN following the OARSI atlas (MCPJs following the PIPJs atlas).[12,13] Joints with the highest score or with arthroplasty were in end-stage. Reader WD scored paired in known order, blinded for demographic and clinical data. Intraobserver reliability (based on 10% of pairs), was high: cross-sectional intra-class correlation coefficients (ICC) were 0.89-0.91 and longitudinal percentages exact agreement for progression 92-96% for the different methods.

Radiographic progression was defined as an increase in score above the Smallest Detectable Change (SDC):[14] SDCs on joint level 0.28-0.39, so ≥1 grade defined progression. For subanalysis, joints were classified as incident OA when they changed from no OA at baseline (KL score 0) to radiographic osteoarthritic damage (KL score 1-4). Joints progressed when they had signs of OA at baseline (KL score ≥ 1) and increased in score.

Scores of KL (range 0-120), osteophytes or JSN (both 0-86) of all 30 hand joints were summated to study progression on patient level. SDCs were 2.2, 1.4 and 1.8, respectively. Therefore, increase ≥3 grades in KL or ≥2 grades in osteophyte or JSN summated scores defined progression.

MR Imaging

MR imaging of the right PIPJs and DIPJs (n=8 joints per patient) was performed at baseline, using an ONI-MSK-Extreme 1.5 Tesla (T) extremity MR imaging scanner (GE, Wisconsin, USA), acquiring coronal and axial T1-weighted pre- and post-contrast injection and coronal and axial T2-weighted images (protocol in supplement).

MR imaging scoring was performed blinded for demographic and clinical data by RL, using a modified version of the Oslo hand OA MR imaging scoring.[15] Cross-sectional intra-reader reliability was high: ICC 0.84-1.00 (based on 11 patients).

Synovitis and BMLs were scored 0-3, while effusion, flexor tenosynovitis (PIPJs) or flexor tendon involvement (DIPJs), extensor tendon involvement and cysts were scored present/absent (detailed scoring in supplement).

BML and synovitis scores were summated (range 0-24) for patient level analysis.

Statistical analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were estimated to study the association of MR features (determinant) with radiographic progression (outcome) on joint level using generalised estimating equations (GEE) to account

for the patient effect (joints within a patient as within-subject variable), while adjusting for age, sex and BMI. An exchangeable working correlation matrix, a log link function and the Poisson distribution with robust standard errors were used.[16] Joints without the MR feature served as reference. BML or synovitis grades 2 and 3 were merged. Joints in radiographic end-stage at baseline, were excluded, as they have no potential for progression.

The association between summated scores of MR features (8 joints) and presence of radiographic progression on patient level (both hands) was studied using the modified Poisson approach for binary data (i.e. a Poisson regression model with robust standard errors).

Statistical software from SPSS for Windows, V.23.0 (IBM SPSS statistics, New York, USA) was used.

RESULTS

Study population and prevalence of imaging features

Baseline MR imaging was performed in 107 patients, whereof 87 (83%) (82% women, mean age 59 years, follow-up time 2.1 years, supplement) had follow-up available. Reasons for no follow-up: 11 patients stopped, 2 were excluded, 5 skipped visit and 2 radiographs missed. Patients with and without follow-up did not differ (not shown).

At baseline, 28 (4%) joints were in end-stage for KL, 38 (6%) for osteophytes and 42 (6%) for JSN. Progression was seen in 12%, 9% and 10% of joints not in end-stage, respectively (supplement). At follow-up, one PIPJ had an arthroplasty and 25 patients showed no progression.

BMLs were present in 14.7% (102/693) of joints, while 41.4% (286/691) had synovitis, with missing data in 3 and 5 joints, respectively. Effusion, flexor- or extensor tendon involvement or cysts were present in 8% (57/693), 3% (20/692), 7% (48/692) and 3% (23/696) of joints, respectively.

MR features and radiographic progression

BMLs grade 2/3 were associated with KL progression (vs 0 RR (95%CI) 3.3 (2.1; 5.3), figure 1, supplement), while BML grade 1 was not. Synovitis showed graded associations with KL progression. Similar results were found for associations with osteophyte and JSN progression (supplement). Adjustment for BMLs decreased the strength of the association between synovitis and progression, and vice versa. Neither effusion (present vs absent RR 0.8 (0.3; 2.0)), nor flexor- (1.1 (0.2; 5.9)), nor extensor tendon involvement (0.9 (0.3; 2.5)) nor cysts (1.3 (0.5; 3.3)) were associated with KL progression.

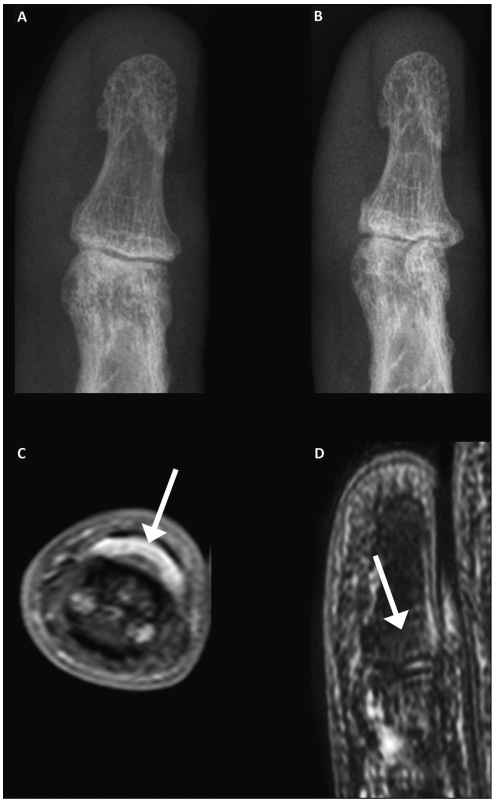

Figure 1. Radiographic progression of a second distal interphalangeal joint. Radiograph at baseline (A) and after two years (B) with corresponding magnetic resonance features (C, D) at baseline.

A. Dorsovolar conventional radiograph at baseline shows discrete joint space narrowing and subchondral cyste formation on the medial side.
B. Dorsovolar conventional radiograph after two years shows progression of joint space narrowing, subchondral cyst- and osteophyte formation.
C. Axial T1-weighted fast spin echo (FSE) image with frequency-selective fat-suppression (FSFS) post-Gd at baseline, shows synovial enhancement (synovitis grade 2) at the dorsal side (arrow).
D. Coronal T2-weighted FSE image with FSFS at baseline, shows high signal in the trabecular bone (bone marrow lesion grade 2) (arrow).

MR features and onset or progression of radiographic osteoarthritic damage

Of joints that increased in KL score, 33 had baseline KL=0 (incident OA), while the other 45 joints had baseline KL≥1 (prevalent OA). Both BML and synovitis were associated with onset and progression and these associations were similar in strength (table 1).

Table 1. Baseline Magnetic Resonance (MR) imaging features associated with radiographic progression in the same joint# after two years of follow-up in 87 patients with hand osteoarthritis in the HOSTAS cohort, stratified to the presence radiographic osteoarthritic damage at baseline.

1a. In 324 joints with no radiographic osteoarthritic damage at baseline (KL= 0), i.e. incident radiographic damage.

MR feature (joint)	Number of joints with progression/ total (% progressed)	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
		Kellgren-Lawrence incidence		
BML				
Grade 0, absent	29/309 (9)	1	1	1
Grade 1	2/12 (17)	1.9 (0.5 to 6.8)	2.0 (0.5 to 7.0)	1.6 (0.6 to 4.2)
Grade 2 + 3	2/3 (67)	6.8 (3.1 to 15.1)	8.8 (3.5 to 22.0)	4.3 (1.4 to 13.5)
Present	4/15 (27)	2.9 (1.2 to 7.2)	3.1 (1.3 to 7.3)	2.6 (1.4 to 5.0)
Synovitis				
Grade 0, absent	17/248 (7)	1	1	1
Grade 1	12/67 (18)	2.6 (1.4 to 5.0)	2.6 (1.4 to 5.0)	2.6 (1.4 to 5.0)
Grade 2 + 3	4/8 (50)	7.0 (3.0 to 16.1)	7.2 (3.1 to 16.7)	5.1 (2.1 to 12.3)
Present	16/75 (21)	3.1 (1.6 to 5.8)	3.1 (1.7 to 5.8)	3.0 (1.6 to 5.5)

1b. In 344 joints, not in end-stage, with progression of radiographic osteoarthritic damage (KL baseline = 1 to 3).

		Kellgren-Lawrence progression		
BML				
Grade 0, absent	25/273 (9)	1	1	1
Grade 1	8/51 (16)	1.8 (0.8 to 3.7)	1.7 (0.8 to 3.6)	1.3 (0.6 to 2.6)
Grade 2 + 3	11/17 (65)	7.2 (4.5 to 11.4)	7.3 (4.7 to 11.6)	3.5 (2.1 to 6.0)
Present	19/68 (28)	3.1 (1.9 to 5.1)	3.0 (1.8 to 4.9)	2.5 (1.5 to 4.1)
Synovitis				
Grade 0, absent	8/149 (5)	1	1	1
Grade 1	12/119 (10)	2.0 (0.8 to 4.9)	2.0 (0.8 to 5.0)	1.9 (0.8 to 4.7)
Grade 2 + 3	24/72 (33)	6.4 (2.9 to 13.8)	6.2 (2.8 to 13.6)	4.2 (1.8 to 9.9)
Present	36/191 (19)	3.6 (1.7 to 7.5)	3.5 (1.6 to 7.5)	3.0 (1.4 to 6.6)

*model adjusted for age, sex and Body Mass Index (BMI).
**model adjusted for age, sex, BMI, BML and synovitis.
#Due to no information, 5 and 3 joints were not taken into account in the synovitis and BML analysis, respectively. Joints in radiographic end-stage at baseline were excluded from the analysis, as they had no potential for progression.
KL = Kellgren-Lawrence, BML = bone marrow lesion, RR = Risk Ratio, CI = confidence interval.

Summated MR features and progression on patient level

Median (range) summated BML score was 1 (0; 10) and synovitis score was 4 (0; 13). Both BML and synovitis summated scores were crudely associated with

progression. However, after adjustment, only the associations for synovitis remained statistically significant (table 2).

Table 2. Associations between summated scores of Magnetic Resonance (MR) imaging features and progression of radiographic osteoarthritis on patient level in 87 hand osteoarthritis patients*.

MR feature	KL progression (95% CI)	Osteophyte progression (95% CI)	JSN progression (95% CI)
Patients with progression/total	44/87	47/87	34/87
BML (0-24)			
Crude RR	1.08 (1.01 to 1.2)	1.05 (0.98 to 1.1)	1.11 (1.02 to 1.2)
RR adjusted for synovitis	1.00 (0.9 to 1.1)	1.01 (0.9 to 1.1)	1.00 (0.9 to 1.1)
RR adjusted age, sex and BMI	1.06 (0.99 to 1.1)	1.07 (0.98 to 1.2)	1.11 (1.01 to 1.2)
Synovitis (0-24)			
Crude RR	1.09 (1.04 to 1.1)	1.05 (1.004 to 1.1)	1.13 (1.1 to 1.2)
RR adjusted for BML	1.09 (1.04 to 1.2)	1.05 (0.99 to 1.1)	1.12 (1.05 to 1.2)
RR adjusted age, sex and BMI	1.08 (1.03 to 1.1)	1.07 (1.02 to 1.1)	1.14 (1.1 to 1.2)

*RR's should be interpreted as increased risk per point increase in summated BML or synovitis scores. E.g. Our observed range for summated BML score was 0-10, so patients with the highest BML score have a 1.08^10=2.16 times (216%) higher risk for KL progression than patients without any BML
KL = Kellgren Lawrence, JSN = joint space narrowing, CI = Confidence Interval, BML = bone marrow lesion, RR = Risk Ratio, BMI = Body Mass Index

DISCUSSION

MR imaging-defined BMLs, like synovitis, showed dose-response associations with radiographic progression in hand OA already after 2 years, confirming earlier studies on ultrasound-detected synovitis,[3] but indicating that BMLs in hand OA, like in knee OA,[2,9] are an important additional factor in the disease process. Also, because presence of BMLs decreases the strength of the association between synovitis and progression, and vice versa.

A strength of our study is inclusion of patients in all disease stages from early to severe. Other cohorts have more severely affected hand OA patients with more joints in end-stage at baseline;[3,10] these joints have no potential for onset of OA or progression and are thus excluded from the analysis.
Another strength is the distinction in onset and progression of radiographic damage in individual hand joints. Of note, this distinction resulted in few joints in some groups and therefore results should be interpreted with caution. We used a cut-off at doubtful to definite OA (KL 1), since lesions can already be present at KL=1. Like in knees, where KL=1 at baseline was a strong predictor for progression

and considered as early OA.[17] We showed that both BML and synovitis were associated with onset and progression and that these associations were similar in strength. This is in line with results for ultrasound-detected synovitis,[4] but was not described before in MR-detected BMLs and synovitis.

Novel is our approach to investigate progression on patient level, which is most relevant from a clinical perspective. Summated BML or synovitis score showed crude associations with progression, although only for synovitis this remained statistically significant after adjustment. This means that the more severe the inflammatory state is, the higher the risk of progression in both hands. We hypothesize that inflammatory MR imaging features could be modified by anti-inflammatory medication like steroids. Future proof-of-concept randomised controlled trials could explore this hypothesis.

This is the first study using 1.5 Tesla MR scanner in hands, enabling more precise identification of lesions with a higher signal-to-noise ratio compared to 1.0 Tesla. Consequences are indicated by our results: we found an association between JSN progression and synovitis grade 1, where another hand OA MR study using 1.0 Tesla did not.[10]

Our study also had some limitations and restrictions in interpretation of results. First, we did not have information whether MR imaging features are persistent or fluctuating. Especially persistent or progressing lesions have shown to be associated with progression and onset of OA.[3,18,19] Nevertheless, we already found the association with only one time measurement. Another limitation is the number of patients in our study. However, the circumstance that in every patient 8 joints can be studied provided enough power to study associations with progression.

Our study indicates that all joints tissues, including BMLs, are important in the disease course of hand OA and it illustrates the use of MR imaging, visualizing BMLs, in detecting early OA and detection of joints and patients prone to progress. Future studies should focus on the persistent or fluctuant nature of BMLs in hands and on hand MR imaging on the short term.

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SUPPLEMENT

MRI protocol

MR imaging was performed using an ONI-MSK-Extreme 1.5 Tesla (T) extremity MR imaging scanner (GE, Wisconsin, USA). The right hand PIPJs and DIPJs (n=8 joints) of each patient were examined, regardless of clinical features or dominance.

The following sequences were used: coronal T1-weighted (T1-w) fast spin echo (FSE) images (repetition time (TR)/echo time (TE) 575/11 milliseconds (ms), acquisition matrix (AM) 388×288, echo train length (ETL) 2, minimum TE), axial T1-w FSE images (TR/TE 500/10.2 ms, AM 340×288, ETL 2, minimum TE), coronal T2-w FSE images with frequency-selective fat-saturation (FSFS) (TR/TE 3000/61.8 ms, AM 300×224, ETL 7) and axial T2-w FSE images with FSFS (TR/TE 3000/57 ms, AM 336×192, ETL 7) before contrast injection, and coronal T1-w FSE images with FSFS (TR/TE 600/10.4 ms, AM 364×224, ETL 2, minimum TE) and axial T1-w FSE images with FSFS (TR/TE 650/7.7 ms, AM 320×192, ETL 2, minimum TE) after intravenous injection of gadolinium-chelate (Gd) (gadoteric acid, Guerbet, France, standard dose 0.1 mmol/kg). Coronal images had a field of view (FOV) of 120 mm and 18 slices with slice thickness 2 mm and slice gap 0.2 mm. Axial sequences had a FOV of 100 mm and 24 slices with slice thickness 3 mm and slice gap 0.3 mm. Total acquisition time was 30 minutes.

