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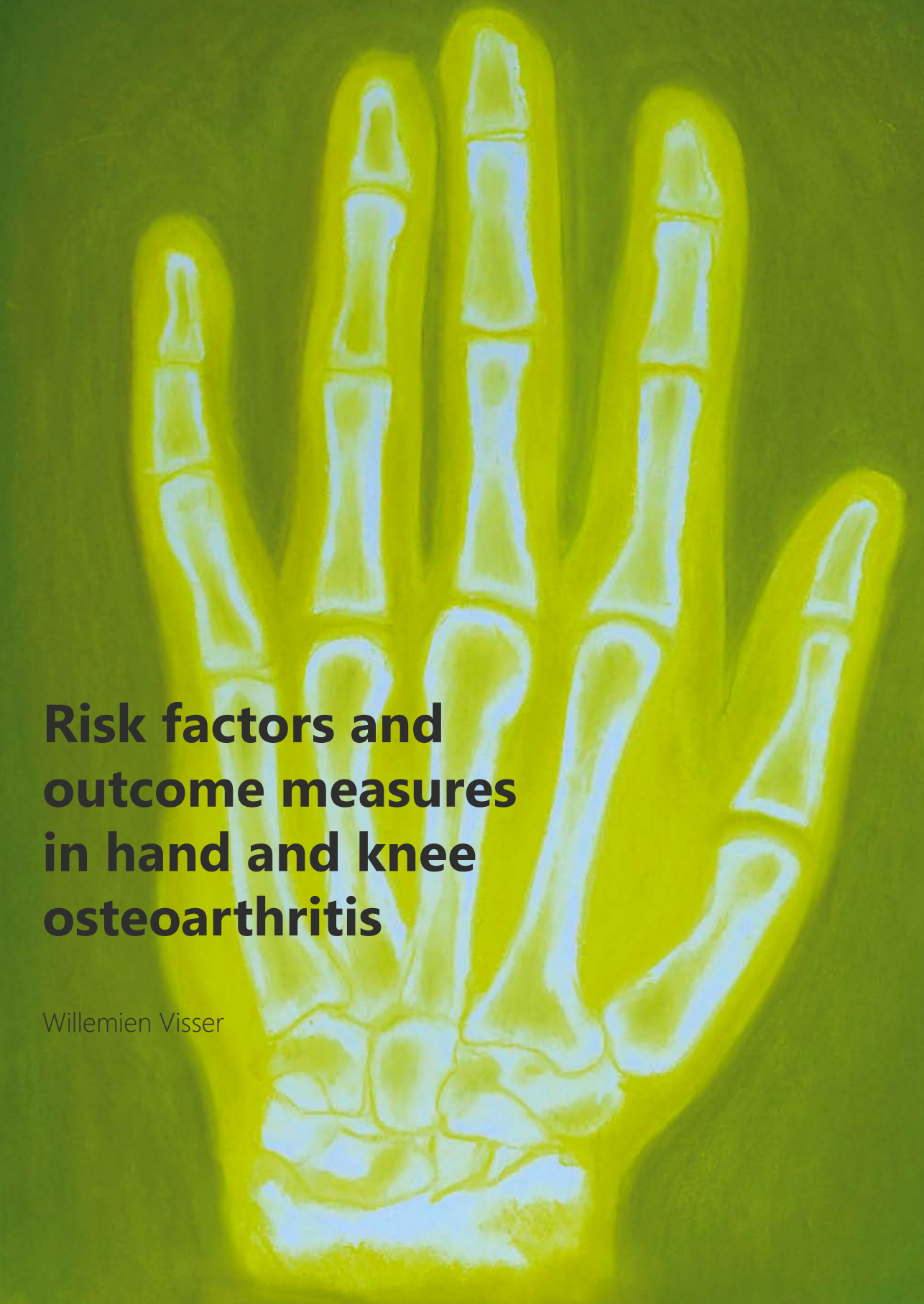

Risk factors and outcome measures in hand and knee osteoarthritis

Willemien Visser

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Risk factors and outcome measures in hand and knee osteoarthritis

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CHAPTER 1

General introduction

OSTEOARTHRITIS

Osteoarthritis (OA) is the most common musculoskeletal disease and the second largest contributor to disability within the musculoskeletal disorders.[1] Recently, new definitions to address OA have been developed.[2] The OsteoArthritis Research Society International defined OA as "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness".[3] The hands and knees are among the most frequently affected joints.[4,5]

Classification criteria

Clinical characteristics of OA are pain, stiffness and disability. During physical examination a decreased range of motion, bony enlargements and deformities of the joint can be observed. Radiographic examination reveals structural abnormalities of the joint as osteophytes, joint space narrowing and sclerosis of the subchondral bone (Figure 1). Magnetic resonance imaging can also visualize soft tissue abnormalities as synovitis, and subchondral bone lesions (Figure 1).

OA can be measured and defined according to different sets of classification criteria, focusing on either clinical or radiographic characteristics of OA, or on both. The most commonly used classification criteria are listed in Table 1.[6-8] Recently, preliminary criteria for OA assessment based on magnetic resonance imaging have been proposed.[9]

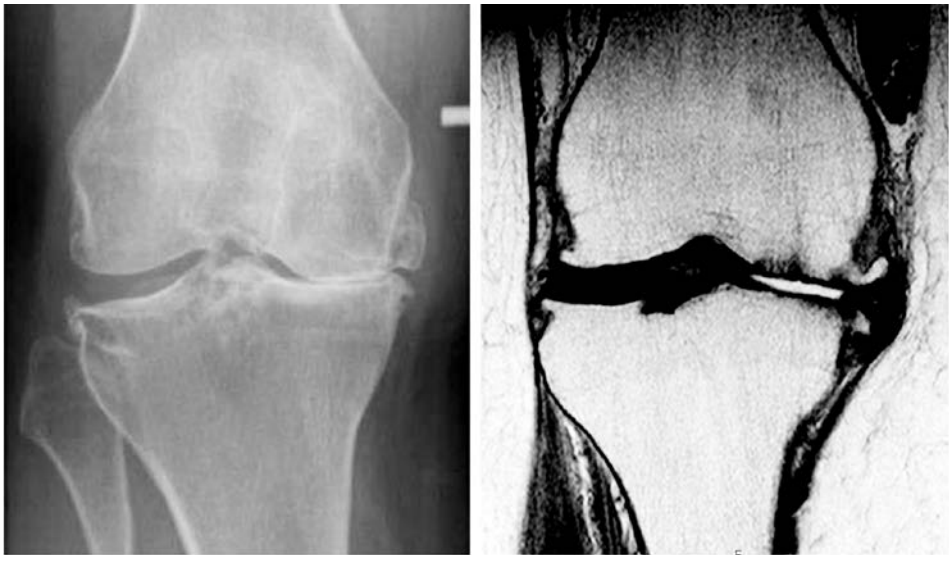

Figure 1. Radiographic examination of the knee by X-ray (left) and T1-weighted magnetic resonance image (right).

Table 1. Classification criteria for osteoarthritis (OA)

Hand OA	**Knee OA**
Clinical criteria#	**Clinical criteria#**
Pain, aching or stiffness	Pain
≥ 3 of the 4 following:	≥ 3 of the 6 following:
- Bony swelling in ≥ 2 of 10 selected joints*	- Age > 50 years
- Bony swelling of ≥ 2 DIP joints	- Stiffness < 30 minutes
- < 3 swollen MCP joints	- Crepitus on active motion
- Deformity of ≥ 1 of 10 selected joints*	- Bony tenderness
	- Bony enlargement
	- No palpable warmth
	Clinical and radiographic criteria#
	Pain
	Osteophytes
	≥ 1 of the 3 following:
	- Age > 50 years
	- Stiffness < 30 minutes
	- Crepitus
Radiographic criteria§	**Radiographic criteria§**
Doubtful OA: possible osteophytes, doubtful JSN	Doubtful OA: possible osteophytes, doubtful JSN
Minimal OA: definite osteophytes, possible JSN	Minimal OA: definite osteophytes, possible JSN
Moderate OA: moderate osteophytes, definite JSN, some sclerosis and bone deformity	Moderate OA: moderate osteophytes, definite JSN, some sclerosis and bone deformity
Severe OA: large osteophytes, severe JSN, severe sclerosis and bone deformity	Severe OA: large osteophytes, marked JSN, severe sclerosis and bone deformity

American College of Rheumatology criteria
§ Kellgren and Lawrence grading system
* Selected joints: bilateral DIP II and III, PIP II and III, and first CMC joints
CMC, carpometacarpal; DIP, distal interphalangeal; JSN, joint space narrowing; MCP, metacarpaphalangeal; OA, osteoarthritis; PIP, proximal interphalangeal.