MRI scoring

MR imaging scoring was performed using a modified version of the Oslo hand OA MR imaging scoring. Effusion and extensor tendor involvement (see definition) were added to the scoring. As there is no tendon sheet around the extensor tendon on PIPJ and DIPJ level or around the flexor tendon on DIPJ level*, we renamed tenosynovitis to involvement.

BMLs, synovitis, flexor tenosynovitis and cysts were scored in the same manner as described in the atlas, using T2-weighted images instead of STIR. Data for flexor pathology were dichotomized in presence and absence after scoring.

Synovitis was defined as an area in the synovial compartment showing post-Gd enhancement (on T1-w post-Gd images) of a thickness greater than the width of synovium (≥ 1 mm). Score 0 = no synovitis; 1 = mild, 1/3 of synovium thickened; 2 = moderate, 2/3 thickened; 3 = severe, all synovium thickened.

BMLs were defined as lesions within the trabecular bone with signal characteristic consistent with increased water content on T2-w images: 0 = no BML, 1 = 1-33% of bone with BML, 2 = 34%-66% with BML, 3= 67%-100% with BML. Distal and proximal joint sites were scored separately and the highest score was taken as the score for the whole joint.

Effusion, fluid in the joint, was present when an area showed increased signal

intensity on T2-w images, non-enhancing on T1-w post-Gd images and only when synovitis was present.
Flexor tenosynovitis (PIPJs) or flexor tendon involvement (DIPJs) was present when an area in the flexor tendon (sheath) showed post-Gd enhancement on T1-w images more than normally expected.
Extensor tendon involvement was present when opposite sides of the tendon showed post-Gd enhancement on T1-w images more than normally expected.
Cysts were defined as sharply marginated bone lesions without a cortical break with low signal on T1-w pre-Gd images and high signal on T2-w images.

*Nieuwenhuis WP, Krabben A, Stomp W, *et al.* Evaluation of Magnetic Resonance Imaging–Detected Tenosynovitis in the Hand and Wrist in Early Arthritis. *Arthritis Rheumatol* 2015;**67**:869–76. doi:10.1002/art.39000

Clinical assessment

Demographic and disease characteristics were collected by standardised questionnaires. Self-reported hand pain was assessed by visual analogue scale (range 0-100 millimeter). Self-reported hand function (0-30) was assessed by the Functional Index for Hand OsteoArthritis (FIHOA)*. Higher scores indicate worse health.

Physical examination was performed by a trained research nurse, assessing the distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), interphalangeal joints, metacarpophalangeal joints (MCPJs) and 1st carpometacarpal joints of both hands (n=30 joints per patient) for tenderness upon palpation and bony and soft swelling.

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Supplementary table 3. Baseline characteristics of 87 hand osteoarthritis (OA) patients with available contrast-enhanced magnetic resonance imaging at baseline and follow-up radiographs from the HOSTAS cohort.

Patient level, 87 patients	
Age, mean (SD), years	59.4 (7.6)
BMI, mean (SD), kg/m^2	27.3 (4.4)
Women, number (%)	71 (82)
Self-reported symptom duration, median (range), years	5.5 (0.3 to 36.8)
Dominance, n (%)	
- Right	63 (72)
- Unclear	8 (9)
Fulfilling ACR criteria*, number (%)	80 (92)
VAS pain, mean (SD), 0-100^	
- Right hand	33.6 (21.4)
- Left hand	33.9 (22.5)
Self-reported function, median (range), 0-30	8 (0 to 24)
Median number of involved joints per patient (range)	
- Tender joints upon palpation 0-30	3 (0 to 24)
- Bony swellings 0-30	12 (0 to 22)
- Soft swellings 0-30	0 (0 to 17)
Radiographic erosive disease**, n of patients (%)	26 (30)
Joint level, 696 joints (n=8 per patient)	
Physical exam findings, n/total (%)	
- Tenderness upon palpation	120/696 (17)
- Bony swelling	420/696 (60)
- Soft swelling	49/696 (7)

BMI = body mass index, ACR = American College of Rheumatology, VAS = visual analogue scale.
^n=86
*Altman R, Alarcon G, Appelrouth D, *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;**33**:1601–10.
Erosive disease was present when having ≥1 joint with an eroded or remodelled subchondral plate following Verbruggen-Veys anatomical phase scoring (Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis Rheum* 1996;39**:308–20).

Supplementary table 4. Baseline Magnetic Resonance (MR) imaging features associated with radiographic progression in the same joint# after two years of follow-up in 87 patients with hand osteoarthritis in the HOSTAS cohort.

MR feature (joint)	Number of joints with progression/ total (% progressed)	Crude RR (95% CI)	Adjusted RR (95% CI)*	Adjusted RR (95% CI)**
		Kellgren-Lawrence progression		
BML				
Grade 0	54/582 (9)	1	1	1
Grade 1	10/63 (16)	1.7 (0.8 to 3.3)	1.6 (0.8 to 3.2)	1.2 (0.7 to 2.1)
Grade 2 + 3	13/20 (65)	6.9 (4.7 to 10.1)	7.2 (4.9 to 10.6)	3.3 (2.1 to 5.3)
Synovitis				
Grade 0	25/397 (6)	1	1	1
Grade 1	24/186 (13)	2.1 (1.2 to 3.6)	2.2 (1.3 to 3.7)	2.1 (1.2 to 3.6)
Grade 2 +3	28/80 (35)	5.6 (3.4 to 9.3)	5.7 (3.4 to 9.5)	4.0 (2.2 to 7.1)
		Osteophyte progression		
BML				
Grade 0	41/577 (7)	1	1	1
Grade 1	9/61 (15)	2.0 (0.8 to 4.9)	2.0 (0.8 to 4.8)	1.4 (0.7 to 3.0)
Grade 2 + 3	10/17 (59)	7.9 (4.4 to 14.2)	8.7 (5.0 to 15.1)	3.7 (2.2 to 6.4)
Synovitis				
Grade 0	15/397 (4)	1	1	1
Grade 1	23/182 (13)	3.6 (1.9 to 7.1)	3.6 (1.8 to 7.3)	3.4 (1.7 to 6.8)
Grade 2 +3	22/74 (30)	8.3 (4.5 to 15.4)	8.3 (4.2 to 16.1)	5.7 (3.0 to 11.1)
		Joint space narrowing progression		
BML				
Grade 0	46/580 (8)	1	1	1
Grade 1	11/60 (18)	1.8 (0.8 to 3.9)	1.8 (0.8 to 3.9)	1.3 (0.6 to 2.8)
Grade 2 + 3	9/11 (82)	7.7 (4.3 to 13.8)	7.8 (4.2 to 14.5)	3.5 (1.7 to 7.2)
Synovitis				
Grade 0	20/394 (5)	1	1	1
Grade 1	23/184 (13)	2.3 (1.3 to 4.1)	2.3 (1.3 to 4.1)	2.1 (1.1 to 3.9)
Grade 2 +3	23/71 (32)	5.5 (2.9 to 10.6)	5.5 (2.7 to 11.1)	3.5 (1.7 to 7.4)

*model adjusted for age, sex and Body Mass Index (BMI).
**model adjusted for age, sex, BMI, BML and synovitis. The JSN analysis was also adjusted for presence of baseline JSN (score≥1).
#Due to no information, 3 and 5 joints were not taken into account in the BML and synovitis analysis, respectively. Joints in radiographic end-stage at baseline were excluded from the analysis, as they had no potential for progression.
BML = bone marrow lesion, RR = Risk Ratio, CI = confidence interval.

PART II

Mortality in osteoarthritis

6

Chapter 6

Mortality in osteoarthritis patients

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Rheumatology (Oxford). 2016 Mar;55(3):411-8.

ABSTRACT

OBJECTIVE

To investigate whether all-cause and cardiovascular mortality is increased in patients who have consulted primary or secondary health care with osteoarthritis (OA) symptoms and signs.

METHODS

383 patients with symptomatic OA at multiple sites from the 'Genetics ARthrosis and Progression' (GARP) study (mean age 60 years, 82 % women, 3693 person years of follow-up) and 459 patients with primary hand, knee or hip OA from the 'Osteoarthritis Care Clinic' study (mean age 61, 88 % women, 1890 person years of follow-up) were followed. Standardized mortality ratios (SMRs) with 95% confidence intervals (CI) were calculated for all-cause mortality and causes of deaths in comparison to the general population. Cox proportional hazard ratios (HR) with 95% CI were used to associate baseline characteristics with all-cause mortality.

RESULTS

In GARP 26 patients died, while 48 deaths were expected (SMR 0.54 (0.37-0.79)). The SMR was 0.47 (0.29-0.76) in women and 0.73 (0.39-1.35) in men. Similar results were found in the Osteoarthritis Care Clinic study (SMR 0.45 (0.25-0.82)). Malignancy and cardiovascular disease were the main causes of deaths in GARP. Male sex (HR 3.04 (1.38-6.69)), increasing age (HR 1.10 (1.05–1.16) and self-reported cancer (HR 8.29 (3.12-22.03) were associated with increased mortality in GARP.

CONCLUSION

Patients consulting health care for their OA are not at higher risk of death than the general population. These results suggest that the management of OA patients may not need to focus specifically on the treatment of cardiovascular risk factors and comorbidities.

INTRODUCTION

Osteoarthritis (OA) is a common disease with rising prevalence. Recently, increased all-cause mortality was found among subjects surveyed from the general population with hip and knee pain and radiographic OA signs.[1] Next to atherosclerosis, diabetes, walking disability and use of NSAIDs may explain a possible association between OA and mortality.[1,2] For clinical practice this could mean that management of patients with OA should focus on effective treatment of cardiovascular risk factors and comorbidities.[1,3]
Therefore, we investigated whether OA patients who present themselves in health care with OA experience an increased mortality and whether this is due to cardiovascular causes.

PATIENTS AND METHODS

Study design

We investigated two prospective observational cohorts of OA patients.
The 'Genetics ARthrosis and Progression'(GARP) cohort comprised 192 Caucasian sibling pairs (384 patients) with symptomatic primary OA at multiple sites in the hand or in at least 2 of the following sites: hand, knee, hip or spine, that were diagnosed by rheumatologists, orthopaedic surgeons and general practitioners.[4] They were included between August 2000 and March 2003, after informed consent. Twenty patients with shortened life expectancy were excluded; eleven older than 75 years at time of inclusion and nine with poor health. The study was approved by the medical ethical committee.
The 'Osteoarthritis Care Clinic'(OCC) cohort consisted of 460 consecutive patients who were diagnosed by the rheumatologist with primary hand, knee or hip OA and referred to the clinical nurse specialist for education between August 2005 and April 2009.[5]

Demographics and clinical characteristics

Demographic characteristics, smoking status and comorbidities (verified by a physician) were collected by standardized questionnaires. Self-reported pain and functional limitations were assessed by subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for knee and hip, and the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index for hand.
WOMAC subscales ,VAS format (range 0-100, higher scores=worse outcome), were available of 383 GARP patients. A Likert scale (0=none to 4=extreme) was used for the AUSCAN subscales pain (range 0-20) and function (range 0-36) (in 351 GARP and all OCC patients).

Follow-up and assessment of mortality

Observation time started on date of inclusion and ended on either November 2nd 2011, date of death, emigration or loss to follow-up, whichever occurred first (complete follow-up for 98% of the cohort). Person-years were counted for all participants.

Vital status was verified by using municipal registries (Gemeentelijke Basis Administratie) and primary causes of death of GARP patients by the Central Bureau of Statistics Netherlands (CBS), national repository for death certificates. These data were compared with causes of deaths (coded to ICD-10 classification) in the general population.

Data analysis

Standardized Mortality Ratios (SMR) with 95% confidence intervals (CI) were calculated for all-cause mortality and cause-specific mortality, using STATA version 10.1 (Statacorp, College station, TX). For expected numbers of deaths from age and sex specific mortality data of the general population, we used the mid of the follow-up time as reference year.

'Healthy cohort' effects may occur due to exclusion of patients with shortened life span, Since this effect ebbs away after a couple of years, enabling unbiased analyses [6], SMRs were also calculated by delaying the start of follow-up.

Associations between characteristics of patients at baseline and all-cause mortality in GARP were studied using univariate and multivariate Cox proportional hazards models, adjusting for age and sex. To take a potential family effect into account in GARP, shared frailty was applied in the Cox proportional hazard models (using STATA), assuming that observations of siblings have the same frailty. However, the variance of shared frailty was very small and including it had a negligible influence on the hazard ratios. We therefore decided to perform the analyses without the family effect using SPSS version 20 (SPSS Inc, Chicago,IL).

RESULTS

Population descriptions

For the present analysis 383 patients from the GARP cohort (mean age 60 years, 82% women, see supplementary Appendix 1, available online) were included (one patient only seen at baseline and lost to follow-up), accounting for 3693 person-years of follow-up (median 9.9 years, range 1.83-11.9 years). In the OCC cohort 459 patients (mean age 61 years, 88% women, supplementary Appendix 1)

were included (one patient only evaluated at baseline and lost to follow-up) and accounted for 1890 person-years of follow-up (median 3.9 years, range 0.87-6.8 years).

Mortality

In GARP, 26 OA patients (16 females, 10 males) died during follow-up, resulting in a SMR of 0.54, 95% CI 0.37 - 0.79. The SMR was lower in women than in men (Table 1). In patients from the OCC cohort we found similar results (Table 1).
No excess mortality was observed in our two cohorts of OA patients when compared to the general population.

Causes of death

In the GARP study 21 of the 26 deaths occurred due to either cancer (most common cause of death in women) or cardiovascular disease (most common cause of death in men) (Table 1).

Healthy cohort effect and sib pairs

A potential healthy cohort effect was investigated in GARP. The SMR did not increase when the start of follow-up was delayed. (Figure 1)
The SMRs calculated separately for probands and siblings, did not differ.

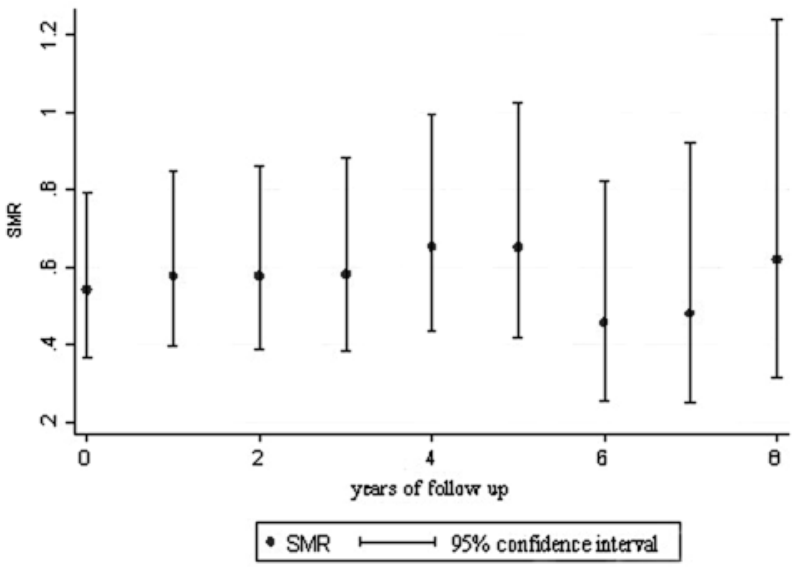

Figure 1. The Standardized Mortality Ratio (SMR) with 95% confidence interval bars calculated by delaying the year follow-up started in the GARP study

Table 1. Mortality and causes of death in 2 patient cohorts with primary osteoarthritis, compared with the Dutch population

Cohort	Cause of death	All patients		SMR (95% CI)	Men		SMR (95% CI)	Women		SMR (95% CI)
		Observed	Expected		Observed	Expected		Observed	Expected	
GARP	All causes	26	48	0.54 (0.37-0.79)	10	14	0.73 (0.39-1.35)	16	34	0.47 (0.29-0.76)
		9	14	0.66 (0.34-1.26)	5	4	1.13 (0.47-2.72)	4	9	0.43 (0.16-1.15)
	Cancer	12	20	0.59 (0.33-1.04)	3	6	0.54 (0.17-1.66)	9	15	0.61 (0.32-1.17)
	All causes	11	24	0.45 (0.25-0.82)	3	5	0.66 (0.21-2.06)	8	20	0.40 (0.20-0.81)

Risk factors associated with mortality

Univariate analysis revealed that male sex, increasing age and self-reported cancer were associated with increased mortality in the GARP cohort. In multivariate analysis male sex, age and self-reported cancer were associated with increased mortality. Hip OA was associated with mortality in the univariate analysis, but no longer when adjusted for sex and age. The WOMAC questions on walking, walking on flat surfaces and pain when walking, were not associated with mortality. A strong trend can be seen for smoking (Table 2).

Table 2. Univariate and multivariate analysis of hazard ratios with 95% confidence intervals (95% CI) for mortality in 383 osteoarthritis patients

Characteristic at baseline	Univariate Model HR (95% CI)	Multivariate Model HR (95% CI)*
Male sex	3.04 (1.38-6.69)	2.67 (1.21-5.90) ‡
Age, years	1.10 (1.05-1.16)	1.10 (1.04-1.16) §
BMI, kg/m^2	0.98 (0.90-1.07)	0.97 (0.88-1.07)
Knee OA**	0.73 (0.31-1.73)	0.59 (0.25-1.41)
Hip OA***	2.31 (1.06-5.03)	1.55 (0.70-3.45)
AUSCAN pain#	0.95 (0.87-1.04)	0.98 (0.89-1.07)
AUSCAN function#	0.98 (0.93-1.03)	0.99 (0.94-1.04)
WOMAC pain#	0.99 (0.97-1.01)	0.99 (0.97-1.01)
WOMAC function#	0.99 (0.98-1.01)	1.00 (0.98-1.01)
Smoking	1.99 (0.87-4.58)	2.14 (0.91-5.04)
Cardiovascular disease	0.62 (0.08-4.54)	0.43 (0.06-3.18)
Diabetes	1.77 (0.42 - 7.47)	1.14 (0.27-4.88)
Cancer	8.29 (3.12-22.03)	13.56 (4.69-39.19)

*Adjusted for age, sex, unless stated otherwise
‡Adjusted for age
§Adjusted for sex
**patients without knee OA as the reference category
***patients without hip OA as the reference category
#HR's given per unit standardised score
HR, hazard ratio; BMI, body mass index; OA, osteoarthritis; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

DISCUSSION

In two observational cohorts of OA patients who consulted health care for their OA, no increased mortality rate was found. Risk factors for death were male sex, age and the co-morbid condition of cancer, but no OA-associated factors. These results suggest that management of OA patients may not need to focus specifically on treatment of cardiovascular risk factors and comorbidities.

Evidence concerning mortality in OA has been contradictory. Hochberg's review concluded on an increased risk of death in OA with moderate evidence due to methodological problems, such as lack of adjustment for confounding variables.[7] Additionally, patients with hip and knee OA undergoing arthroplasty experienced prolonged survival. Our results are in line with these studies.[8,9]

Our findings do not support the results by Nuesch et al, who found excess mortality,[1] which may be due to differences in study populations. The British cohort included subjects with knee or hip OA, recruited via general population survey, whereas our cohorts included patients with knee or hip OA, but also hand and spine OA, who actively consulted health care from a medical specialist or general practitioner for their OA complaints.

We hypothesized that subjects who actively sought care for OA would be especially at risk for mortality, because these patients suffer from severe forms of OA. However our study results do not support this hypothesis. Several explanations can be given. These patients may be healthier because they possess behavioural traits which distinguish them from other OA patients who do not seek health care. These personality traits may also prompt them to pursue a healthy life-style and seek early care for diseases.

Both GARP and OCC participants were more often overweight when compared to the general population.[5,10] Though patients are not actively screened for metabolic syndrome, patients with OA who consult health care will also receive care for other known medical conditions, which could result in lowered mortality rates. Since we did not find a specific cause of death which stood out, nor an effect of OA-related factors, these explanations seem more likely than an effect of OA per se on mortality.

Our study has limitations. First, in a prosthetic study it has been suggested that reduced mortality may be explained by preoperative selection of healthier people.[11] To preclude that our results may have resulted from exclusion of patients with a shortened life span in GARP, we tested the presence of this 'healthy cohort' effect and did not find it. Exclusion of patients above 75 years is unlikely to have biased our SMR, as the number of deaths in age- matched general population would have been high as well. We also coped with this limitation by replication in the OCC cohort.

Second, the reliability of the death certificates, often filled in late at night, is limited. However, this misclassification will occur to our OA patients and control population alike.

Self-reported diseases can also be misclassified.

Finally, cardiovascular disease, the WOMAC function and BMI were not associated with mortality in our GARP cohort. These negative findings may be due to the limited number of events that occurred. Many unknown factors may act as confounders for the association between some factors and mortality (e.g. influence of NSAIDs for the association between physical function and mortality). Unfortunately, due to the limited number of events in our cohorts, we were unable to investigate the extensive list of potential confounders in this study.

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TABLES

Appendix 1. Baseline characteristics of patients in the GARP study and 'Osteoarthritis Care Clinic' patients

Baseline characteristics	GARP patients (n = 383)	'Osteoarthritis Care Clinic' patients (n = 459)
Women (n (%))	314 (82)	404 (88)
Age (mean (SD))	60 (7.6)	61 (9.8)
Hand OA (n (%))	276 (72)	438 (95)
Knee OA (n (%))	130 (34)	101 (22)
Hip OA (n (%))	93 (24)	NA
BMI >25 (kg/m^2 (%))	237 (62)	225 (60)
Smoking (n (%))	206 (54)	164 (40)
AUSCAN pain (range 0-20)	6 (0-19)	10 (0-20)
AUSCAN function (range 0-36)	10 (0-33)	18 (0-36)
WOMAC pain (range 0-100)	24 (0-96)	NA
WOMAC function (range 0-100)	20 (0-96)	NA
Cardiovascular disease (n (%)) *	23 (6)	NA
Diabetes (n (%))*	18 (5)	NA
Cancer (n (%))*	13 (3)	NA

*Self-reported
Values are medians plus range unless stated otherwise.
BMI, body mass index; OA, osteoarthritis; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

7

Chapter 7

Mortality in osteoarthritis: a systematic review

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Submitted

ABSTRACT

OBJECTIVE

To summarize and to determine the association between osteoarthritis (OA) and mortality in three clinical settings: patients undergoing arthroplasty or seeking care for their OA or persons in the general population.

METHODS

A systematic search was performed up to October 2016. Two independent reviewers identified studies that reported mortality for OA patients, compared with a non-OA population. Study quality was also assessed. Information on study design, patient characteristics, OA status, duration of follow-up, mortality assessment and mortality rates were extracted for each study. Meta-analysis was performed when appropriate.

RESULTS

Of 5121 individual references, 33 articles reporting on 35 studies including 499103 participants were selected.

Seven high quality joint arthroplasty studies reported either an equal or reduced overall mortality rate for OA patients when compared to the general population.

Two high quality studies of OA patients seeking care reported no association between OA and mortality.

Results of ten population-based studies of high quality were equivocal. Some studies found a positive association between OA and mortality, while others did not. Meta-analysis of 6 studies showed no association. (HR 1.04 (95% Confidence Interval 0.91-1.18)). The association may depend on OA subtype.

CONCLUSION

There is no clear association between the presence of OA and mortality.

INTRODUCTION

Osteoarthritis (OA) is a common disease and its prevalence is rising. It has been estimated that more than 40 million of European adults suffer from symptomatic OA.[1] OA often results in pain, disability and decreased quality of life.[2] Whether OA also results in increased mortality is currently not clear.

Evidence concerning mortality due to OA is contradictory. One narrative review and two systematic reviews have broached this topic.[3-5] Unfortunately, these reviews had some shortcomings. In the narrative review the search for evidence was not systematically performed, so relevant and valid studies could have been missed.[3,6] The systematic reviews focused on mortality risk estimates (hazard ratios (HR)), did not include studies that classified OA based on total joint replacement surgery, [4] or only included studies when radiographic OA was present.[5] Furthermore, several new studies on this subject have been published.[7,8]

Therefore, we conducted a systematic review to summarize and to determine the association between OA and mortality for three different settings, i.e., the general population, among patients with OA requiring a total joint replacement, and among patients seeking health care for their OA complaints.

METHODS

Identification of studies

A systematic search (up to October 2016) was performed with a medical librarian in the databases PubMed, Embase, COCHRANE Library, Web of Science, ScienceDirect, CINAHL and Academic Search Premier (see supplementary Appendix I for a detailed overview of the search strategy). Reference lists of included studies were screened to identify additional relevant studies and articles could also added by hand search.

Inclusion and exclusion criteria

Two reviewers (RL and MK) performed the selection of titles, abstracts and full text articles, independently of each other. The exclusion of full text articles and thus selection of articles for inclusion in this review was performed by two independent reviewers (by either RL and MK or RL and MCK). Disagreements were resolved by discussion in consensus meetings. Studies which reported overall mortality in primary OA patients, when compared with a non-OA or general population, were included. Case reports, case series, (meeting) abstracts, reviews, studies investigating other musculoskeletal disease than primary OA and studies in other languages besides English and Dutch were excluded. Studies solely using diseases

with an established increased mortality rate as control groups, e.g. rheumatoid arthritis, were also excluded. Follow-up of at least a year was required to distinguish OA related mortality from mortality as a part of postoperative complications. If multiple publications occurred of the same study, the publication with the largest or most recent analysis was selected.

Data extraction

Information on OA demographics (population size, patient characteristics, age, sex) and duration of follow-up were extracted for each study. We only extracted mortality data for OA patients. In case more than one control group was used, the general population group was chosen if present.

Assessment of study quality

Study quality was assessed by RL and MCK using 14 criteria based on previous systematic reviews in the field of musculoskeletal disorders.[9,10] The criteria were modified to evaluate studies on the association between OA and mortality (see supplementary Appendix II). When a criterion was met in the article, '1' was given, otherwise '0'. A '0' was also given when incomplete or no information was given about the specific criterion or if information was not provided for the OA patients separately. The maximum score obtainable for cohort studies was 10, for nested case-control studies 13. For each study, the total quality score was calculated as the percentage of the maximum score obtainable. A study was rated as a high quality study if ≥67% was scored.

Data analysis

To investigate the association between population based OA studies and mortality, a meta-analysis was performed. The HRs of high quality studies were pooled using a random effect model to account for heterogeneity of the studies. Subgroup analyses were performed for different OA subtypes (knee, hip, hand). If different radiographic scoring systems were used to define OA, the HR based on the most often used was included in the meta-analysis. Additionally, a sensitivity analysis was performed by analyzing radiographic and symptomatic OA separately. All analyses were done using Stata V14 (StataCorp LP, Texas).

RESULTS

Selection of studies

The electronic databases yielded 5121 individual references of which 1525 were duplicates and 561 only contained meeting abstracts, 2551 articles were excluded

on the basis of title and 284 articles on the basis of abstracts. Two hundred articles were screened full-text. Seven articles were additionally excluded due to multiple or overlapping publications for the same population (the most recent or largest cohort publication remained). In the end, 32 articles were included. Two articles reported multiple studies and one article was added by hand-search (Figure 1). In total 33 articles, investigating 35 studies, were selected for the present review. Only one study reported the results of nested case control studies.

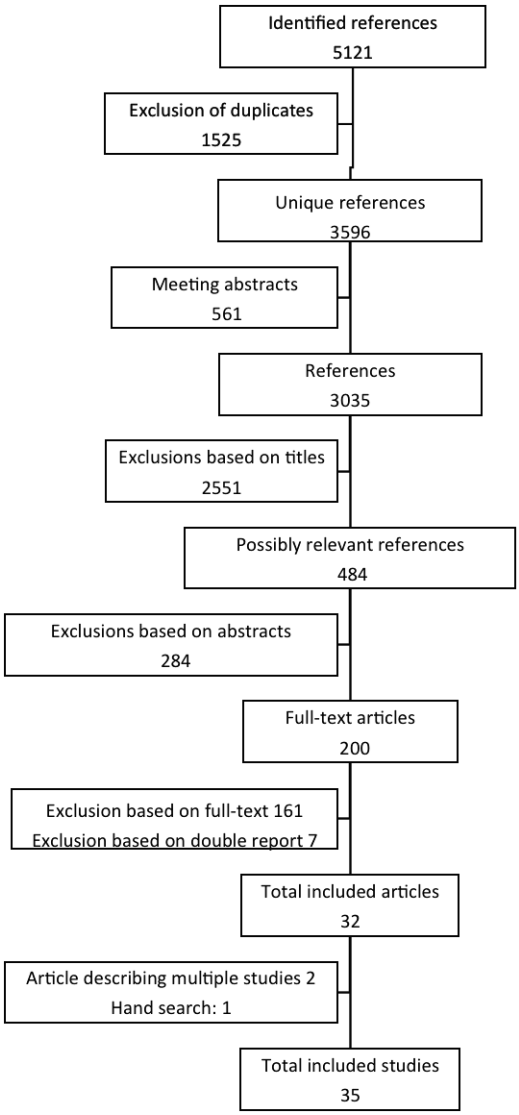

Figure 1. Flow chart of systematic review

Characteristics of included studies

Table 1 lists the characteristics of all OA studies.

A total of 499103 participants were included in 35 studies [2,4,7,8,11-39]. Two studies only included female participants, while both men and women were included in the other reported studies.[12,23] In studies reporting average age of the participants the age averaged between 54.5 and 91.9 years. Follow-up time ranged between 1 year and 42 years.

Most studies focused on knee or/and hip OA (n=24). Only one study reported shoulder OA.[11] Comparisons were mostly made with the general population using information from the country's bureau of statistics. One study used different radiographic scoring systems to define OA, while all other studies only used the Kellgren/Lawrence (K/L) score. Studies were conducted in one of three settings: patients undergoing arthroplasty, patients seeking care for their OA and persons with OA in the general population.

Study quality assessment

There was only one nested case control study and this study was of good quality with a clear description of the study, valid OA definition, cases and controls drawn from the same source population, valid measurements of the outcome and adequate analysis and presentation of the results.[37]

Of the 34 included cohort studies, the mean quality assessment was 62% (median was 70%, range 10 - 90%)(Table 2). ACR criteria were never used to define OA, radiographic definitions were however used in seven studies. One study used radiographic definition for part of the study[23]. Seventeen studies investigated total joint arthroplasty due to OA. Selection bias could sometimes not be determined due to a lack of information about exclusion criteria. The majority of the studies adjusted for age and gender to calculate the effect of OA in mortality. Standardized mortality ratios (SMRs) or HR were not often reported.