Prevalence

The prevalence of OA depends on the classification criteria that are used, and increases with age.[4,5] A national survey among adult Dutch men and women aged from 18 years to over 80 years assessing self-reported diagnosis of OA showed an overall prevalence of knee OA of 5% and a prevalence of hand OA of 3%. When assessing the OA prevalence in different age categories, individuals aged 65 years or older had a 10-fold higher prevalence than individuals aged up to 64 years. From all individuals reporting to be diagnosed as having knee or hand OA, 75% reported severe complaints due to their OA.[10,11] These numbers illustrate the clinical burden of OA, especially in increasing age categories. In a recent survey of a population study in Rotterdam, the Netherlands, comprising 5650 men and women aged 55 years and older, the prevalence of OA of the different hand joints was 5-33%, according to the radiographic ACR criteria. The prevalence of radiographic knee OA was 15%.[12]

Incidence

The incidence of OA also depends on the applied classification criteria and is difficult to assess due to the gradual onset of the disease. Since the prevalence of a disease is equal to its incidence multiplied by the disease duration (lifelong in case of OA), the overall incidence of self-reported knee OA is estimated to be 81 per 100,000 person-years (5 per 100 persons per 62 assessed years) based on the 5% prevalence reported by the above described survey among Dutch men and women aged 18 to over 80 years (mean life expectancy 80 years). The overall incidence of self-reported hand OA is estimated to be 48 per 100,000 person-years (3 per 100 persons per 62 assessed years).[11]

As shown in a large-scale incidence study of symptomatic and radiographic knee and hand OA, the incidence of OA increases with age. This increasing incidence however was found only until the age of 80, above this age the incidence of OA decreased. Furthermore, a higher incidence of OA was found in women than men, especially after the age of 50. The calculated age- and sex-standardized incidence rates were 100 per 100,000 person-years for hand OA and 240 per 100,000 person-years for knee OA.[5]

Risk factors

Although the pathogenesis of OA is not completely understood, several risk factors are known to contribute to the development of the disease and its clinical features (Figure 2). Risk factors can be estimated both from incident and prevalent disease cases. In OA estimation of risk factors is mostly done based on prevalent cases, since this is most time efficient and the incidence-prevalence bias is low.

OA is a multifactorial disease affecting all joint tissues; degenerative changes of cartilage and subchondral bone but also inflammation of the synovial tissue occur. Both systemic factors and local biomechanical factors are thought to play a role in OA development.[13,14] Age and female sex are well-known risk factors. Obesity is another prominent risk factor, for OA of the weight-bearing knee joints as well as for OA of the non-weight-bearing hand joints.[15,16]

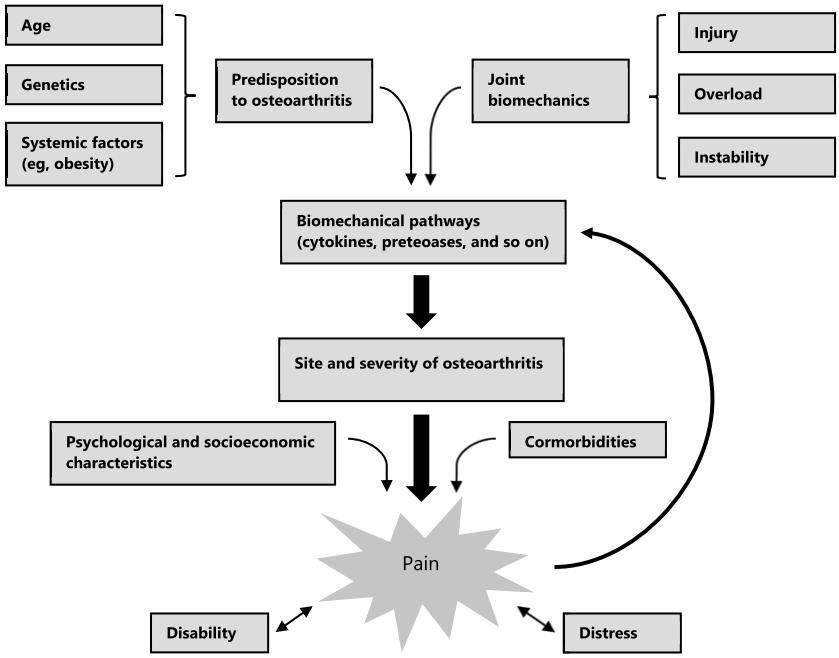

Figure 2. Systemic and local risk factors for OA development and clinical features (Dieppe, 2005)

Obesity

The association between obesity and OA of both weight-bearing and non-weight-bearing joints suggests involvement of biomechanical as well as systemic processes. Several mechanisms are thought to explain the association between obesity and OA (Figure 3).
Besides increased mechanical stress, resulting in damaged joint tissue due to overload,[17] multiple systemic processes seem to play a role. Adipose tissue is known as a source of pro-inflammatory and anti-inflammatory adipokines, which have been suggested to be involved in OA pathogenesis.[18] Obesity-associated hyperglycemia and diabetes have been related to OA,[19-21] possibly acting through different pathways: via insulin-like growth factor I resistance of chondrocytes,[22] via changes in striated muscles due to insulin resistance,[23] or via formation of advanced glycation end (AGE) products.[24,25] The association of OA with measures of atherosclerosis suggests involvement of systemic inflammation or pathology of subchondral bone vasculature.[12,26,27]
The relative importance of different processes in the relationship between obesity and OA remains unclear. Obesity is usually defined by a body mass index (BMI) of ≥30 kg/m2. Since BMI is defined based on height and weight only, it provides little information about body composition. More insight into the underlying mechanisms of the relation between obesity and OA can be obtained by studying different compounds of body composition separately. For example studying the amount and distribution of fat (visceral and subcutaneous adipose tissue) or fat free mass may provide valuable information regarding involvement of these body compositions in OA.

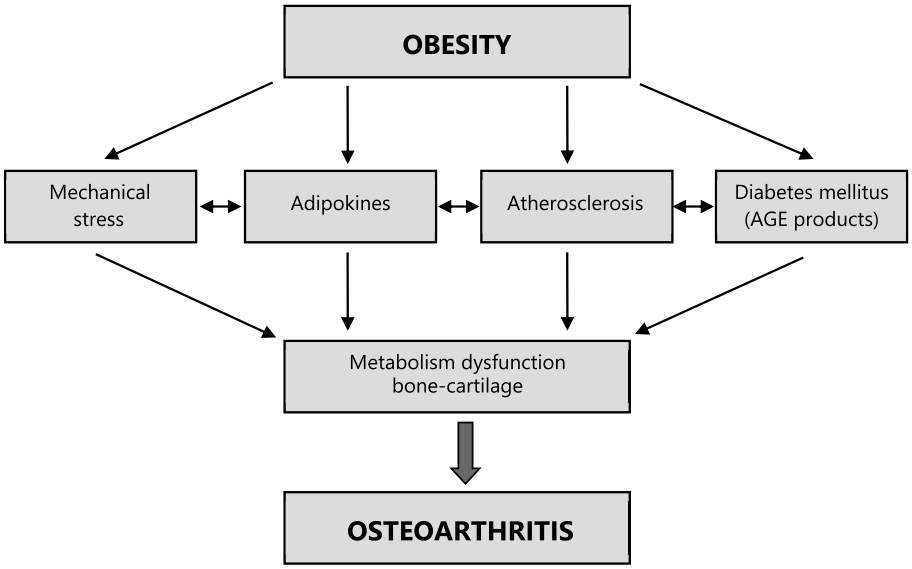

Figure 3. Mechanisms explaining the association between obesity and OA (EULAR textbook on Rheumatic Diseases, 2012)

Treatment of OA

Although the clinical burden of OA is high, treatment modalities are limited to symptom alleviation.[28,29] The lack of structure-modifying treatment is partly caused by the incomplete understanding of underlying disease processes. Furthermore, development of effective treatments is difficult because of the lack of high-quality studies on OA treatment. Especially in hand OA, few high-quality studies have been performed due to the use of many different and poor outcome measures, preventing adequate assessment of the disease and possible treatment effects.[30]

Outcome measures in OA research

The Outcome Measures in Rheumatology (OMERACT) is an initiative of international professionals interested in outcome measures in rheumatology, aiming to improve outcome measures through a data driven, iterative consensus process.[31] Core sets with a minimum number of domains and instruments are described for outcome description in clinical trials.[32] For phase III clinical trials in OA of the knee, hip and hand, four core domains have been identified depending on the setting: pain, (physical) function and patient global assessment for symptom modifying trials, and in addition imaging for structure modifying trials.[33] However, the existing set of core domains for hand OA is not hand OA specific and has several shortcomings.

The OMERACT Hand OA working group comprised health professionals and researchers with interest and experience in hand OA, whose goal is to identify a preliminary set of core domains using the OMERACT framework for four different settings: clinical trials aimed at symptom modification, clinical trials targetted at structure modification, observational studies, and clinical record keeping.[34]

AIM OF THESIS

The objectives of this thesis are:

I. To gain more insight into the mechanisms underlying the association of known risk factors with OA, focusing especially on obesity in association to OA of both weight-bearing and non-weight-bearing joints.

II. To contribute to the identification of appropriate outcome measures that can be applied in hand OA research, in order to enhance performance of high quality studies in hand OA.

OUTLINE OF THESIS

This thesis contains two parts; **part I** covers the first objective, focusing on the underlying mechanisms of the association between known risk factors and OA, and especially on obesity. For this part of the thesis, data of the Netherlands Epidemiology of Obesity (NEO) study have been used.

The NEO study is a population-based prospective cohort study, set up to investigate the underlying mechanisms of the relationship between obesity and related diseases, such as OA. The study population includes 6,673 individuals of the general population, aged 45 to 65 years, with an oversampling of persons with overweight or obesity. Due to the double counting of two individuals, the population was reduced to 6,671 individuals. Patients were included for baseline assessment between September 2008 and September 2012 and are followed for the incidence of obesity-related diseases and mortality. At baseline, data regarding presence of hand and knee OA were collected through questionnaires and physical examination of the hand and knee joints. In addition, in 1,285 participants magnetic resonance imaging of the knee was performed to assess structural abnormalities within the joint. Furthermore, all participants completed questionnaires on demographic and clinical data and underwent extensive physical examination including anthropometry and blood sampling.[35]

Using data of the NEO study, we took advantage of the unique opportunity that extensive data have been collected on metabolic factors associated with obesity simultaneously to extensive sampling of OA in both weight-bearing and non-weight-bearing joints. In **chapter 2** we investigated the relative contribution of mechanical stress and systemic processes in OA of weight-bearing and non-weight-bearing joints, by examining the association of surrogates for both mechanisms with OA of knees, hands or both. **Chapter 3** reports on the association between adiposity and OA. We investigated the association of adipose tissue and its abdominal distribution with the presence of OA in non-weight-bearing joints: the hands. To enhance our understanding of the role of obesity in knee OA, we investigated the association of fat mass and skeletal muscle mass with OA of the knees in **chapter 4**. OA is characterized by degenerative changes of joint structures; however, these structural abnormalities are not specific for OA since they have also been observed in persons without OA.[36-39] To increase the understanding of the disease processes leading to symptomatic OA, in **chapter 5** we investigated which specific structural abnormalities on specific locations within the knee joint could best discriminate presence of symptomatic OA in the same knee.

Symptomatic OA has been associated with decreased health-related quality of life (HRQOL).[40-42] In order to gain insight into possible targets for improvement or prevention of possible decline in HRQOL in knee OA patients, in **chapter 6** we evaluated the impact of knee OA and its modifiable or preventable risk factors obesity, fat free mass (as proxy for muscle mass) and comorbidities. In addition, the interaction between knee OA and these risk factors in relation to HRQOL was examined.

Part II comprises the second objective, focusing on the identification of appropriate outcome measures that can be applied in OA research. In the framework of the OMERACT Hand OA working group we performed two systematic reviews to assess available instruments measuring the previously identified domains pain, physical function, patient global assessment and imaging in more detail.

Chapter 7 evaluates the use of instruments measuring pain, physical function or patient global assessment in studies on hand OA, as well as the metric properties of these instruments. **Chapter 8** focuses on the imaging results, evaluating the use of conventional radiography in studies on hand OA, and to assess the metric properties of the different available radiographic scoring methods.

Finally, **chapter 9** provides a summary and general discussion of the thesis, as well as the future perspectives that result from our conclusions.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163-96.
2. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis Cartilage 2015;23:1233-41.
3. Standardization of osteoarthritis definitions. 2015. http://oarsi.org/research/standardization-osteoarthritis-definitions
4. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
5. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995;38:1134-41.
6. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
7. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-10.
8. Kellgren JH and Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
9. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A et al. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis Cartilage 2011;19:963-9.
10. Nationale Peiling Bewegingsapparaat 2010. http://www.reumafonds.nl
11. Artrose, prevalentie en incidentie. 2014. https://www.volksgezondheidenzorg.info
12. Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco O et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis 2013;72:646-51.
13. Dieppe PA and Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965-73.
14. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133:635-46.
15. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
16. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van OG et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-5.

17. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin North Am 2009;93:1-24, xv.
18. Hu PF, Bao JP, Wu LD. The emerging role of adipokines in osteoarthritis: a narrative review. Mol Biol Rep 2011;38:873-8.
19. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. Ann Rheum Dis 2007;66:916-20.
20. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403-9.
21. Nieves-Plaza M, Castro-Santana LE, Font YM, Mayor AM, Vila LM. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. J Clin Rheumatol 2013;19:1-6.
22. Kelley KM, Johnson TR, Ilan J, Moskowitz RW. Glucose regulation of the IGF response system in chondrocytes: induction of an IGF-I-resistant state. Am J Physiol 1999;276:R1164-R1171.
23. Rojas-Rodriguez J, Escobar-Linares LE, Garcia-Carrasco M, Escarcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860-8.
24. DeGroot J. The AGE of the matrix: chemistry, consequence and cure. Curr Opin Pharmacol 2004;4:301-5.
25. Loeser RF, Yammani RR, Carlson CS, Chen H, Cole A, Im HJ et al. Articular chondrocytes express the receptor for advanced glycation end products: Potential role in osteoarthritis. Arthritis Rheum 2005;52:2376-85.
26. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Ingvarsson T et al. Hand osteoarthritis in older women is associated with carotid and coronary atherosclerosis: the AGES Reykjavik study. Ann Rheum Dis 2009;68:1696-700.
27. Ghosh P and Cheras PA. Vascular mechanisms in osteoarthritis. Best Pract Res Clin Rheumatol 2001;15:693-709.
28. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64:465-74.
29. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. Nat Rev Rheumatol 2014;10:242-51.
30. Mahendira D and Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. Osteoarthritis Cartilage 2009;17:1263-8.
31. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
32. Escorpizo R, Boers M, Stucki G, Boonen A. Examining the similarities and differences of OMERACT core sets using the ICF: first step towards an improved domain specification and development of an item pool to measure functioning and health. J Rheumatol 2011;38:1739-44.
33. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.