Association between osteoarthritis and mortality

Sixteen joint arthroplasty articles reported mortality in 17 studies, receiving either total knee or hip arthroplasty (Table 3A).[8,11,13,16,21,22,25-27,30,31,33-36,38] One study investigated mortality after total shoulder arthroplasty. There were seven high quality studies and all reported equal or lower overall mortality rates for OA patients when compared to the general population. One study reported a lower SMR at follow-up time of less than 10 years and a higher SMR at follow-up time of 10 years or more.[8]

Six studies involved patients consulting either their general practitioner or a medical specialist (Table 3B);[7,15,29,32,39] three of these studies were of high quality. None of these high quality studies reported an association between OA and mortality.

Table 1. Study characteristics of included studies (in alphabetical order of first author name)

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Amundsen; 2016[11]	Shoulder arthroplasty OA; 2006-2012; 1799; 66.5 (10.9); 58.9	General population	1	Death register
Barbour, 2015[12]	Radiographic hip OA from population based cohort; 1986-1988; 635; 71.4 (5.1); 100	Participants without radiographic hip OA	16.1 (6.2)	Death register
Böhm, 2000[13]	TKA; 1972-1994; 208; 72 (range 46-87); 84	General population	6	Hospital patient records
Cacciatore, 2014[14]	OA from population based study; 1992; 698; 74.8 (6.5); 80.1	Participants without OA	12	Death register
Danielsson, 1970[15]	Radiographic knee OA from hospital records; 1950-1958; 3994; NR	General population	NR	NR
Garellick, 1998[16]	THA; 1985-1989; 242; 70 (range 41-85) and 71 (range 40-86); 70% and 64%#	General population	8 (range 6-10)	Death register
Haara, 2003[17]	Finger OA (K/L≥2) from population register, 1978-1980, 1670, age groups 30-75+, 62	Participants without finger OA KL≥2	15-17, 43632 person-years	Death register
Haara, 2004[18]	Thumb CMC OA (K/L≥2) from population register, 1978-1980, 409, age groups 30-75+, 73	Participants without thumb CMC OA KL≥2	Up to 17	Death register
Haugen, 2015[19]	Radiographic or symptomatic hand OA from 'original' population based cohort and 'offspring' cohort; 1990-1994 for original and 1991-1995 for offspring; 1348; radiographic 66.1 (7.6) and symptomatic 66.6 (7.1); radiographic 74.2 and symptomatic 74.2	Participants without hand OA	Up to 19	Death register
Holbrook, 1990[20]	Knee, back, hand or hip OA from population based study; 1973-1975; 104; 50-70+; 63	Participants without OA	Up to 15 years	Death register
Holmberg, 1992[21]	THA;1978-1982; 518; 67 (range 40-88); 62	General population	At 6	Death register
Karuppiah, 2008[22]	THA; 1987-2007; 58; 91.9 (range 90-95); 67	General population	3.4 (range 2.9-3.8)	Hospital records, care taker or family doctor.
Kluzek, 2016[23]	Radiographic and symptomatic knee and hand OA from population based study; 1988-1989; radiographic knee OA 64, symptomatic OA 57, radiographic hand OA 166, symptomatic OA 99; knee 58.7-59.6 (4.9-6.3) hand 59.3-60.0 (5.1-5.5); 100	Participants without knee OA, participants without hand OA	Till 23 (median 21.7)	Death register

Table 1. Study characteristics of included studies (in alphabetical order of first author name) (*Continued)*

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Lee, 2007[24]	OA from national veterans health administration, 2000; 25 231; 58.8; NR	Veterans without common comorbid conditions	5	The Beneficiary Identification and Records Locator System
Lie, 2000[25]	THA; 1987-1998; 26433; age groups 69 (range ≤59 -≥80); 68	General population	Median 5.2 (range 0-10.4)	Death register
Lindahl 2007[26]	THA; 1979 to 2000; 63582; aged 50-90; 57	General population	108 700 py males, 143 000 py females	NR
Lindberg, 1984[27]	THA; 1968-1981; 974; median age group 65-69 (range 30-89); 64	General urban population	Range 0-13	Death register
Liu. Q, 2015[28]	Symptomatic and radiographic knee OA; 2005; symptomatic 63, radiographic 181; symptomatic 62.2 (8.6), radiographic 61.6 (9.2); symptomatic 71.4 radiographic 65.2	Participants without symptomatic OA, participants without radiographic OA	8 years	Interviewing relatives and death register of the local community office
Liu. R, 2015[29]	Multiple OA; 2000-2003; 383; 60 (7.6); 82	General population	Median 9.9 (range 1.83-11.9)	Death register
Liu. R, 2015[29]	Hand, knee or hip OA; 2005-2009; 460; 61 (9.9); 88	General population	Median 3.9 (range 0.0-6.8)	Death register
Lizaur, 2015[30]	TKA; 1994- 2003; 1569; median 68.2 (40-86); 76.7	General population	10	Death register
Michet, 2016[31]	THA and TKA from a population based cohort; 1969-2008; THA 1611, TKA 1938; THA median 68 (range 15-97), TKA 69 (14-93); THA 58 TKA 63#	General white population	11.9 (7.4)	Death register
Monson, 1976[32]	Hospitalized for arthritis; 1930-1960; 617; at death aged 75.9 females and 74,8 males; 73	General white population	12-42, 27% lost to FU	Local death register
Nüesch, 2011[2]	Knee or hip OA from population based cohort; 1994-1995; 1163; aged 35->75; 57	General population	Up to 15	Death register
Ohzawa, 2001[33]	TKA; 1989-1996; 53; 68.4 (range 42-83); NR	General population	2-9	NR

Table 1. Study characteristics of included studies (in alphabetical order of first author name) (*Continued)*

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Pedersen, 2011[34]	THA; 1995-2006; 44558; age range 10->80; 56	Random sample by Danish Civil Registration System matched by age/gender	Up to 12,7 yr. <5 yr n=94410, 5-10 yr n=64453, >10 n=19386	Death register
Robertsson, 2007[35]	TKA; 1980-2002; 57979; 71(range 25-96); 65%	General population	Up to 28 after surgery. 382 427 person years	Death register
Schrøder, 1998[36]	TKA; 1989-1990; 761; aged 23 ->75;73#	General population	Up to 5 postoperatively	Death register
Schrøder, 1998[36]	THA; 1989-1990; 326; 23 ->75; 73#	General population	Up to 5 postoperatively	Death register
Tsuboi, 2011[37]	Knee OA from health checkup screening; 1997-1999; 244; 68.5 (±5.5); 70	Patients without knee OA	10	NR
Turkiewicz, 2016[7]	Health-care visits with diagnostic code knee OA or hip OA; 1998-2012; knee OA 51939, hip OA 29442; knee OA 70 (11), hip OA 72 (10); knee OA 60, hip OA 58	General population seeking health care and general population	10.3 (range 0-16)	Death register
Veronese, 2016[4]	Hand, hip or knee OA from population based cohort; 1995-1997; 1858; 77.5 (7.9); 66.4	Participants without OA	4.4	Death register
Visuri 2010[38]	THA, two surgery techniques: MM: 1967-1973; 579; age range 20- ≥80; 66 MP:1973-1985; 1585; age range 20- ≥80; 61.	General population	20-38	Death register
Visuri 2016[8]	TKA; 1980-1996; 9443; age 30-≥80; 79	General population	14	Death register
Watson, 2003[39]	UK General Practice Research Database; 163274; 54.5 (13.7) in men and 57.2 (15.1) in women; 62#	Patients with neither RA nor OA	Mean 4.7 males and 4.8 females.	Death was assessed by a code of deceased in the patient status field of the patient record, not verified by death records.

*Only data on OA group shown, unless unavailable
#study characteristics were only available for the entire study, which also included other diagnosis than OA.
SD=standard deviation;OA=osteoarthritis;TKA=total knee arthroplasty;NR=not reported;THA=total hip arthroplasty;K/L=Kellgren/Lawrence;CMC=carbometa carpal;MM=metal-on-metal;MP=metal-on-polyethylene

Table 2. Results of quality assessment scores in the cohort studies investigating mortality in osteoarthritis.

Study	Definition of study characteristics	Valid osteoarthritis definition	Description of subjects selection	Participation rate	Valid mortality measures	Valid mortality rates in controls	Frequencies of determinants	Frequencies of deaths	Appropriate analysis techniques	Adjusted for age and gender	Quality score
Amundsen[11]	1	0	1	1	1	1	0	1	1	1	80%
Barbour[12]	1	1	1	1	1	1	1	1	0	1	90%
Böhm[13]	1	0	0	1	0	1	0	1	1	1	60%
Cacciatore[14]	1	0	0	1	1	1	1	1	0	1	70%
Danielsson[15]	0	0	1	0	0	1	0	0	0	0	20%
Garellick[16]	0	0	0	1	1	1	0	1	1	1	60%
Haara 03[17]	1	1	0	1	1	1	1	1	0	1	80%
Haara 04[18]	1	1	0	1	1	1	1	0	0	1	70%
Haugen[19]	1	1	1	1	1	1	1	1	0	1	90%
Holbrook[20]	0	0	0	1	1	1	0	0	0	1	40%
Holmberg[21]	1	0	1	1	1	1	0	1	0	1	70%
Karuppiah[22]	1	0	1	1	0	1	0	1	0	0	50%
Kluzek[23]	1	0	1	1	1	1	1	1	0	1	80%
Kumar[40]	0	0	1	1	1	1	0	1	1	0	60%
Lee[24]	0	0	1	1	0	0	0	1	0	0	30%
Lie[25]	1	0	0	1	1	1	0	1	1	1	70%
Lindahl[26]	0	0	0	0	0	0	0	1	0	1	20%
Lindberg[27]	1	0	0	0	1	1	0	1	1	1	60%
Liu.Q[28]	1	1	1	1	1	1	1	1	0	1	80%
Liu.R GARP[29]	1	0	1	1	1	1	1	1	1	1	90%
Liu.R OCC[29]	1	0	0	1	1	1	1	1	1	1	80%
Lizaur[30]	1	0	1	1	1	1	1	1	1	1	90%
Michet[31]	0	0	0	1	1	1	0	1	1	0	50%
Monson[32]	0	0	1	0	1	1	0	1	1	1	60%
Nüesch[2]	1	0	1	1	1	1	1	1	1	1	90%
Ohzawa[33]	0	0	0	1	0	1	0	1	1	1	50%
Pedersen[34]	1	0	0	0	1	1	0	1	0	1	50%
Robertsson[35]	1	0	0	1	1	1	0	1	1	1	70%
Schrøder TKA[36]	0	0	0	0	1	1	0	1	1	1	50%
Schrøder THA[36]	0	0	0	0	1	1	0	0	0	1	30%
Turkiewicz[7]	1	0	1	1	1	1	0	1	0	1	70%
Veronese[4]	1	0	1	1	1	0	1	1	0	1	70%
Visuri[38]	1	0	0	1	1	1	0	1	1	1	70%
Visuri 2015[8]	1	0	0	1	1	1	0	1	1	1	70%
Watson[39]	0	0	0	0	0	0	0	0	0	1	10%

Table 3A. Results of studies investigating mortality in joint arthroplasty for osteoarthritis

First author [ref]	Mortality	Confounders adjusted for in the analyses
Amundsen[11]	Incidence rate: OA 945/100.000 and general population 1526/100 000	Age, sex
Böhm[13]	SMR: ♂1.14 (0.68-1.80), ♀1.03 (0.76-1.37)	Age, sex
Garellick[16]	Number of deaths in ♂: expected 31.4, observed 25 Number of deaths in ♀: expected 49.2, observed 34	Age, sex
Holmberg[21]	Number of deaths: OA n=83,15% (p<0.001) of expected mortality rate for general population	Age, sex
Karuppiah[22]	Survival times: longer in THA group than age matched general population (p<0.001); mean survival time: THA 96.13 (95%CI 95.35-96.91) and general population 93.72 (95%CI 93.65-93.79)	Age
Lie[25]	SMR: 0.68 (0.66-0.70)	Age, sex
Lindahl [26]	Death hazard: after a year equal to general population for age 60 and below. Higher age group: risk lower.	Age, sex
Lindberg[27]	Death observed/expected: >1 year since operation age 50-69 years ♀ 8/9.40, ♂ 13/16.06; age >70years ♀ 52/69.09, ♂ 45/46.55	Age, sex
Lizaur[30]	SMR: ♀ 0.779 (0.681-0.894), ♂ 0.928 (0.874-1.016)	Age, sex
Michet[31]	SMR: THA 0.81 (0.76-0.87) SMR: TKA 0.77 (0.72-0.83)	Age, sex
Ohzawa[33]	SMR: 0.11 (0.02-0.40)	Age, sex
Pedersen[34]	Mortality rates: THR vs general population.♀: 8.5 vs 11.7, ♂10.1 vs 13.5. Age 10-59 years 2.3 vs 2.4, 60-69 years 5.0 vs 6.8, 70-79 years 11.8 vs 16.1, >80 22.8 vs 35.9. Mortality rate ratios: calculated with adjust gender, age and Charlson comorbidity index. ♀ and ♂ 0.7 (0.7-0.7)	Age, sex, Charlson comorbidity index
Robertsson[35]	SMR: 0.77 (0.76-0.78.	Age, sex
Schrøder TKA[36]	SMR: 1 year FU 0.74 (0.60-0.87) Cumulative 5 year survival: 89%. No postoperative excess mortality	Age, sex
Schrøder THA[36]	Cumulative 5 year survival: 89%. No postoperative excess mortality	Age, sex
Visuri[38]	SMR: MM 0.96 (0.78-1.18) SMR: MP 0.90 (0.66-0.87)	Age, sex
Visuri 2015[8]	SMR: 1.00 (0.98-1.02)	Age, sex

OA=osteoarthritis; SMR=standardized mortality ratios (95% confidence intervals (CI)); THA=total hip arthroplasty; TKA=total knee arthroplasty; FU=follow-up; MM=metal-on-metal; MP=metal-on-polyethylene

Table 3B. Results of studies investigating mortality in osteoarthritis patients seeking health care

First author [ref]	Mortality	Confounders adjusted for in the analyses
Danielsson[15]	Expected death rates: higher in practically all age groups	Age
Liu GARP[29]	SMR: 0.54 (0.37-0.79)	Age, sex
Liu OCC[29]	SMR: 0.45 (0.25-0.82)	Age, sex
Monson[32]	SMR: 1.11	Age, sex
Turkiewicz[7]	HR knee OA: 0.92 (0.90-0.94) HR hip OA: 0.95 (0.93-0.97)	Age, sex, baseline confounders (income, highest level of achieved education, marital status, residential area and year of first health-care visit), comorbidities (ischemic heart diseases, cerebrovascular disease, diabetes mellitus, other malignant neoplasms, chronic obstructive pulmonary disease and malignant neoplasm of bronchus and lung
Watson[39]	SMR ♂: OA/no arthritis 19.5/20.6. ♀: OA/no arthritis 15.9/17.3.	Age, sex

GARP=Genetics ARthrosis and Progression;OCC=osteoarthritis care clinic;SMR=standardized mortality ratios(95% confidence intervals (CI));HR=hazard ratio(95% CI);OA=osteoarthritis

Table 3C. Results of studies investigating mortality in population based osteoarthritis

First author [ref]	Mortality	Confounders adjusted for in the analyses
Barbour[12]	HR: Croft grade ≥2 1.14 (1.05-1.24) HR: K/L grade ≥2 1.10 (0.99-1.22) HR: Croft grade ≥2 excluding THA 1.24 (1.13-1.35)	Age, BMI, education, smoking, health status, diabetes and stroke
Cacciatore[14]	HR: 1.28 (0.98-1.39)	Age, sex, BMI, waist circumference, heart rate, pulse blood pressure, Charlson co-morbidity index, number of drugs, NSAIDs, corticosteroids and geriatric depression scale
Haara 03[17]	RR: OA in any finger joint ♀ 1.17 (0.87-1.56), ♂ 1.02 (0.83-1.27) RR: Symmetrical DIP OA ♀ 1.23(1.01-1.51), ♂ 0.89 (0.68-1.16)	Age, education, history of workload, smoking and BMI
Haara 04[18]	RR: thumb CMC OA KL 2,3,4 no association RR: thumb CMC OA KL 3 or 4 ♀ no association ♂1.32 (1.03-1.69)	Age, sex and other unreported confounders