34. Kloppenburg M, Boyesen P, Smeets W, Haugen IK, Liu R, Visser W et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014;41:810-8.
35. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
36. Beattie KA, Boulos P, Pui M, O'Neill J, Inglis D, Webber CE et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. Osteoarthritis Cartilage 2005;13:181-6.
37. Baranyay FJ, Wang Y, Wluka AE, English DR, Giles GG, Sullivan RO et al. Association of bone marrow lesions with knee structures and risk factors for bone marrow lesions in the knees of clinically healthy, community-based adults. Semin Arthritis Rheum 2007;37:112-8.
38. Guymer E, Baranyay F, Wluka AE, Hanna F, Bell RJ, Davis SR et al. A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women. Osteoarthritis Cartilage 2007;15:1437-42.
39. Hayashi D, Felson DT, Niu J, Hunter DJ, Roemer FW, Aliabadi P et al. Pre-radiographic osteoarthritic changes are highly prevalent in the medial patella and medial posterior femur in older persons: Framingham OA study. Osteoarthritis Cartilage 2014;22:76-83.
40. Alkan BM, Fidan F, Tosun A, Ardicoglu O. Quality of life and self-reported disability in patients with knee osteoarthritis. Mod Rheumatol 2013;24:166-71.
41. Woo J, Lau E, Lee P, Kwok T, Lau WC, Chan C et al. Impact of osteoarthritis on quality of life in a Hong Kong Chinese population. J Rheumatol 2004;31:2433-8.
42. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res 2005;17:255-63.

PART I

Mechanisms underlying the association between risk factors and osteoarthritis

CHAPTER 2

The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study

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ABSTRACT

Objective
To study the relative contribution of surrogates for mechanical stress and systemic processes with osteoarthritis (OA) in weight-bearing and non-weight-bearing joints.

Methods
The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort including 6,673 participants (range 45 to 65 years, 56% women, median BMI 26 kg/m^2). Weight (kg) and fat mass (FM) (kg) were measured, fat-free mass (FFM) (kg) was calculated. The metabolic syndrome was defined following the Adult Treatment Panel III criteria. Knee and hand OA were defined according to the American College of Rheumatology clinical criteria.
Logistic regression analyses were performed to associate surrogates for mechanical stress (such as weight, FFM) and systemic processes (such as metabolic syndrome) with OA in knees alone, knees and hands or hands alone, adjusted for age, sex, height, smoking, education and ethnicity, and when appropriate for metabolic factors and weight.

Results
Knee, knee and hand, and hand OA were present in 10%, 4% and 8% of the participants, respectively. Knee OA was associated with weight and FFM, adjusted for metabolic factors (OR 1.49 (95% CI 1.32 to 1.68) and 2.05 (1.60 to 2.62) respectively). Similar results were found for OA in knees and hands (OR 1.51 (95% CI 1.29 to 1.78) and 2.17 (1.52 to 3.10) respectively). Hand OA was associated with the metabolic syndrome, adjusted for weight (OR 1.46 (95% CI 1.06 to 2.02)).

Conclusion
In knee OA, whether or not in co-occurrence with hand OA, surrogates for mechanical stress are suggested to be the most important risk factors, whereas in hand OA alone, surrogates for systemic processes are the most important risk factors.

INTRODUCTION

Overweight and obesity are well-known risk factors for osteoarthritis (OA) in weight-bearing and non-weight-bearing joints.[1,2] Several mechanisms are thought to explain the association between obesity and OA. First, increased mechanical stress can result in damaged joint tissue.[3] Second, systemic processes seem to be involved. Adipose tissue is known as a source of proinflammatory and anti-inflammatory adipokines, which have been suggested to play a role in OA pathogenesis.[4-7] Furthermore, hyperglycaemia and diabetes have been related to OA,[8-12] possibly via insulin-like growth factor I resistance of chondrocytes,[13] via changes in striated muscles due to insulin resistance,[14] or via formation of advanced glycation end products.[15,16] The association of OA with measures of atherosclerosis suggests another systemic link with OA,[17,18] possibly via systemic inflammation or pathology of subchondral bone vasculature.[19]

The relative contribution of mechanical stress and systemic processes to different types of OA remains unclear. In OA of weight-bearing joints as the knees, the concept of excessive mechanical stress leading to OA is supported by previous reported associations of weight or lean body mass with knee OA.[20-23] The role of systemic processes in OA of weight-bearing joints is questionable, and difficult to identify since in obese individuals increased mechanical stress and systemic processes frequently occur together. Two recent studies on the metabolic syndrome, as surrogate for systemic processes, in relation to knee OA reported conflicting results. One observed an association between the metabolic syndrome and increased OA incidence even after adjustment for BMI, whereas the other did not.[24,25] So far, no studies examined knee OA in the presence of OA of non-weight-bearing joints as the hands, while this type of polyarticular OA might be particularly driven by systemic processes.

In hand OA, being non-weight-bearing joints, systemic processes may be most important in the association between obesity and OA. Although a number of studies assessed individual metabolic factors in relation to hand OA,[8,17,18] the association between the metabolic syndrome and presence of hand OA has not been investigated.

To gain more insight into the relative contribution of mechanical stress and systemic processes to OA of both weight-bearing and non-weight-bearing joints, we examined the association of surrogates for both mechanisms with OA of knees, hands or both. We hypothesized that surrogates for mechanical stress associate predominantly with knee OA, whereas surrogates for systemic processes associate predominantly with presence of hand OA, whether or not co-occurring with knee OA.

METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study with an oversampling of persons with overweight or obesity, aiming to investigate pathways leading to obesity-related diseases. The present study is a cross-sectional analysis of baseline measurements of the NEO study. Detailed information about the study design and data collection has been described previously.[26] In short, men and women between 45 years to 65 years of age with a self-reported BMI ≥27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate in the NEO study, resulting in 5,002 participants. In addition, all inhabitants aged 45 to 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, resulting in 1,671 participants (including 605 with BMI ≥27 kg/m^2) allowing for a reference distribution of BMI.

All participants completed questionnaires on demographic and clinical data and visited the NEO study center for several baseline measurements including extensive physical examination and blood sampling. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Measures of body composition

Measured weight (kg) and height (cm) were used to calculate the BMI (kg/m^2). Fat mass (FM) (kg) was measured by bioelectrical impedance analysis (BIA) using the Tanita foot-to-foot BIA system TBF-300A Body Composition Analyzer.[27] Fat-free mass (FFM) (kg) was calculated on weight and FM. Waist circumference (cm) was measured midway between the lower costal margin and iliac crest with a precision of 0.1 cm.

Measurement of metabolic factors

Blood pressure was measured three times, the average was used as diastolic and systolic pressures. Serum concentrations of triglycerides (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L) and glucose (mmol/L) were measured after an overnight fast.

The metabolic syndrome was defined according to the Adult Treatment Panel III criteria, based on presence of at least three of the following: (1) elevated waist circumference (men ≥102 cm, women ≥88 cm), (2) elevated triglycerides (≥1.7 mmol/L or drug treatment for elevated triglycerides), (3) reduced HDL cholesterol (men <1.03 mmol/L, women <1.3 mmol/L or drug treatment for reduced HDL cholesterol), (4) elevated blood pressure (systolic ≥130 mm Hg, diastolic ≥85 mm Hg or antihypertensive medication), (5) elevated fasting glucose (≥5.6 mmol/L or glucose lowering medication).[28]

Clinical assessment and OA diagnosis

Self-reported pain on most days of the prior month and presence of morning stiffness with ≤30 minutes duration were measured using standardized questions. Physical examination of knees and hands was performed by trained research nurses, using a standardized scoring form. Bony swelling, palpable pain and warmth, crepitus and movement restriction of both knees were assessed. Regarding the hands, bony and soft swellings as well as deformities of the distal interphalangeal, proximal interphalangeal, metacar-

pophalangeal, carpometacarpal and wrist joints were assessed. Clinical OA was defined according to the American College of Rheumatology clinical criteria.[29,30] Presence of a knee prosthesis was considered as knee OA.

Statistical analysis

Data were analyzed using SPSS V.20 and STATA V.12.