Table 3C. Results of studies investigating mortality in population based osteoarthritis *(Continued)*

First author [ref]	Mortality	Confounders adjusted for in the analyses
Haugen[19]	HR: Radiographic hand OA 0.82 (0.63-1.07) HR: Symptomatic hand OA 0.79 (0.57-1.10)	Age, sex, cohort, BMI, total cholesterol: HDL ratio, current lipid lowering treatment, increased blood pressure, current anti-hypertensive treatment, elevated fasting or non-fasting blood glucose, current antidiabetic treatment, previous cardiovascular events, previous cancer, current use of NSAIDs, daily use of aspirin, current/previous smoking, alcohol use.
Holbrook[20]	RR: ♀ 0.9, ♂ 0.8 For specific OA sites, mortality is not increased	Age, sex
Kluzek[23]	HR: Radiographic knee OA 1.05 (0.58-1.88) HR: Symptomatic knee OA 1.97 (1.20-3.22) HR: Radiographic hand OA, 0.91 (0.60-1.39) HR: Symptomatic hand OA 1.05 (0.66-1.66)	Age, smoking total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medication, occupation, BMI, hormone replacement therapy, past physical activity, current/previous CVD disease, non-ASA NSAIDs and glucose levels
Lee[24]	RR: 0.62 (0.58-0.67)	Age
Liu, Q[28]	HR: symptomatic knee OA: 1.9 (1.0-3.5) HR: radiographic knee OA: 1.2 (0.7-1.9)	Age, sex, BMI, income level, education, levels of occupational physical activity and comorbidities
Nüesch[2]	SMR: 1.55 (1.41-1.70)	Age, sex
Tsuboi [37]	Deaths after 10 years: OR 2.316 (1.412-3.801)	Age, sex, BMI and lifestyle
Veronese[4]	HR: All OA 0.95 (0.77-1.15) HR: Hand OA 1.00 (0.78-1.29) HR: Hip OA 0.96 (0.77-1.20) HR: Knee OA 0.86 (0.66-1.12)	Age, sex, BMI, educational level, alcohol drinking, monthly income, physical activity, presence at baseline of cardiovascular diseases, fractures, chronic obstructive pulmonary disease, orthostatic hypotension, hypertension, diabetes, frailty and cancer, number of medication smoking status, activities of daily living, mini-mental state, geriatric depression scale and geriatric nutrition risk index scores.

HR=hazard ratio (95% confidence intervals (CI)); K/L=Kellgren/Lawrence; THA=total hip arthroplasty; BMI=body mass index; NSAIDs=non-steroidal anti-inflammatory drugs; RR=relative risk (95% CI); OA=osteoarthritis; DIP=distal interhalangeal joint; CMC=carbometacarpal; HDL=high density lipoprotein; CVD non-ASA=non-acetylsalicylic acid; SMR=standardized mortality ratios (95% CI); OR=odds ratio (95% CI)

Twelve studies were based in the general population, of which ten were high quality studies (Table 3C).[2,4,12,14,17-20,23,24,28,37] Some studies reported separate results for more than one subtype of OA.[2,4,12,14,17-20,23,24,28,37] A meta-analysis was performed of the high quality studies based in the general population.

Four studies were excluded from the meta-analysis because of lack of outcome that could be summarized. Two of the excluded studies reported an association between mortality,[2,37] while two studies did not (Figure 2).[17,18] A meta-analysis of six studies (n=5169) resulted in a pooled HR of 1.04 (0.91-1.18).
Radiographic and symptomatic OA were also not associated with mortality when analyzed separately (data not shown).

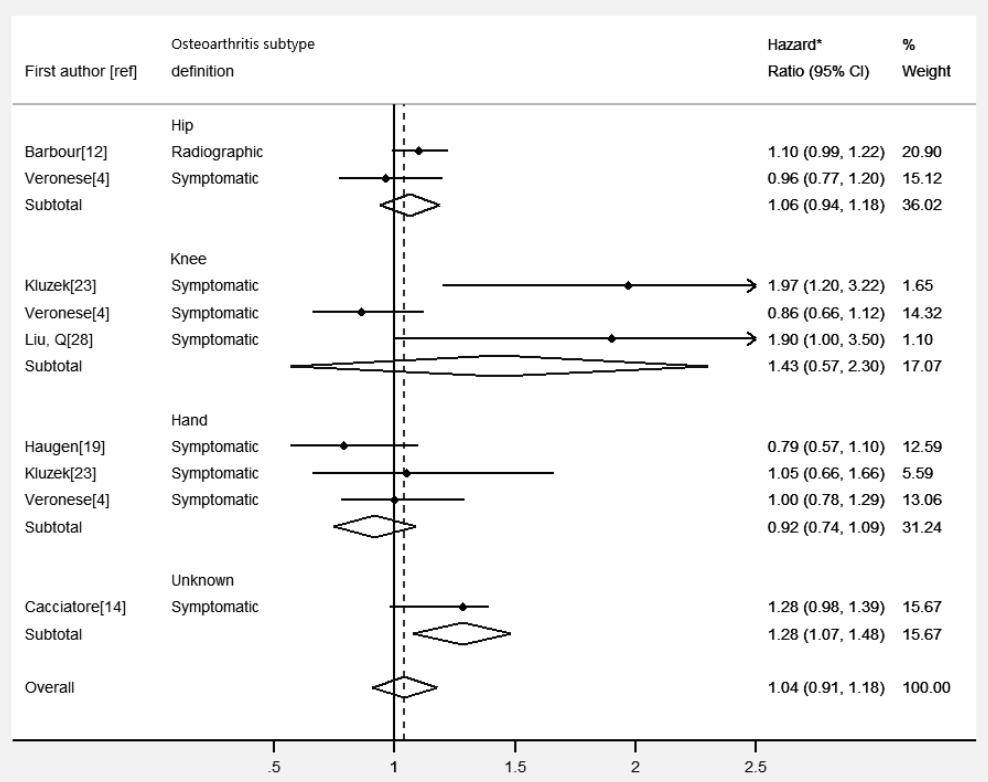

Figure 2. Meta-analysis

DISCUSSION

Overall we did not identify an association between OA and mortality when analyzing almost half a million patients. We explored whether patients with OA who presented themselves in a specific clinical setting could have an increased mortality risk that warrants attention. We investigated three clinical settings: OA patients receiving an arthroplasty, patients seeking care for their OA and OA in persons from the general population. All high quality studies which investigated

mortality in patients receiving a joint replacement for OA and in patients who sought help for their OA reported an equal or lower mortality rate for OA. However, the results from high quality population based studies were more diverse.

Two meta-analyses were performed previously and both studies found that OA was not significantly associated with mortality.[4,5] For the high quality studies investigating patients who received a joint arthroplasty and patients who consulted general practitioner or a medical specialist, no meta-analysis was done due to the heterogeneous outcomes used in the studies. These studies also had similar results and reported either equal or lower mortality rate. The meta-analysis summarizing 6 high quality studies investigating OA in persons from the general population also did not show an association of OA with mortality. In the latter meta-analysis four high quality studies were excluded due to a lack of similar outcomes. However, since two studies reported an increased risk and two studies did not, the influence of this exclusion on the overall pooled mortality rate is likely very limited.

One study [8] suggested that a follow-up time of 10 years or more may lead to a higher mortality rate in OA. This 'healthy cohort' effects may occur due to exclusion of patients with shortened life span. A 'healthy cohort' effect could also be present in studies including patients that have received a joint arthroplasty. Since this effect ebbs away after a couple of years, one article tested this hypothesis by delaying the start of follow-up.[29] However, mortality for OA patients did not increase. In the studies including patients that received a joint arthroplasty follow-up time differed, but especially in the high quality studies this was relatively long, making the 'healthy cohort' effect less likely. The absence of a 'healthy cohort' is further supported by several studies with longer follow up time, which also did not find an increased risk for mortality.[19,38]

Another possible explanation may be that patients seeking care for their OA and receiving a knee or hip arthroplasty are also patients who in general take better care of themselves or possess a better general health. Population studies also include patients who are less in tune with their health. However, in the study by Turkiewicz et al, additional analyses were done using patients without OA who sought care as a control group.[7] These analyses did not change the lack of association between OA and mortality. So, this aspect cannot explain the total difference.

OA subtypes were not equally investigated. The majority of the studies included knee or hip OA patients while only five studies reported mortality for hand OA.

Some studies did not specify the subtype of OA or combined subtypes and could thus offer no additional insights into the influence of the individual subtype. Though not significant, higher rates of mortality were more often reported for patients with knee OA. It is possible that the association between OA and

mortality may depend upon the OA subtype, possibly in combination with potential confounders. However, since these confounders were not equally investigated in previous studies, too little evidence is currently available to conclude the influence of the OA subtype on mortality.

The majority of the analyses were performed using only age and sex as confounding factors and the general population as controls. One study[23] reported different results when different combinations of additional confounders were used, while another study found similar results. As too few studies were performed using different sets of additional confounders, it is possible that some additional confounders than age and sex should be used. However, this would only be statistically feasible if large cohorts with long follow-up time were used.
The presence of publication bias cannot be ruled out. It is possible that negative associations between OA and mortality have been underreported. A few smaller sized studies in knee or hip OA reported an association between OA and mortality, while a large study in which more confounders were used found no association.
The results of this systematic review suggest that OA is not associated with mortality in patients receiving knee or hip arthroplasty or seeking care. Mortality associated with OA in persons in the general population was not increased, however these studies were equivocal and results may depend on the OA subtype and potential confounders. More well conducted and large studies with long follow-up periods will be necessary to analyze the association between OA and mortality.

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APPENDICES (ONLINE SUPPLEMENTAL FILES)

Appendix I. Overview of search strategy and results

	Key Words	Number of Articles
PubMed	"Osteoarthritis/mortality"[Mesh] OR (("osteoarthritis"[Majr] OR Osteoarthrosis[ti] OR Osteoarthroses[ti] OR Osteoarthritides[ti] OR Osteoarthritis[ti] OR Osteoartrosis[ti] OR Osteoartroses[ti] OR Osteoartritides[ti] OR Osteoartritis[ti] OR "Degenerative Arthritis"[ti] OR "Degenerative Arthritides"[ti] OR Arthrosis[ti] OR Arthroses[ti] OR Arthritides[ti] OR Artrosis[ti] OR Artroses[ti]) AND (Mortality OR "Mortality"[mesh] OR "mortality"[Subheading] OR Mortality[tw] OR Mortalities[tw] OR "Case Fatality Rate"[tw] OR "Case Fatality Rates"[tw] OR "Death Rate"[tw] OR "Death Rates"[tw] OR "Cause of Death"[tw] OR "Fatal Outcome"[tw] OR "Fatal Outcomes"[tw] OR "Survival Rate"[tw] OR "Survival Rates"[tw] OR "Death"[mesh] OR "Survival"[mesh] OR "Survival Analysis"[mesh] OR survivorship[tw])) OR (("osteoarthritis"[Mesh] OR Osteoarthrosis[tw] OR Osteoarthroses[tw] OR Osteoarthritides[tw] OR Osteoarthritis[tw] OR Osteoartrosis[tw] OR Osteoartroses[tw] OR Osteoartritides[tw] OR Osteoartritis[tw] OR "Degenerative Arthritis"[tw] OR "Degenerative Arthritides"[tw] OR Arthrosis[tw] OR Arthroses[tw] OR Arthritides[tw] OR Artrosis[tw] OR Artroses[tw]) AND ("Mortality"[majr] OR "mortality"[Subheading] OR Mortality[ti] OR Mortalities[ti] OR "Case Fatality Rate"[ti] OR "Case Fatality Rates"[ti] OR "Death Rate"[ti] OR "Death Rates"[ti] OR "Cause of Death"[ti] OR "Fatal Outcome"[ti] OR "Fatal Outcomes"[ti] OR "Survival Rate"[ti] OR "Survival Rates"[ti] OR "Death"[majr] OR "Survival"[majr] OR "Survival Analysis"[majr] OR survivorship[ti]))	1541
Embase	((exp *osteoarthritis/ OR (Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses).ti) AND (exp mortality/ OR exp Death/ OR exp survival rate/ OR (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship).ti,ab)) OR ((exp osteoarthritis/ OR (Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses).ti,ab) AND (exp *mortality/ OR exp *Death/ OR exp *survival rate/ OR (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship).ti))	2452
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	180

Appendix I. Overview of search strategy and results *(Continued)*

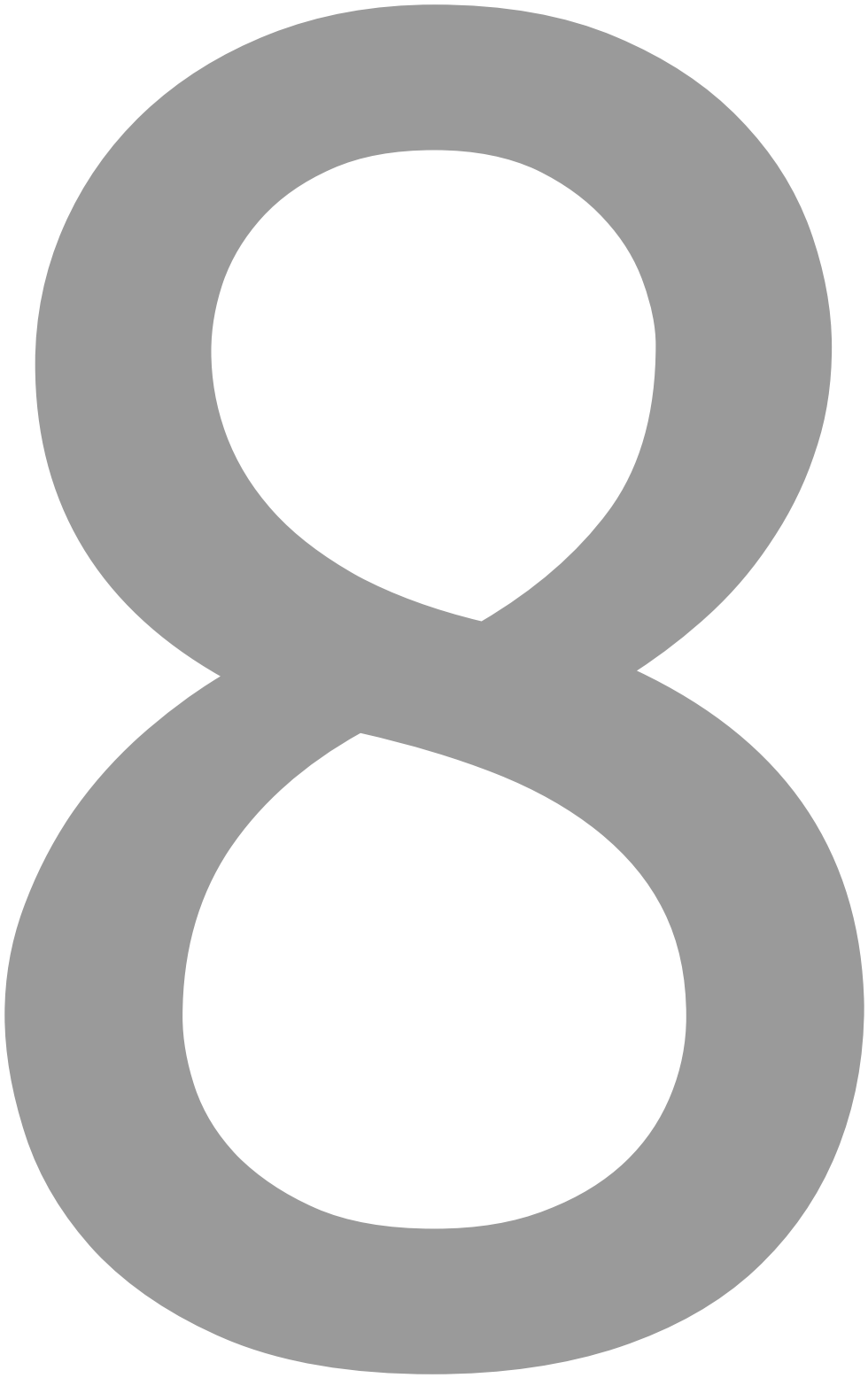
	Key Words	Number of Articles
Web of Science	(TI=(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND TS=(Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)) OR (TS=(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND TI=(Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship))	546
	TITLE-ABSTR-KEY(Osteoarthritis AND Mortality)	154
	TITLE-ABSTR-KEY((Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR Degenerative Arthritis OR Degenerative Arthritides OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR Case Fatality Rate OR Case Fatality Rates OR Death Rate OR Death Rates OR Cause of Death OR Fatal Outcome OR Fatal Outcomes OR Survival Rate OR Survival Rates OR Survival Analysis OR survivorship))	
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR Degenerative Arthritis OR Degenerative Arthritides OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR Case Fatality Rate OR Case Fatality Rates OR Death Rate OR Death Rates OR Cause of Death OR Fatal Outcome OR Fatal Outcomes OR Survival Rate OR Survival Rates OR Survival Analysis OR survivorship)	
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	

Appendix I. Overview of search strategy and results *(Continued)*

	Key Words	**Number of Articles**
CINAHL	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	228
Academic Search Premier	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	20
Hand Search		1

Appendix II

Item	Criteria	Applicable for:
1	Definition of study Sufficient description of characteristics of study groups *A '1' is given when a paper describes at least setting and time of period of the study, ages of patients (and its range) and man:woman ratio*	C/NCC
2	Presence of OA was according to valid definition and the classification was standardized. *A '1' will than given for a study which used ACR criteria for OA or a valid OA radiographic scoring method (such as Kellgren and Lawrence, OARSI or Croft)*	C/NCC
3	Presence of OA was measured identically in cases and controls. *A '1' is given if assessment of mortality was the same in controls as in cases.*	NCC
	Selection bias	
4	Clear description of selection of study subjects. When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.	C/NCC
5	Cases and controls were drawn from the same source population. This is to exclude the possibility of selection bias.	NCC
	Follow-up	
6	Participation rate ≥ 80% for study groups	C/NCC
7	80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.	NCC
8	No difference in withdrawal in both groups, including information on completers and withdrawals	C/NCC
	Assessment of the outcome: Death	
9	Mortality measures were valid, e.g. the use of national register or objective observations	C
10	Valid mortality rates in controls *A '1' is given if mortality rates in controls are valid, e.g. country life tables or register*	NCC
11	Mortality was assessed identical in cases and controls A '1' is given if assessment of mortality was the same in controls as in cases.	C/NCC
	Analysis and Data Presentation	
12	Frequencies of the most important determinants were given, such as age, BMI, sex	C/NCC
13	Frequencies of deaths were given Appropriate analysis techniques with estimates were used *A '1' is given if SMRs are calculated or may be calculated from observed/ expected*	C/NCC
14	Adjusted for at least age and gender	C/NCC



Chapter 8

Summary and discussion

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder characterized by degradation of cartilage and changes in subchondral bone, which are accompanied by synovial involvement. It can affect any joint, but the knee, hand and hip joints are most frequently affected. It results in pain, disability and is associated with substantial morbidity. Its societal impact is considerable, since in a world of which the population is ageing, it is associated with a rapidly growing medical and financial burden. Whether it also leads to increased mortality is unclear.
In this thesis we evaluated both mortality and morbidity due to OA. With regard to the latter, we focused on the disease course with respect to the outcomes pain, disability, aesthetic damage and structural damage, especially in patients with hand OA. To investigate whether we can modify these outcomes we also investigated its determinants, including those that can be modified.

DISEASE COURSE AND ITS DETERMINANTS OF OUTCOME IN HAND OSTEOARTHRITIS IN SECONDARY CARE

In the first part of this thesis the focus is on hand OA. This thesis capitalises on the results from the Hand OSTeoArthritis in Secondary care (HOSTAS) study, an ongoing observational cohort study in which more than 500 patients with hand OA have been enrolled since 2009. Participants were included when they had consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center (LUMC) for hand complaints and when these hand complaints had been diagnosed as primary hand OA. Baseline and 1-year and 2-year follow-up data have been used.
In **chapter 2** we investigated hand disability at baseline and after 1 year follow-up, and the role of both joint-specific and non-joint specific determinants. Disability was assessed by the Functional Index for Hand OA (FIHOA). We were especially interested in the role of coping strategies in patients with hand OA, which were assessed by the Coping with Rheumatic Stressors (CORS) questionnaire.
First, we showed that disability was associated with the number of painful hand joints and of hand joints with limitations in motion. Next, we investigated coping strategies in patients with hand OA. Coping strategies, next to illness perceptions, are determinants of health outcomes, according to Leventhal's common sense model (CSM). In the CSM model, patients' symptoms may be interpreted and elaborated upon to form into representations or illness perceptions, subsequently guiding coping responses and leading ultimately to the appraisal of outcomes.
The strategy 'optimism', with a median score of 16 (maximal potential range 5-20),

is a strategy to cope with limitations and this was the most often used coping strategy. Of the strategies to cope with pain, the strategy 'comforting cognitions' was the most frequently used. Finally, the coping strategy 'consideration' was more used by patients as a strategy to cope with dependency.
The strategy 'decreasing activity', a strategy to cope with hand pain, and the strategy 'pacing', a strategy to cope with limitations due to hand OA, were associated with disability at baseline and after 1 year follow-up. These associations remain present when adjusted for joint-specific factors. A likely explanation for these associations could be that limitation of activity may result in deterioration of muscular strength and endurance and patients who use 'limiting' activity as a way of coping with pain are more at risk of developing disability, regardless of disease status.
At baseline patients who used the strategy 'comforting cognitions' less often to cope with pain, reported more disability than those who used this strategy more often. However, the use of this strategy at baseline was not associated with disability after 1 year. This finding could suggest that disability drives the use of the coping style 'comforting cognitions'.
In previous studies, it has been demonstrated that education about OA may improve clinical outcomes. Early evidence is now available for the efficacy of psychological interventions such as pain coping strategies skills training in OA patients.[1-3] Our study has shown which coping strategies may influence physical limitations, thereby identifying potential targets for psychological interventions such as psychoeducation and cognitive restructuring.

Aesthetically unattractive appearance of the hands, or aesthetic damage, is an outcome that is reported by patients with hand OA to be of importance. This outcome is also included in the latest Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) endorsed core set of domains that have to be assessed when performing clinical trials and observational studies in hand OA. Aesthetic damage has been included as a subdomain, that is part of the domain structural damage. Though aesthetic damage in hand OA has been described previously, the impact of dissatisfaction with hand appearance on daily life remains unclear. **Chapter 3** focused on the prevalence of aesthetic dissatisfaction in hand OA patients, its impact on daily life and their determinants. To assess both aspects (dissatisfaction in itself and the impact on daily life) of aesthetic damage the Michigan Hand Outcomes Questionnaire(MHQ) was used, a reliable and validated questionnaire which includes a scale for the aesthetics of the hands.
Only 63 (26%) of the 247 studied patients were aesthetically dissatisfied, while even fewer patients (33 (13%)) reported impact on daily life due to dissatisfaction. Patients with deformed hand joints were at higher risk to be dissatisfied with

the aesthetic appearance of their hands. A previous French study, in which 34% of hand OA patients reported high aesthetic concern, reported a relationship between bony enlargements and aesthetic dissatisfaction.[4] Although we found a graded ('dose response') relationship between bony joint enlargements and aesthetic dissatisfaction in univariate analyses, the association was attenuated in multivariate analysis, which could be due to collinearity between deformed joints and bony joint enlargements. In accordance, radiographic damage as assessed by the Kellgren-Lawrence grade was associated with aesthetic dissatisfaction. Furthermore, patient-reported hand pain or disability was not associated with aesthetic dissatisfaction.

In contrast, the impact of aesthetic dissatisfaction was associated with hand pain and disability. Dose response relationships were also seen between deformed joints, bony joint enlargements and radiographic severity and impact due to aesthetic dissatisfaction, although the associations were not all statistically significant in multivariate models. Moreover, patients who reported impact, also reported more depression and negative illness perceptions, than those who did not report impact.

In line with our expectations, aesthetic dissatisfaction especially depends upon joint-specific determinants and less on psychosocial determinants. However, patients with more symptoms, a higher depression score and negative illness perceptions experienced more impact. These results demonstrated the influence of psychosocial factors on outcome measures in hand OA patients. The incorporation of self-management training could be considered as a part of treatment in hand OA patients, as patients with negative illness perceptions may benefit from these programs.

Chapters 4 and 5 focused on joint-specific determinants that can be assessed by Magnetic Resonance (MR) imaging and their association with joint pain and radiographic progression.

Activity in the subchondral bone, identified as bone marrow lesions (BMLs) on MR images, have been widely investigated in knee OA and have been shown to play a role in knee pain.[5] Also synovitis has been reported as a process that plays a role in osteoarthritic pain; also in hand OA in ultrasonographic studies. Studies investigating BMLs in patients with hand OA are sparse. MR imaging offers the possibility to investigate both the presence of BMLs and synovitis, thus enabling us to determine what is the contribution of BMLs and synovitis separately and which target is most promising for treatment.

Chapter 4 focused on the occurrence and interaction between BMLs and synovitis with respect to pain in patients with hand OA that had undergone contrast-enhanced MR imaging. A total of 840 interphalangeal joints from the right hands

in 105 hand OA patients were scored for MR features following a modified version of the Oslo hand OA MR imaging scoring system. The MR imaging features BMLs, (teno)synovitis, tendon inflammation and cysts were frequently seen. The features BMLs and synovitis on joint level were both associated with site specific pain upon palpation, when adjusted for age, sex, BMI, Kellgren-Lawrence grade and patients being present with multiple joints in the analysis. A clear interaction between BMLs and synovitis was seen, with a joint effect larger than the sum of the separate effects. We also found that severe synovitis alone was associated with pain while BMLs alone was not. Site specific pain upon palpation was observed in 53% of joints with BMLs and moderate to severe synovitis. A nearly 7-fold increased risk for pain was found in these joints when compared to interphalangeal joint without BMLs or synovitis.

We therefore concluded that in hand OA patients severe synovitis in the interphalangeal joints is associated with joint pain, which is worsened when BMLs co-occur. These results suggest that synovitis could be a target for treatment.

However, summarized scores of BMLs or synovitis for the total patient were not associated with self-reported pain on questionnaires and this might be explained by an inability to correct for patient effect such as psychosocial factors, that are of great influence on self-reported pain in patients, but also due to the lack of involving the finger joints of the left hand and the thumb base joints in the analyses.

The MR imaging features flexor tenosynovitis, extensor tendon inflammation and cysts were not associated with pain. Though a previous study found an association between flexor tenosynovitis and pain, these results were not replicated and this may be explained by a difference in study population and methods used.[6]

More studies will be necessary to investigate the feature extensor tendon inflammation for its association with clinical parameters. No association was found between extensor tendon inflammation and pain, but this feature may possibly be associated with other clinical properties, such as hand mobility. The reliability for the scoring of this feature was also lower than for other features scored and more studies may investigate whether it is perhaps a more difficult feature to define and whether an adaptation of the current definition is necessary.

Future studies could also analyze the DIP and PIP joints separately since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ between DIP and PIP joints.

The association between MR imaging features and both onset and progression of radiographic damage in hand OA were studied in **chapter 5**. Of 696 interphalangeal joints of the right hand in 87 patients with hand OA, 324 joints had no radiographic OA damage at baseline (Kellgren-Lawrence score=0). After two years of follow-up 78 joints had onset or progression of radiographic osteoarthritic damage. Our

results demonstrated that BMLs grade 2/3 were associated with Kellgren-Lawrence progression. BML grade 1 however was not associated. A graded association was found between synovitis and Kellgren-Lawrence progression. The association of these MR imaging features with osteophyte and JSN progression was similar.
Both BMLs and synovitis were associated with both onset and radiographic progression on joint level. In adjusted analyses the presence of BMLs decreased the strength of the association between synovitis and progression, while synovitis in turn also decreased the strength of the association between BMLs and progression.
We concluded that BMLs, next to synovitis, play a role in radiographic progression already after 2 years, and that therefore both joint tissues could be important targets for therapy.
One of the strengths of the study is that patients from early to severe stages of OA were included in this study. Furthermore, progression was not only investigated on joint level, but also on patient level. Crude associations were found between summated BMLs or synovitis score, but only synovitis remained associated after adjustment. Our results suggest that the more severe the inflammatory state is, the higher the risk of progression. This would mean that future randomized controlled trails could explore if anti-inflammatory medication like oral steroids could modify inflammatory MR imaging features. This study did not investigate whether MR imaging features are persistent or fluctuate in its occurrence. Future studies could focus on the persistent and fluctuant nature of these features and the progression of structural damage over time.

MORTALITY IN OSTEOARTHRITIS

A study by Nuesch et al reported that mortality was increased among subjects surveyed from the general population with hip and knee pain and radiographic OA signs.[7] A possible association between OA and mortality could be explained by factors such as atherosclerosis, diabetes, walking disability and use of NSAIDs. If an association is indeed present, this could mean that management of patients with OA should focus on effective treatment of cardiovascular risk factors and comorbidities in clinical practice.
In **chapter 6** we studied two observational cohorts of OA patients who consulted health care for their OA: The 'Genetics ARthrosis and Progression'(GARP) cohort comprised 192 Caucasian sibling pairs (384 patients) with symptomatic primary OA at multiple sites in the hand or in at least 2 of the following sites: hand, knee, hip or spine, that were diagnosed by rheumatologists, orthopaedic surgeons and general practitioners. The 'Osteoarthritis Care Clinic'(OCC) cohort consisted of

460 consecutive patients who were diagnosed by the rheumatologist with primary hand, knee or hip OA and referred to the clinical nurse specialist for education. We found no increased mortality rate when compared with the general population for either cohort. The factors male sex, increasing age and co-morbid condition of cancer were associated with mortality in GARP, as was expected, but OA was not. Hip OA was associated with mortality in univariate analysis, but this association was no longer present when adjusted for sex and age. Self-reported cardiovascular disease, physical function and body mass index were not associated with increased mortality.

Previous arthroplasty studies in hip and knee OA found prolonged survival in OA patients. Our results are in line with these studies.

So, although an association between OA and risk of death was reported by Nuesch et al, we could not replicate these results, which could be due to differences in study populations: their study included subjects with knee or hip OA recruited via a survey of the general population, whereas the patients in our OA cohorts actively consulted a medical specialist or general practitioner for their OA complaints. An explanation might be that our patients possessed personality traits which prompted them to actively seek health care. This personality trait might also be accompanied by a pursuit for healthy life-style and a search for early care in case of illness. Moreover, by consulting health care for their musculoskeletal complaints due to OA they could have received treatment for other known medical conditions as well. However, it is also possible that an opposite mechanism explained the findings of Nuesch et al, i.e., that those who respond to a survey and self-report knee or hip complaints, suffer from co-morbidities affecting life expectancy, which confounded the results. Since our study did not find a specific cause of death nor an effect of OA-related factors, these explanations seem more likely than an effect of OA per se on mortality.