In the NEO study there is an oversampling of persons with a BMI ≥27 kg/m^2. To correctly represent associations in the general population,[31] adjustments for this oversampling were made by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality (n = 1,671),[32] whose BMI distribution was similar to the BMI distribution in the general Dutch population.[33] All results were based on weighted analyses. Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.

Based on OA diagnosis, four groups were defined: (1) individuals without knee or hand OA, (2) individuals with only knee OA, (3) individuals with knee and hand OA, and (4) individuals with only hand OA. We performed logistic regression analyses to examine cross-sectional associations of each of the surrogates for mechanical stress (weight, FFM, FM) and systemic processes (FM, metabolic syndrome) with each of the three OA types, using individuals without knee or hand OA as reference group. FM probably is a surrogate for mechanical stress and systemic processes. To approximate FM as surrogate for mechanical stress, adjustment for metabolic factors was performed, and adjustment for weight was performed to approximate FM as surrogate for systemic processes. Associations were expressed as odds ratios (OR) with 95% confidence intervals (CI).

All continuous variables were standardized by dividing individual values by the standard deviation (SD) to be able to compare ORs. Consequently, all ORs describe the risk of OA associated with an increase of 1 SD of the studied variable. All analyses have been adjusted for age, sex, height, smoking, education and ethnicity. Analyses on surrogates for mechanical stress were additionally adjusted for metabolic factors (presence of metabolic syndrome, hypertension, hyperglycaemia, hypertriglyceridaemia and reduced HDL cholesterol) and analyses on surrogates for systemic processes were adjusted for weight. Finally, to illustrate the relative importance of mechanical stress and systemic processes, age, sex, height, smoking, education and ethnicity adjusted ORs were calculated for presence of each OA type in three weight categories (based on tertiles of weight of the total study population: <75 kg, 75-90 kg, >90 kg), stratified by the metabolic syndrome. Participants in the lowest weight category without metabolic syndrome served as reference.

RESULTS

Population characteristics

After exclusion of individuals with missing data of BIA (n = 31) or physical examination (n = 14), data from 6,628 participants were analyzed. Unweighted baseline characteristics, that is, without taking the oversampling into account, are shown in the online supplementary table. Table 1 shows the weighted baseline characteristics stratified by OA; these characteristics represent the population on which all subsequent results apply. Median (25th to 75th centiles) age of the total study population was 56 years (50 to 61 years), BMI 26 kg/m^2 (23 to 28 kg/m^2), 56% women.

The prevalence of knee OA alone was 10% (95% CI 9% to 11%), knee and hand OA 4% (95% CI 4% to 5%) and hand OA alone 8% (95% CI 7% to 8%). The prevalence of a knee prosthesis was 1% (95% CI 1% to 1%).
The percentage of women and median age were higher in individuals with knee, knee and hand, or hand OA as compared with individuals without OA. Furthermore, individuals with knee, hand or knee and hand OA had a higher median FM and metabolic syndrome prevalence than individuals without OA.

Table 1. Baseline characteristics of the NEO study population, stratified by OA status

Prevalence	**No knee/hand OA 78%**	**Knee OA 10%**	**Knee and hand OA 4%**	**Hand OA 8%**
Age (year)	55 (49-61)	58 (53-61)	59 (55-62)	59 (55-63)
Sex (% women)	52	63	86	76
Smoking (% current)	12	11	9	8
Education (% high)	39	28	25	32
Ethnicity (% Caucasian)	95	96	92	95
BMI (kg/m^2)	25.5 (23.2-28.0)	26.9 (24.6-30.3)	26.7 (24.6-29.8)	25.9 (23.0-28.8)
Height (m)	1.74 (1.67-1.81)	1.71 (1.66-1.79)	1.68 (1.63-1.73)	1.68 (1.63-1.75)
Weight (kg)	77.8 (67.6-88.8)	80.4 (70.8-92.8)	75.6 (66.8-86.8)	73.4 (63.8-85.6)
Fat-free mass (kg)	51.8 (44.0-64.6)	49.2 (44.2-64.0)	45.9 (43.2-50.3)	45.1 (41.8-54.4)
Fat mass (kg)	22.7 (18.2-29.0)	27.5 (21.0-34.7)	27.5 (22.4-35.0)	24.4 (19.8-31.9)
Metabolic syndrome (%)	28	39	36	38

Results are based on weighted analyses of the study population (n = 6,628).

Numbers represent medians (25th-75th centiles) or percentages.

BMI, body mass index; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis.

Surrogates for mechanical stress and different OA types

First, we investigated associations of surrogates for mechanical stress with the OA types (Table 2).
Weight, FFM and FM were positively associated with all OA types. The ORs were highest for presence of knee OA and OA in knee and hand. The ORs per SD weight for example, were 1.55 (95% CI 1.39 to 1.73) for knee OA and 1.52 (1.31 to 1.76) for knee and hand OA, meaning that 1 SD of weight (15.95 kg) was associated with a 55% higher odds of having knee OA and a 52% higher odds of having knee and hand OA. The OR for hand OA was 1.25 (1.09 to 1.42).
After additional adjustment for metabolic factors, weight, FFM and FM remained associated with knee OA and with OA in knee and hand. The associations with hand OA on the contrary decreased.
In addition, we assessed if associations between surrogates for mechanical stress and knee OA were stronger for bilateral than for unilateral knee OA. Fully adjusted ORs of weight, FFM and FM were higher for bilateral OA (OR 1.68 (1.44 to 1.97), 2.29 (1.58 to 3.34) and 1.54 (1.36 to 1.75), respectively), than for unilateral OA (OR 1.38 (1.19 to 1.59), 1.92 (1.44 to 2.57) and 1.27 (1.12 to 1.44), respectively).

Table 2. Associations of surrogates for mechanical stress with different types of OA (individuals without OA served as reference)

		OR (95% CI)					
		Knee OA		**Knee and hand OA**		**Hand OA**	
	SD	Adjusted*	Adjusted incl. metabolic factors#	Adjusted*	Adjusted incl. metabolic factors#	Adjusted*	Adjusted incl. metabolic factors#
Weight (kg)	15.95	1.55	1.49	1.52	1.51	1.25	1.12
		(1.39-1.73)	(1.32-1.68)	(1.31-1.76)	(1.29-1.78)	(1.09-1.42)	(0.96-1.32)
Fat-free mass (kg)	11.68	2.33	2.05	2.29	2.17	1.43	1.17
		(1.83-2.96)	(1.60-2.62)	(1.63-3.22)	(1.52-3.10)	(1.06-1.93)	(0.83-1.63)
Fat mass (kg)	9.97	1.43	1.37	1.42	1.41	1.21	1.11
		(1.30-1.57)	(1.24-1.52)	(1.25-1.61)	(1.22-1.63)	(1.09-1.35)	(0.97-1.27)

Results are based on weighted analyses of the study population.

All ORs express the risk of OA per SD of the independent variable.

* Adjusted for age, sex, height, smoking, education, ethnicity.

Adjusted for age, sex, height, smoking, education, ethnicity, metabolic syndrome, hypertension, hyperglycaemia, hypertriglyceridaemia, low high density lipoprotein cholesterol. CI, confidence interval; OA, osteoarthritis; OR, odds ratio; SD, standard deviation.

Surrogates for systemic processes and different OA types

Next, we assessed associations of surrogates for systemic processes with OA (Table 3). Although the OR of FM for hand OA was higher (1.17 (0.74 to 1.86)) than for knee OA or OA in knee and hand (OR 0.88 (0.61 to 1.26) and OR 1.03 (0.51 to 2.11), respectively), the associations were not statistically significant after adjustment for weight.

The metabolic syndrome, surrogate for systemic processes particularly, was associated with all OA types. However, after additional adjustment for weight the associations with knee OA and knee and hand OA disappeared whereas the metabolic syndrome remained associated with hand OA (OR 1.46 (1.06 to 2.02).