Additional analyses were performed to preclude that our results might be explained by the exclusion of patients with a shortened life span in the GARP study. We did not find a 'healthy cohort' effect and this was supported by the replication of our results in the OCC study, where this exclusion criterion was not applied.

The reliability of the death certificates could be questioned, but possible misclassification of causes of death will occur for both OA patients and in the general Dutch population. This is therefore not a likely explanation of the results.

As evidence concerning mortality due to OA has been contradictory, we performed a systematic literature review to summarize and determine the true association between OA and mortality in **chapter 7**. A total of 33 articles, investigating 35 studies, reported on the association between OA and mortality. Studies could be distinguished in three clinical settings: patients receiving an arthroplasty, patients seeking care for their OA or participants from the general population. Seven high

quality studies investigating patients receiving an arthroplasty found an equal or lower overall mortality rate for OA patients when compared to the general population. In line, are the results of three high quality studies investigating patients seeking care for their OA, that also reported no association between OA and mortality. Finally, ten high quality studies investigated participants from the general population. We could perform a meta-analysis of six studies of these ten studies and found a pooled hazard ratio (HR) of 1.04 (0.91-1.18). Two of the four studies that were not included in the meta-analysis found an association between OA and mortality, while two did not. Separate analyses for radiographic and symptomatic OA did not result in an increased hazard ratio.

So, in conclusion, we did not demonstrate a clear association between the presence of OA and mortality nor does a pooled estimate of the literature suggests such an association.

Although we did not find an association between OA and mortality in OA patients who received a joint arthroplasty and in those who sought care from a health professional for their OA complaints, we cannot rule out that such an association between OA and overall mortality might exist in another clinical setting, since the results in population based studies were more varied. Factors which could influence these differences could be the 'healthy cohort' effect, the attitude of patients to take better care of themselves or possess a better general health, the OA subtype, adjustment for confounders and publication bias.

FUTURE PERSPECTIVES

This thesis has provided more knowledge on the disease course and its determinants of outcome in hand OA. Simultaneously, we have also uncovered topics which warrant future research.

We have shown that patients' perceptions of hand OA and the coping strategies that patients with hand OA use are important for patient-reported outcomes such as disability, not only at the same moment in time, but also after 1 year. Therefore, these coping strategies could serve as potential targets for interventions such as psychoeducation and cognitive restructuring. Additionally, these interventions could also be considered as a part of treatment in patients with negative illness perceptions. As we have shown patients with negative illness perceptions experience more impact due to aesthetic dissatisfaction. Though aesthetic damage has been suggested as a part of the domain structural damage, patients with negative illness perceptions seems especially influenced and could possibly also benefit from these interventions.

The 'Grip on pain' study is an ongoing trial performed in the department of Rheumatology of the Leiden University Medical Center, which will hopefully soon provide the first data on this topic. This randomized controlled trial aims to investigate the effectiveness of an online self-management intervention in patients with hand OA. Therefore, patients that have consulted a rheumatologist for their hand OA are either randomized to care as usual, comprising a consultation by the nurse specialist and occupational therapist, or to care as usual plus the online self-management intervention led by a health psychologist. The trial will not only increase our insight whether targeting psychosocial factors will improve quality of life and symptoms in patients with hand OA, but will, when positive, also supply a new treatment modality to improve the management for patients with hand OA.

In the current studies we have investigated the disease course of hand OA over 2 years. However, hand OA is a chronic slowly progressive disease. Therefore, it would be highly relevant to extend the investigation of disease course and its determinants to a time-frame over 2 years. Since the HOSTAS study is an ongoing observational cohort with already patients with a follow-up duration of 8 years this would be valuable to evaluate. On the other hand, the HOSTAS study is a Dutch study, and therefore it could be that the results are not generalizable to hand OA patients in other countries. It could be that cultural differences exist for instance with an outcome as aesthetic damage. Therefore, it is important to collaborate with other cohorts, such as DIGICOD in France and Nor-Hand in Norway, to replicate results.

MR imaging is a promising method to evaluate diseases processes and outcomes in hand OA. The features BMLs and synovitis on joint level were both associated with site specific pain upon palpation and a clear interaction could also be seen. Other MR imaging features such as extensor tendon inflammation were not associated with pain. Since this was the first study to investigate the latter feature in OA, more studies will be necessary to investigate the association between this feature and other clinical parameters, such as hand mobility. Future studies could perform separate analyses of the DIP and PIP joints since insertion sites of the deep and superficial parts of the flexor and extensor tendons differ. Since BMLs and synovitis were not associated with pain on the patient level, it will be challenging to discover which other known and unknown variables could contribute to the patient effect. Especially the role of the thumb base joints are highly relevant. Furthermore, it would also be interesting to see if MR imaging features change over time, which can be done by using the follow-up data from the HOSTAS study.

We showed that BMLs and synovitis were both associated with onset and radiographic progression after two years of follow-up. Therefore, future randomized double-blind placebo-controlled trials could explore if anti-

inflammatory medication could modify inflammatory MR imaging features and symptoms in patients with hand OA. One such trial is the Hand Osteoarthritis Prednisolone Efficacy (HOPE) study, whose main objective is to identify a possible new treatment to alleviate pain and diminish inflammation in hand OA patients.
A part of this thesis focused on the association between OA and mortality. We studied two observational cohorts of OA patients who consulted health care for their OA and found no association. In a subsequently performed systematic literature review we have shown that OA was not associated with mortality in patients receiving arthroplasty or seeking care, while this association has been reported in population-based OA studies. OA subtypes and other factors could play a role in this association and have not been sufficiently investigated till now. Large scaled population based studies, such as the Netherlands Epidemiology of Obesity (NEO) study, a population-based prospective cohort study which was started to investigate underlying mechanisms of the relationship between obesity and related diseases such as OA, can be used to further our understanding of the relations between OA, co-morbidities and mortality . Ideally, these large scaled studies will also aid us in our quest for treatment options.

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9

Chapter 9

Nederlandse samenvatting

INLEIDING

Artrose is de meest voorkomende musculoskeletale aandoening die gekarakteriseerd wordt door de afbraak van kraakbeen, veranderingen in het subchondrale bot en afwijkingen in het synovium. Het kan elk gewricht aantasten, maar de knie-, hand- en heupgewrichten worden het vaakst getroffen. Artrose resulteert in pijn en beperkingen. De maatschappelijke impact is aanzienlijk. In een wereld waarin de bevolking vergrijst, gaat dit gepaard met een snelgroeiende medische en financiële last. Of artrose ook leidt tot eerdere sterfte is onduidelijk. In dit proefschrift hebben we zowel ziektelast als sterfte door artrose onderzocht. We hebben ons gericht op het verloop van pijn, functionele beperkingen, uiterlijk veranderingen ('esthetische gevolgen') en blijvende schade aan de gewrichten bij patiënten met handartrose. Om te onderzoeken of het mogelijk is hier tot verbetering te komen, hebben we onderzocht welke factoren deze uitkomsten bepalen, met name ook juist die factoren die kunnen worden beïnvloed.

ZIEKTEBELOOP EN DETERMINANTEN VAN UITKOMSTEN BIJ HANDARTROSE IN DE TWEEDE LIJN

In het eerste deel van dit proefschrift ligt de focus op handartrose. In dit proefschrift werd gebruik gemaakt van de resultaten uit de HOSTAS (Handatrose in de tweede lijn) studie. HOSTAS is een lopende observationele cohortstudie, waaraan meer dan 500 patiënten met handartrose vanaf 2009 hebben deelgenomen. De deelnemers werden gezien op de polikliniek reumatologie van het Leids Universitair Medisch Centrum (LUMC) in verband met klachten van de handen. Wanneer deze klachten van de hand werden gediagnosticeerd als primaire handartrose werd de patiënten gevraagd aan het onderzoek mee te doen. In dit proefschrift zijn de gegevens bij het begin van het onderzoek, na 1 jaar en na 2 jaar gebruikt.
In **hoofdstuk 2** hebben we functionele beperkingen bij diagnose en na 1 jaar onderzocht. Daarbij hebben we de rol van zowel gewrichtsspecifieke als niet-gewrichtsspecifieke factoren geëvalueerd. Functionele beperkingen werden vastgesteld met behulp van een gestandaardiseerde vragenlijst, namelijk de Functional Index for Hand OA (FIHOA). We hebben laten zien dat functionele beperkingen zijn geassocieerd met het aantal pijnlijke handgewrichten en het aantal handgewrichten met bewegingsbeperkingen. Daarnaast onderzochten we copingstijlen bij patiënten met handartrose en hun invloed op functionele beperkingen. Volgens het Common Sense Model (CSM) van Leventhal zijn copingstijlen en ziektepercepties bepalende factoren voor gezondheidsresultaten. Volgens het CSM model ervaart een patiënt symptomen en interpreteert deze en

werkt ze uit tot ideeën of ziektepercepties, die vervolgens leiden tot copingreacties en uiteindelijk tot de ervaren uitkomsten. De coping stijlen werden gemeten met behulp van de gestandaardiseerde vragenlijst Coping with Rheumatic Stressors (CORS).
'Optimisme' is een copingstijl voor het omgaan met beperkingen. Deze copingstijl was de meest gebruikte in de HOSTAS populatie. 'Geruststellen' was de meest gebruikte copingstijl voor het omgaan met pijn. Verder werd de copingstijl 'rekening houden' veel gebruikt door patiënten voor het omgaan met afhankelijkheid.
De copingstijlen 'activiteit beperken', die kan worden ingezet om om te gaan met pijn in de hand, en 'activiteit aanpassen', die kan worden ingezet voor het omgaan met de beperkingen door handartrose, waren geassocieerd met functionele beperkingen bij aanvang van het onderzoek en na 1 jaar. Een mogelijke verklaring voor deze bevindingen is dat het beperken van activiteiten kan resulteren in verslechtering van spierkracht en uithoudingsvermogen en patiënten die 'beperken van activiteiten' gebruiken als een manier om met pijn om te gaan, meer risico lopen op het ontwikkelen van functionele beperkingen, ongeacht de ziektestatus. Patiënten die de copingstijl 'geruststellen' minder vaak gebruikten voor het omgaan met pijn bij het begin van het onderzoek meldden meer beperkingen dan degenen die deze stijl vaker gebruikten. Echter, het gebruiken van deze copingstijl bij aanvang was niet geassocieerd met functionele beperkingen na 1 jaar. Deze bevinding suggereert dat functionele beperkingen leiden tot het gebruiken van de copingstijl 'geruststellen'.
In eerdere onderzoeken is aangetoond dat voorlichting over artrose de klinische uitkomsten kan verbeteren. Ook is er nu bewijs beschikbaar voor de effectiviteit van psychologische interventies, zoals vaardigheidstraining van copingstijlen voor pijn bij artrose patiënten. Onze studie laat zien welke copingstijlen van invloed zijn bij fysieke beperkingen. Hierdoor zijn mogelijke doelen voor psychologische interventies zoals psycho-educatie en cognitieve herstructurering geïdentificeerd.

Een onaantrekkelijk uiterlijk van de handen, oftewel esthetische schade, wordt door patiënten met handartrose gerapporteerd als een uitkomst die mogelijk van belang is. Deze uitkomst is onderdeel van de recent opgestelde kernuitkomstmaten, die door de Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) in 2014 werd ondersteund, en die altijd moeten worden gemeten bij het uitvoeren van klinische studies en observationele studies in patiënten met handartrose. Esthetische schade valt als subdomein onder het domein structurele schade. Hoewel esthetische schade bij handartrose eerder is beschreven, blijft de impact van ontevredenheid met het uiterlijk van de handen op het dagelijkse leven onduidelijk. **Hoofdstuk 3** richt zich op het vóórkomen van esthetische onvrede in handartrosepatiënten, de impact op het dagelijkse leven

en de bepalende factoren. Om beide aspecten (ontevredenheid en invloed op het dagelijkse leven) van de esthetische schade te meten werd de Michigan Hand Outcomes Questionnaire (MHQ) gebruikt. Dit is een betrouwbare en gevalideerde standaardvragenlijst waarbij er een schaal is voor de esthetiek van de handen.
Slechts 63 (26%) van de 247 onderzochte patiënten waren ontevreden over het uiterlijk van hun handen, terwijl nog minder patiënten (33 (13%)) melding maakten van invloed op het dagelijkse leven van het uiterlijk van de handen. Patiënten met vervormde handgewrichten waren wel vaker ontevreden met de esthetiek van hun handen dan mensen die dit niet hadden. In een eerdere Franse studie hadden 34% van de handartrosepatiënten zorgen over de esthetiek van hun handen; benige gewrichtszwellingen waren geassocieerd met ontevredenheid over het uiterlijk. Ook wij vonden een dosis-response relatie tussen benige gewrichtszwellingen en ontevredenheid met het uiterlijk, maar deze leek vooral veroorzaakt door andere factoren doordat vervormde gewrichten en benige gewrichtszwellingen sterk met elkaar gecorreleerd zijn. Ook radiologische schade was geassocieerd met ontevredenheid met het uiterlijk. Door de patiënt gerapporteerde handpijn of functionele beperkingen waren niet geassocieerd met ontevredenheid met het uiterlijk.
Daarentegen was de invloed van ontevredenheid over het uiterlijk wel geassocieerd met handpijn en functionele beperkingen. Hoe ernstiger gewrichtsvervorming, benige gewrichtszwellingen en radiologische schade, hoe groter de invloed van ontevredenheid over het uiterlijk. Bovendien hadden patiënten met een dergelijke invloed van vervormingen op het dagelijkse leven ook vaker depressieve stemmingen en negatieve ziektepercepties .
In overeenstemming met onze hypothese hangt ontevredenheid over het uiterlijk vooral af van gewrichtsspecifieke factoren en minder van psychosociale determinanten. Echter, patiënten met meer symptomen, een hogere depressiescore en negatieve ziektepercepties ervaren meer invloed. Deze resultaten laten de rol zien van psychosociale factoren op uitkomstmaten bij handartrosepatiënten. Er zou kunnen worden overwogen om zelfmanagementtrainingen onderdeel te laten uitmaken van de behandeling van handartrose, omdat patiënten met een negatieve ziekteperceptie mogelijk baat hebben bij deze programma's.

In **hoofdstukken 4 en 5** werden gewrichtsspecifieke factoren die kunnen worden beoordeeld met behulp van MRI bestudeerd en hun associatie met gewrichtspijn en radiologische progressie.
Activiteit in het subchondrale bot, geïdentificeerd als beenmerglaesies op MRI, is uitgebreid onderzocht in knieartrose en er is aangetoond dat dit geassocieerd is met kniepijn. Ook is synovitis gerapporteerd als een proces dat een rol speelt bij pijn bij artrose. Dit laatste is ook ondersteund door echo studies in

handartrose. Onderzoeken naar beenmerglaesies bij patiënten met handartrose zijn schaars. Bovendien biedt MRI de mogelijkheid om zowel de aanwezigheid van beenmerglaesies als synovitis te onderzoeken, waardoor we kunnen vaststellen wat de bijdrage van beenmerglaesies en synovitis afzonderlijk is en welk het meest veelbelovend doel is voor behandeling.