Table 3. Associations of surrogates for systemic processes with different types of OA (individuals without OA served as reference)

		OR (95% CI)					
		Knee OA		**Knee and hand OA**		**Hand OA**	
	SD	Adjusted*	Adjusted incl. weight#	Adjusted*	Adjusted incl. weight#	Adjusted*	Adjusted incl. weight#
Fat mass (kg)	9.97	1.43 (1.30-1.57)	0.88 (0.61-1.26)	1.42 (1.25-1.61)	1.03 (0.51-2.11)	1.21 (1.09-1.35)	1.17 (0.74-1.86)
Metabolic syndrome		1.56 (1.24-1.97)	1.08 (0.85-1.39)	1.48 (1.07-2.05)	1.03 (0.72-1.46)	1.62 (1.23-2.13)	1.46 (1.06-2.02)

Results are based on weighted analyses of the study population.

The OR of fat mass expresses the risk of OA per SD.

* Adjusted for age, sex, smoking, education, ethnicity, height.

Adjusted for age, sex, smoking, education, ethnicity, height, weight.

CI, confidence interval; OA, osteoarthritis; OR, odds ratio; SD, standard deviation.

Relative contribution of weight and metabolic syndrome to different OA types

Figure 1 illustrates the relative contribution of weight as surrogate for mechanical stress and metabolic syndrome as surrogate for systemic processes to the OA types.

The ORs for knee OA were stronger in higher weight categories as compared with the lowest weight category. In addition to the depicted OR representing the highest weight category compared with the lowest in individuals without metabolic syndrome 2.62 (1.77 to 3.88), we calculated the OR of highest versus lowest weight category in individuals with metabolic syndrome (2.30 (1.29 to 4.12)). Presence of metabolic syndrome, adjusted for the weight categories, did not result in a higher OR for knee OA (OR 1.16 (0.91 to 1.47). The same was observed in relation to OA in knee and hand.

In hand OA on the contrary, ORs did not increase with increasing weight (highest vs. lowest weight category: OR 1.40 (0.89 to 2.21) in individuals without metabolic syndrome (Figure 1) and 0.77 (0.39 to 1.51) in individuals with metabolic syndrome. The metabolic syndrome on the other hand was associated with presence of hand OA, adjusted for the weight categories; individuals with metabolic syndrome had a higher OR for hand OA as compared with individuals without metabolic syndrome (OR 1.52 (1.10 to 2.09)).

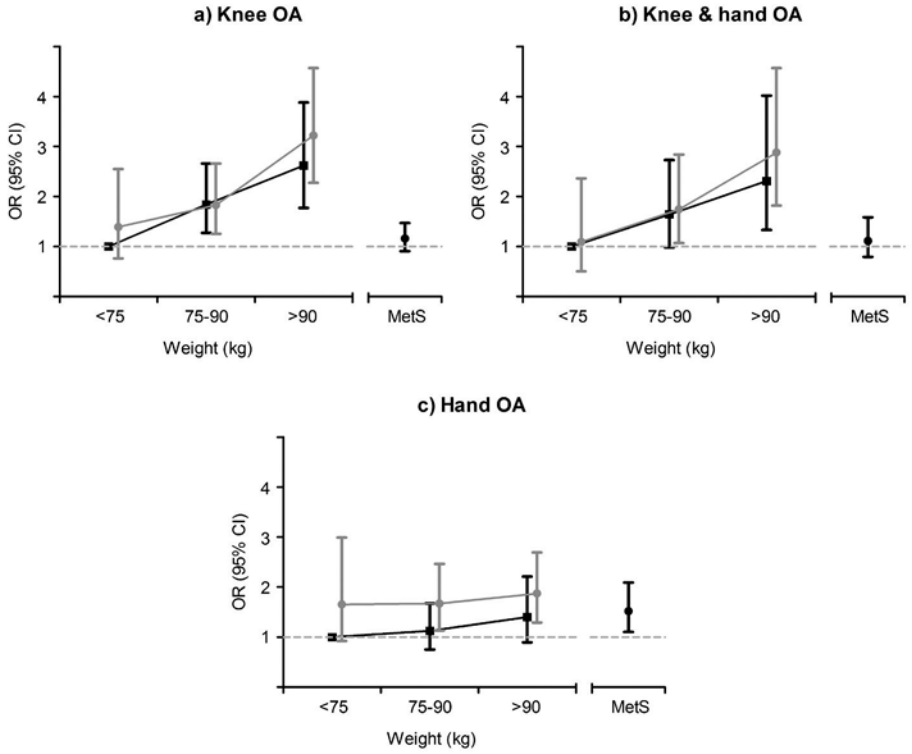

Figure 1. The adjusted ORs and corresponding 95% CIs for osteoarthritis (OA) stratified by weight and metabolic syndrome. Participants in the lowest weight category without metabolic syndrome served as reference. Gray connected lines represent individuals with metabolic syndrome, black connected lines represent individuals without metabolic syndrome. Results are based on weighted analyses of the study population, adjusted for age, sex, smoking, education, ethnicity and height. MetS, metabolic syndrome, representing the odds ratio of the metabolic syndrome for OA, adjusted for the weight catagorie

DISCUSSION

This study aimed to increase insight into the relative contribution of mechanical stress and systemic processes in the relation between overweight or obesity and OA of weight-bearing and non-weight-bearing joints. Knee OA was associated with surrogates for mechanical stress, adjusted for metabolic factors. Similar results were found for OA in knees and hands. Hand OA was associated with the metabolic syndrome, adjusted for weight.

A growing body of literature exists on mechanical stress and systemic processes in OA pathogenesis, however innovative in this study is the investigation of the relative contribution of both mechanisms to OA of weight-bearing and non-weight-bearing joints, or of both.

The association of surrogates for mechanical stress with knee OA has been described previously,[20-23,34] supporting the concept of excessive mechanical stress on the joint surface of obese individuals resulting in damaged joint tissue. Compression of cartilage might activate mechanoreceptors on chondrocytes, inducing signaling cascades leading to synthesis of inflammatory mediators and tissue remodeling.[35,36] It is unclear which biomechanical factors are involved in the relation between weight and OA, since a recent study showed that neither a decrease nor increase in knee peak compression force was associated with OA progression.[37]

Our finding regarding the metabolic syndrome in relation to knee OA is in accordance with a recent study of Han et al.,[24] reporting no association between metabolic syndrome and knee OA. Another recent study, by Monira Hussain et al.,[25] did report an association between metabolic syndrome and knee OA, adjusted for BMI. This discrepancy might be due to differences in OA definition. Where in this study clinical knee OA was assessed following the ACR criteria, Monira Hussain et al. defined severe knee OA requiring total knee replacement as OA. Han et al. defined knee OA by self-reported physician-made diagnosis. The strength of our study is that knee OA was assessed in all 6628 patients by physical examination. Consequently, OA was diagnosed following the ACR criteria, providing an objective and well validated definition.

Presence of knee and hand OA has not been investigated before. Our hypothesis was that this type of polyarticular OA might be driven by systemic processes, however we observed no association with surrogates for systemic processes after adjustment for weight. Presence of knee and hand OA was associated with surrogates for mechanical stress, even after adjustment for metabolic factors, like presence of knee OA alone. This observation suggests that co-occurrence of knee and hand OA may not be based on a common underlying pathogenic mechanism, but may represent presence of two different types of OA. Since the association between mechanical stress and knee OA was relatively strong, this association could dominate the association with OA at both sites.

The association between metabolic syndrome and hand OA, adjusted for weight, has not been reported before. A number of studies assessed individual metabolic factors in relation to OA, however the metabolic syndrome, as composition of different metabolic processes, might act as risk factor beyond the risk of its individual components.[38]

The association between metabolic syndrome and hand OA might be explained by systemic inflammation, a main characteristic of the metabolic syndrome. Adipose tissue is known as source of proinflammatory and anti-inflammatory cytokines, which have been related to the metabolic syndrome[39] and have been suggested to affect joint tissues.[4,6,7] Visceral fat has been described as the most actively secreting type of adipose tissue,[40] and has been associated with the metabolic syndrome.[41-45] In addition, in a recently performed study we associated visceral fat with hand OA in men.[46]

Strengths of this study are the large study population, extensive characterization of participants and availability of information of both weight-bearing and non-weight-bearing joints.