Hoofdstuk 4 richt zich op de aanwezigheid en interactie tussen beenmerglaesies en synovitis in relatie tot handpijn bij patiënten met handartrose die een MRI met contrast hebben ondergaan in de HOSTAS studie. De interfalangeale gewrichten uit de rechterhand werden gescoord op MRI kenmerken met een aangepaste versie van de Oslo Handartrose scoringsmethode. De MRI kenmerken beenmerglaesies, (teno) synovitis, peesontsteking en cysten werden vaak gezien. Beenmerglaesies en synovitis op gewrichtsniveau waren beiden geassocieerd met locatie specifieke pijn bij palpatie, indien gecorrigeerd voor leeftijd, geslacht, BMI, radiologische ernst gescoord volgens de Kellgren - Lawrence score en het patiënt effect. Er werd voor het patiënt-effect gecorrigeerd omdat patiënten met meerdere gewrichten deelnemen in de analyse. Er werd een duidelijke interactie tussen beenmerglaesies en synovitis gezien, met een gezamenlijk effect dat groter was dan de som van de afzonderlijke effecten. We toonden ook aan dat ernstige synovitis zonder beenmerglaesies met pijn was geassocieerd, terwijl de aanwezigheid van beenmerglaesies zonder synovitis niet was geassocieerd met pijn. Locatiespecifieke pijn bij palpatie werd waargenomen in 53% van de gewrichten met beenmerglaesies en matige tot ernstige synovitis. Een bijna 7-voudig verhoogde aanwezigheid van pijn werd gevonden in deze gewrichten in vergelijking met interfalangeale gewrichten zonder beenmerglaesies of synovitis. We concludeerden daarom dat bij handartrose ernstige synovitis in de interfalangeale gewrichten geassocieerd is met gewrichtspijn in hetzelfde gewricht en dat dit verergert wanneer er tegelijkertijd ook beenmerglaesies aanwezig zijn. Deze resultaten suggereren dat synovitis een doel voor behandeling is.

Echter, gesummeerde scores van beenmerglaesies of synovitis voor alle handgewrichten van een patiënt waren niet geassocieerd met zelf-gerapporteerde handpijn, gemeten met een gestandaardiseerde vragenlijst in beide handen. Dit zou verklaard kunnen worden door patiëntgebonden effecten zoals psychosociale factoren die een grote rol spelen bij pijn. Daarnaast ontbraken de MRI kenmerken van de vingergewrichten van de linker hand en de duimbasisgewrichten.

De MRI-kenmerken flexor tenosynovitis, extensorpees ontsteking en cysten waren niet geassocieerd met pijn. Hoewel in een eerdere studie een verband werd gevonden tussen flexor tenosynovitis en pijn, werden deze resultaten niet gerepliceerd en dit kan worden verklaard door een verschil in studiepopulaties en de gebruikte methoden.

Meer studies zullen nodig zijn om ontsteking in de extensorpees te onderzoeken en de associatie daarvan met klinische parameters. Er werd geen verband gevonden tussen ontsteking van de extensorpees en pijn, maar mogelijk zijn hier andere klinische factoren van belang, zoals handmobiliteit. De betrouwbaarheid van het scoren van deze afwijking was ook lager dan voor andere afwijkingen en daarom zouden studies kunnen worden opgezet om na te gaan of het mogelijk is om deze afwijking beter te definiëren en of een aanpassing van de huidige definitie noodzakelijk is.
Het is ook waardevol om onderzoeken op te zetten om de distale en proximale interfalangeale gewrichten afzonderlijk te bestuderen, omdat de insertieplaatsen van de diepe en oppervlakkige delen van de pezen verschillen tussen deze gewrichtsgroepen.

In **hoofdstuk 5** werd de associatie tussen MRI -kenmerken van artrose en het ontstaan en de verergering van radiologische schade bij handartrose bestudeerd**.** Bij aanvang hadden 324 interfalangeale gewrichten geen radiologische artroseschade. Na twee jaar follow-up was er in 78 gewrichten radiologische artrose ontstaan of was de radiologische artroseschade verergerd. Onze resultaten toonden aan dat matige en ernstige beenmerglaesies geassocieerd waren met verergering van de radiologische artrose. Er werd een graduele associatie gevonden tussen synovitis en verergering van radiologische artrose. De associatie van deze MRI afwijkingen met osteofyten en gewrichtsspleetversmalling progressie op de röntgenfoto was vergelijkbaar. Beenmerglaesies en synovitis waren beiden geassocieerd met het ontstaan en de verergering van radiologische artrose op gewrichtsniveau. In de gecorrigeerde analyses was de associatie tussen synovitis en verergering van artrose minder sterk in de aanwezigheid van beenmerglaesies, terwijl synovitis een vergelijkbaar effect had op de associatie tussen beenmerglaesies en verergering van artrose.
Concluderend kunnen we zeggen dat beenmerglaesies en synovitis al na 2 jaar een rol spelen bij verergering van radiologische artrose. Beide gewrichtsafwijkingen zouden daarom belangrijke doelen kunnen zijn voor therapie.
Een van de sterke punten van de studie is de inclusie van patiënten met een breed spectrum van ziekte-ernst, van een vroeg tot ernstige stadium van artrose. Ook werd verergering van radiologische artrose niet alleen onderzocht op gewrichtsniveau, maar ook op patiëntniveau. Alleen synovitis was geassocieerd op patiëntniveau. Onze resultaten suggereren dat de mate van ontsteking ook gepaard gaat met een hoger risico op verergering van radiologische handartrose. In de toekomst zouden studies kunnen onderzoeken of ontstekingsremmende medicatie zoals orale steroïden ontstekingskenmerken op MRI kunnen veranderen. Ook zouden studies kunnen onderzoeken of MRI afwijkingen persistent zijn of fluctueren in de loop van tijd.

STERFTE BIJ ARTROSE

Uit een eerder uitgevoerd onderzoek bleek dat de sterftekans verhoogd was onder deelnemers met heup- en kniepijn en radiologische artrose uit de algemene populatie. Een verklaring zou kunnen zijn dat factoren zoals bijkomende ziekten, zoals atherosclerose en diabetes, functionele beperkingen bij lopen en gebruik van NSAID's dit veroorzaken. Een dergelijke associatie zou kunnen betekenen dat de behandeling van artrosepatiënten uitgebreid zou moeten worden met behandeling voor cardiovasculaire risicofactoren en andere ziekten.
In **hoofdstuk 6** hebben we de associatie tussen artrose en sterftekansen bestudeerd in twee studiepopulaties: de 'Genetics ARthrosis and Progression' (GARP) studie, die bestond uit 192 zussen/broer-zus paren (384 patiënten) met symptomatische primaire artrose in meerdere gewrichten, en de 'Artrose Care Clinic' (OCC), die bestond uit 460 patiënten met primaire hand-, knie- of heupartrose die verwezen waren naar de reumaverpleegkundige voor uitleg over artrose in het 'artrose zorgpad'. Wij vonden geen verhoogd sterftecijfer in vergelijking met de algemene bevolking voor beide studiepopulaties. Mannelijk geslacht, leeftijd en kanker waren geassocieerd met een verhoogde sterftekans in GARP, zoals werd verwacht, maar artrose niet. Zelf-gerapporteerde cardiovasculaire ziekte, fysieke functie en BMI waren ook niet geassocieerd met sterfte.
In tegenstelling tot een eerdere studie vonden wij geen associatie tussen artrose en sterfte. Een verklaring kan gezocht worden in verschillen van studiepopulaties, waarbij deelnemers in eerder onderzoek uit de algemene bevolking kwamen en onze deelnemers artrosepatiënten waren die actief een medisch specialist of huisarts raadpleegden voor hun artroseklachten. Mogelijk hebben onze patiënten persoonlijkheidstrekken die hen motiveren om actief een behandelende arts te zoeken en gaan deze persoonlijkheidstrekken ook gepaard met het streven naar een gezonde levensstijl en het bezoeken van een behandelaar in het begin van een ziekte. Het is echter ook mogelijk dat een tegengesteld mechanisme een rol speelt: individuen die reageren op een onderzoek en knie- of heupklachten rapporteren hebben co-morbiditeiten die hun levensverwachting negatief beïnvloeden. Omdat ons onderzoek geen specifieke doodsoorzaak of een effect van artrosegerelateerde factoren heeft gevonden, lijken deze verklaringen meer waarschijnlijk dan een effect van artrose als zodanig op sterfte.
Aanvullende analyses werden uitgevoerd om te voorkomen dat onze resultaten zouden kunnen worden verklaard door de uitsluiting van patiënten met een verkorte levensduur in het GARP-onderzoek. We hebben geen ‹gezond cohort› effect gevonden en dit werd gesteund door de replicatie van onze resultaten in de OCC studie, waarin deze exclusiecriteria niet waren toegepast.

De betrouwbaarheid van de overlijdensakten kan in twijfel worden getrokken, maar mogelijke misclassificatie van doodsoorzaken zal optreden voor zowel artrosepatiënten als voor de algemene Nederlandse bevolking. Dit is daarom geen waarschijnlijke verklaring voor de resultaten.
De resultaten van studies omtrent de associatie tussen artrose en sterfte zijn tegenstrijdig. Daarom werd in **hoofdstuk 7** een systematische literatuurstudie uitgevoerd om het werkelijke verband tussen artrose en sterfte samen te vatten en te bepalen. In totaal hadden 35 studies de associatie tussen artrose en sterfte onderzocht. Studies konden worden onderscheiden in drie groepen: patiënten die een prothese van een gewricht kregen, patiënten die zorg nodig hadden voor hun artrose of deelnemers uit de algemene bevolking. Onderzoeken bij patiënten met een prothese, van knie of heup, vonden een gelijke of lagere sterfte voor artrosepatiënten in vergelijking met de algemene populatie. Ook bij patiënten die zorg nodig hadden voor hun artrose werd geen verband gerapporteerd tussen artrose en sterfte. Voor de onderzoeken met deelnemers uit de algemene populatie kon een meta-analyse worden uitgevoerd met zes van de tien studies, waarbij een gepoolde hazard ratio (HR) van 1,04 werd gevonden, d.w.z. geen verband. Twee van de vier studies die niet waren opgenomen in de meta-analyse vonden een verband tussen artrose en sterfte, terwijl twee dat niet deden. Afzonderlijke analyses voor radiologische en symptomatische artrose resulteerden niet in een verhoogd risico. We vonden dus geen associatie tussen artrose en sterfte en een gecombineerde analyse van de literatuur gaf ook geen aanwijzing voor een dergelijke associatie .

TOEKOMSTPERSPECTIEVEN

Dit proefschrift heeft meer kennis opgeleverd over het beloop van artrose en de determinanten van de uitkomst in handartrose. Tegelijkertijd hebben we ook onderwerpen gevonden die toekomstig onderzoek rechtvaardigen.
We hebben aangetoond dat de percepties van patiënten met handartrose en de copingstijlen die ze gebruiken een rol kunnen spelen in uitkomsten die patiënten zelf rapporteren, zoals functionele beperkingen. Interventies zouden zich op deze copingstijlen kunnen richten zoals gebeurd bij psycho-educatie en cognitieve herstructurering. Mogelijk kunnen deze interventies ook worden toegepast bij de behandeling van patiënten met een negatieve ziekteperceptie. Patiënten met negatieve ziektepercepties ervaren meer invloed op hun leven van ontevredenheid met het uiterlijk van hun handen. Hoewel esthetische schade valt onder het domein structurele schade, lijken patiënten met een negatieve ziekteperceptie vooral beïnvloed te worden en kunnen zij mogelijk profiteren van deze interventies.

De studie 'Grip on pain' is een lopende studie op de afdeling reumatologie van het Leids Universitair Medisch Centrum. Deze gerandomiseerde gecontroleerde trial heeft als doel de effectiviteit van online zelfmanagement bij patiënten met handartrose te onderzoeken. Dit onderzoek zal ons inzicht vergroten of een behandeling gericht op psychosociale factoren de kwaliteit van leven en symptomen bij patiënten met handartrose zal verbeteren. Daarnaast zal dit onderzoek, bij positieve bevindingen, een nieuwe behandelingsmodaliteit opleveren en zo de behandeling van patiënten met handartrose verbeteren.
In de huidige onderzoeken hebben we het ziekteverloop van handartrose gedurende 2 jaar onderzocht. Handartrose is echter een chronische langzaam progressieve ziekte, waarbij het zeer relevant kan zijn het onderzoek naar ziekteverloop en determinanten uit te breiden naar een tijdsperiode van meer dan 2 jaar. Daarnaast is de HOSTAS-studie een Nederlands onderzoek en is het mogelijk dat de resultaten wegens bijvoorbeeld cultuurverschillen niet gegeneraliseerd kunnen worden naar artrosepatiënten in andere landen en culturen. Het is daarom belangrijk om samen te werken met andere cohorten, zoals DIGICOD in Frankrijk en Nor-Hand in Noorwegen, om de resultaten te repliceren.
MRI is een veelbelovende methode om ziekteprocessen en uitkomsten in handartrose te evalueren. Beenmerglaesies en synovitis waren op gewrichtsniveau beide geassocieerd met locatiespecifieke pijn bij palpatie en er was ook een duidelijke interactie te zien. Andere MRI afwijkingen zoals ontsteking van de extensorpees waren niet geassocieerd met pijn. Meer studies naar de associatie tussen deze afwijking en andere klinische parameters, zoals handmobiliteit, kunnen waarschijnlijk meer inzicht geven in de rol van deze afwijkingen. Ook kunnen studies in de toekomst afzonderlijke analyses uitvoeren van de distale en proximale interfalangeale gewrichten. Omdat beenmerglaesies en synovitis op patiëntniveau niet geassocieerd waren met pijn, zal het een uitdaging zijn om te ontdekken welke andere bekende en onbekende variabelen kunnen bijdragen aan patiëntgebonden effecten. Mogelijk spelen de duimbasis gewrichten ook een rol. Verder zou het ook interessant zijn om te zien of MRI afwijkingen veranderen in de loop van de tijd, door follow-up gegevens uit het HOSTAS-onderzoek te gebruiken. We toonden aan dat beenmerglaesies en synovitis beide geassocieerd waren met het ontstaan en verergering van radiologische artrose na twee jaar follow-up. Daarom kunnen gerandomiseerde dubbelblinde placebo-gecontroleerde onderzoeken in de toekomst onderzoeken of ontstekingsremmende geneesmiddelen MRI ontstekingskenmerken en symptomen bij hand artrose patiënten kunnen veranderen. Een voorbeeld van zo›n onderzoek is de Hand Osteoarthritis Prednisolone Efficacy (HOPE) -studie, waarbij het hoofddoel is om een mogelijke nieuwe behandeling te identificeren om pijn te verlichten en ontsteking te verminderen bij handartrose patiënten.

Een deel van dit proefschrift richtte zich op de associatie tussen artrose en sterfte. We bestudeerden twee observationele cohorten van artrosepatiënten die de gezondheidszorg raadpleegden voor hun artrose en vonden geen associatie. In een later uitgevoerd systematische literatuurstudie hebben we aangetoond dat artrose niet geassocieerd was met sterfte bij patiënten die een gewrichtsprothese kregen of een behandelaar bezocht voor hun artrose klachten, terwijl deze associatie soms wel gerapporteerd werd in studies met de algemene bevolking. Artrose-subtypes en andere factoren kunnen een rol spelen in deze associatie en zijn tot nu toe niet voldoende onderzocht. Grootschalige populatie gebaseerde studies zoals de Nederlandse Epidemiologie van Obesitas (NEO) studie, een studie die gestart was om de onderliggende mechanismen van de relatie tussen obesitas en gerelateerde ziekten zoals artrose te onderzoeken, kan worden gebruikt om relaties tussen artrose, comorbiditeiten en sterfte beter te begrijpen. Idealiter zullen deze grootschalige onderzoeken ons ook helpen bij onze zoektocht naar nieuwe behandelingsopties.

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