However, there are a number of potential limitations. The observed associations were not very strong, however since this study aimed to assess the relative contribution of mechanical stress and systemic processes to the OA types the different ORs provide valuable insight.

Increased mechanical stress and systemic processes are highly correlated in overweight or obese individuals. Therefore, we adjusted for surrogates for mechanical stress in our analyses on systemic processes and vice versa. Although these analyses identified the relative contribution of both mechanisms for OA, residual confounding may still be present in this observational study. We further minimized residual confounding by adjusting for possible confounders as age, sex and surrogates for socioeconomic status (education, smoking, ethnicity). Unfortunately we did not have information on previous knee injury, which may be a confounder in the associations with knee OA.

Furthermore, since this is a cross-sectional study, causality is difficult to identify. Since the direction of associations cannot be determined, reverse causation may be present. Longitudinal studies are needed to confirm and further explore associations of mechanical stress and systemic processes with OA.

Knee and hand OA were diagnosed based on clinical criteria, no X-rays were available. However, the ACR clinical criteria are well validated and have high sensitivity and specificity in diagnosing OA.[29,30] This criteria include findings at physical examination and presence of symptoms as pain. Since it is known that obese individuals are more likely to report pain,[47] they could be more prone to be diagnosed as having OA than non-obese individuals. However, the OA prevalence observed in this study is comparable with the prevalence observed in other population-based studies.[18,48]

Furthermore, FM was measured using foot-to-foot BIA. Although this method has been suggested to overestimate FM,[49] studies comparing foot-to-foot BIA with hand-to-foot BIA, underwater weighing and dual-energy X-ray absorptiometry reported strong correlations.[27,50]

We assessed all body composition measures in relation to OA per SD to be able to compare strength of associations observed in this study. It must be noted that the OR of the metabolic syndrome, analysed dichotomously, cannot be directly compared to the ORs of the body composition measures.

This study suggests that in knee OA, whether or not co-occurring with hand OA, mechanical stress is the most important underlying mechanism, whereas in hand OA alone, systemic processes might contribute most. To gain more insight into the underlying mechanisms, longitudinal research could help to understand how excessive mechanical stress leads to degeneration of joint tissue. In hand OA, the role of the metabolic syndrome might be explored by studying the contribution of the different components of the metabolic syndrome to OA development. Furthermore, future research should focus on the role of systemic inflammation.

REFERENCES

1. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
2. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van OG et al. Association between weight or body mass index and osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-5.
3. Brandt KD, Dieppe P, Radin E. Etipathogenesis of osteoarthritis. Med Clin North Am 2009;93:1-24, xv.
4. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;48:3118-29.
5. Hu PF, Bao JP, Wu LD. The emerging role of adipokines in osteoarthritis: a narrative review. Mol Biol Rep 2011;38:873-8.
6. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-5.
7. Tilg H and Moschen AR. Adipocy tokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-83.
8. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. Ann Rheum Dis 2007;66:916-20.
9. King KB, Findley TW, Williams AE, Bucknell AL. Veterans with diabetes receive arthroplasty more frequently and at a younger age. Clin Orthop Relat Res 2013;471:3049-54.
10. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403-9.
11. Nieves-Plaza M, Castro-Santana LE, Font YM, Mayor AM, Vila LM. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. J Clin Rheumatol 2013;19:1-6.
12. Jungmann PM, Kraus MS, Alizai H, Nardo L, Baum T, Nevitt MC et al. Metabolic risk factors are associated with cartilage degradation assessed by T relaxation time at the knee. Arthritis Care Res (Hoboken) 2013;65:1942-50.
13. Kelley KM, Johnson TR, Ilan J, Moskowitz RW. Glucose regulation of the IGF response system in chondrocytes: induction of an IGF-I-resistant state. Am J Physiol 1999;276:R1164-R1171.
14. Rojas-Rodriguez J, Escobar-Linares LE, Garcia-Carrasco M, Escarcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860-8.
15. DeGroot J. The AGE of the matrix: chemistry, consequence and cure. Curr Opin Pharmacol 2004;4:301-5.
16. Loeser RF, Yammani RR, Carlson CS, Chen H, Cole A, Im HJ et al. Articular chondrocytes express the receptor for advanced glycation end products: Potential role in osteoarthritis. Arthritis Rheum 2005;52:2376-85.
17. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Ing-

varsson T et al. Hand osteoarthritis in older women is associated with carotid and coronary atherosclerosis: the AGES Reykjavik study. Ann Rheum Dis 2009;68:1696-700.
18. Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco O et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis 2013;72:646-51.
19. Ghosh P and Cheras PA. Vascular mechanisms in osteoarthritis. Best Pract Res Clin Rheumatol 2001;15:693-709.
20. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis 2007;66:1244-8.
21. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. Osteoarthritis Cartilage 2008;16:367-72.
22. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. Obesity (Silver Spring) 2006;14:1274-81.
23. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008;16:232-40.
24. Han CD, Yang IH, Lee WS, Park YJ, Park KK. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). BMC Public Health 2013;13:603.
25. Monira HS, Wang Y, Cicuttini FM, Simpson JA, Giles GG, Graves S et al. Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: A prospective cohort study. Semin Arthritis Rheum 2014;43:429-36.
26. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
27. Ritchie JD, Miller CK, Smiciklas-Wright H. Tanita foot-to-foot bioelectrical impedance analysis system validated in older adults. J Am Diet Assoc 2005;105:1617-9.
28. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
29. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-10.
30. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteo-arthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
31. Korn EL and Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health 1991;81:1166-73.

32. Lumley T. Analysis of complex survey samples. 2004. http://www. jstatsoft. org/v09/i08/paper
33. Misisterie van VWS. Hoeveel mensen hebben overgewicht? 2013. http:// www.rivm.nl/ nldemaat
34. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1995;22:488-93.
35. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol 2013;25:114-8.
36. Ramage L, Nuki G, Salter DM. Signalling cascades in mechanotransduction: cell-matrix interactions and mechanical loading. Scand J Med SciSports 2009;19:457-69.
37. Henriksen M, Hunter DJ, Dam EB, Messier SP, Andriacchi TP, Lohmander LS et al. Is increased joint loading detrimental to obese patients with knee osteoarthritis? A secondary data analysis from a randomized trial. Osteoarthritis Cartilage 2013;21:1865-75.
38. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415-28.
39. Mattu HS and Randeva HS. Role of adipokines in cardiovascular disease. J Endocrinol 2013;216:T17-T36.
40. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev 2006;2:367-73.
41. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39-48.
42. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke 2007;38:2422-9.
43. Ditomasso D, Carnethon MR, Wright CM, Allison MA. The associations between visceral fat and calcified atherosclerosis are stronger in women than men. Atherosclerosis 2010;208:531-6.
44. Indulekha K, Anjana RM, Surendar J, Mohan V. Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). Clin Biochem 2011;44:281-7.
45. Hanley AJ, Wagenknecht LE, Norris JM, Bryer-Ash M, Chen YI, Anderson AM et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study IRAS) Family study. Diabetologia 2009;52:2079-86.
46. Visser AW, Ioan-Facsinay A, de Mutsert R, Widya RL, Loef M, de RA et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Res Ther 2014;16:R19.
47. Hitt HC, McMillen RC, Thornton-Neaves T, Koch K, Cosby AG. Co-morbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. J Pain 2007;8:430-6.
48. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis 2011;70:1581-6.
49. Gagnon C, Menard J, Bourbonnais A, Ardilouze JL, Baillargeon JP, Car-

pentier AC et al. Comparison of foot-to-foot and hand-to-foot bioelectrical impedance methods in a population with a wide range of body mass indices. Metab Syndr Relat Disord 2010;8:437-41.
50. Nunez C, Gallagher D, Visser M, Pisunyer FX, Wang Z, Heymsfield SB. Bioimpedance analysis: evaluation of leg-to-leg system based on pressure contact footpad electrodes. Med Sci Sports Exerc 1997;29:524-31.

Supplementary table. Unweighted baseline characteristics of 6,628 participants of the NEO study with an over-sampling of BMI ≥ 27 kg/m^2, stratified by OA status

	No knee/hand OA n = 4,890	**Knee OA n = 854**	**Knee and hand OA n = 339**	**Hand OA n = 545**
Age (year)	55 (50-61)	57 (53-61)	59 (55-62)	58 (54-62)
Sex (% women)	47	62	84	70
Smoking (% current)	12	12	8	8
Education (% high)	32	25	20	24
Ethnicity (% Caucasian)	95	94	94	95
BMI (kg/m^2)	29.3 (27.1-32.0)	30.8 (28.2-34.1)	30.5 (27.9-34.0)	29.8 (27.6-33.2)
Height (m)	1.74 (1.67-1.81)	1.71 (1.65-1.79)	1.68 (1.63-1.73)	1.69 (1.63-1.76)
Weight (kg)	89.6 (79.4-99.8)	91.6 (81.4-102.4)	87.6 (78.2-96.4)	86.2 (76.6-98.0)
Fat free mass (kg)	58.6 (47.5-68.3)	52.9 (47.0-66.5)	48.6 (45.4-54.3)	49.8 (45.0-61.5)
Fat mass (kg)	30.2 (24.0-37.8)	35.0 (28.2-42.5)	36.1 (29.9-43.8)	33.4 (26.9-40.8)
Metabolic syndrome (%)	48	57	55	56

Numbers represent medians (25th to 75th percentiles) or percentages.

BMI, body mass index; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis.

CHAPTER 3

Adiposity and hand osteoarthritis: the NEO study

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ABSTRACT

Introduction
Obesity, usually characterized by the body mass index (BMI), is a risk factor for hand osteoarthritis (OA). We investigated whether adipose tissue and abdominal fat distribution are associated with hand OA.

Methods
The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort aged 45 to 65 years, including 5,315 participants (53% women, median BMI 29.9 kg/m^2). Fat percentage and fat mass (FM) (kg) were estimated using bioelectrical impedance analysis. The waist-to-hip ratio (WHR) was calculated. In 1,721 participants, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (cm^2) were assessed using abdominal MR imaging. Hand OA was defined according to the ACR criteria.
Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the association of fat percentage, FM, WHR, VAT and SAT with hand OA using logistic regression analyses per standard deviation, stratified by sex and adjusted for age.

Results
Hand OA was present in 8% of men and 20% of women. Fat percentage was associated with hand OA in men (OR 1.34 (95% CI 1.11 to 1.61)) and women (OR 1.26 (1.05 to 1.51)), as was FM. WHR was associated with hand OA in men (OR 1.45 (1.13 to 1.85)), and to a lesser extent in women (OR 1.17 (1.00 to 1.36)). Subgroup analysis revealed that VAT was associated with hand OA in men (OR 1.33 (1.01 to 1.75)). This association increased after additional adjustment for FM (OR 1.51 (1.13 to 2.03)).

Conclusion
Fat percentage, FM and WHR were associated with hand OA. VAT was associated with hand OA in men, suggesting involvement of visceral fat in hand OA.

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder. Although the pathogenesis of OA remains largely unknown, several risk factors are known to contribute to disease development. One of the most prominent risk factors is overweight or obesity, usually defined by a body mass index (BMI) of 25 to 30 or ≥30 kg/m^2, respectively.[1] Obesity acts as a risk factor of both weight-bearing and non-weight-bearing joints, suggesting that obesity-associated systemic factors could play an important role in OA.[2,3] The relative contribution of systemic factors and excessive biomechanical stress in the association between obesity and OA remains to be elucidated and could be different for different subtypes of OA, such as hand OA versus knee OA.

Although the systemic effects of obesity are most probably dependent on the amount and distribution of adipose tissue, most studies on OA performed until now used BMI as marker for obesity. However, since BMI is defined based only on height and weight, it provides little information about body composition and the amount and distribution of adipose tissue. More insight into the relation between adiposity and OA can be obtained when alternative measures of body composition are investigated, such as the fat percentage, fat mass (FM) and waist-to-hip ratio (WHR). Previous research assessing these body composition measures mostly studied knee OA and showed inconclusive results regarding FM,[4-9] whereas WHR was not associated with OA.[4,7,10] Only a few studies focused on OA in non-weight-bearing joints like the hands, showing no association with fat percentage and waist circumference and conflicting results regarding the WHR.[8,11-13]

Adipose tissue is a source of several cytokines that could influence whole-body metabolism. Secretion of these bioactive mediators depends on the type of adipose tissue; they are secreted more actively by visceral fat than by subcutaneous fat.[14] In addition, visceral fat has been shown to be associated more strongly with obesity-related co-morbidities, such as diabetes mellitus and the metabolic syndrome, and with markers of inflammation as compared with subcutaneous fat.[15,16] Cytokines have the potential to affect joint tissues,[17-19] and therefore visceral fat could also be involved in the pathogenesis of OA. No research has so far been performed regarding different body fat depots in relation to OA. The aim of the present study was to gain more insight into the mechanisms underlying the association of adiposity and OA. To this end, we investigated the association of adipose tissue and its abdominal distribution with the presence of OA in non-weight-bearing joints, the hands.

METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in lean, overweight and obese individuals aged between 45 and 65 years. The present study is a cross-sectional analysis of the baseline measurements of the 5,313 participants included in the NEO study between September 2008 and January 2012. Detailed information about the study design and data collection has been described previously.[20] Men and women with self-reported BMI ≥27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate in the NEO study. In addition, in one municipality (Leiderdorp) all inhabitants aged 45 to 65 years were invited, irrespective of their BMI.

All participants completed questionnaires on demographic and clinical data and visited the NEO study center for several baseline measurements. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Body composition measures

Measured body weight (kg) and height (cm) were used to calculate the BMI (kg/m^2). Waist and hip circumference (cm) were used to calculate the WHR. The percentage of body fat and amount of FM (kg) were measured by bioelectrical impedance analysis (BIA) using the Tanita foot-to-foot BIA system TBF-300A Body Composition Analyzer (Tanita Corporation of America, Inc, Arlington Heights, IL, USA).[21] To test the reliability, repeated measurements were performed after approximately 3 months in a random sample of 72 participants; the calculated intraclass correlation coefficient was 0.98.

Abdominal adipose tissue

A random sample (about 30%) of the study participants without contraindications (metallic devices, claustrophobia and a body circumference ≥170 cm) underwent magnetic resonance imaging (MRI) of the abdomen. Abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (cm^2) were measured by a turbo spin echo imaging protocol, performed on a 1.5 T system (Philips, Medical Systems, Best, the Netherlands): echo time 11 milliseconds; repetition time, 168 milliseconds; flip angle, 90°; slice thickness, 10 mm. The total acquisition time, including the initial survey sequence, was 3 minutes. At the level of the fifth lumbar vertebra, three transverse images with a slice thickness of 10 mm were obtained during a breath-hold. The MASS software package (Medis, Leiden, the Netherlands) was used to quantify VAT and SAT, allowing a semi-automated detection of the VAT and SAT area. The mean values of VAT and SAT (cm^2) were calculated.

Osteoarthritis definition

Self-reported pain was measured using standardized questionnaires. Physical examination of the hand joints was performed by trained research nurses, using a standardized scoring form. Bony and soft swellings of the distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), carpometacarpal (CMC) and wrist joints were scored, as well as deformities of the DIP, PIP, first MCP, CMC and wrist joints. OA was defined according to the criteria of the American College of Rheumatology as pain or stiffness on most days of the prior month in addition to three of the following criteria: bony swelling of ≥2 of the 10 selected joints (bilateral DIP II and III, PIP II and III, and first CMC joints), bony swelling of ≥2 DIP joints, <3 swollen MCP joints, and deformity of ≥1 of the 10 selected joints.[22]

Statistical analysis

Data were analyzed using SPSS version 20 (SPPS, Chicago, IL, USA) and STATA version 12 (StataCorp LP, College Station, TX, USA).

In the NEO study there is an oversampling of persons with BMI ≥27 kg/m^2. To correctly represent associations in the general population,[23] adjustments were made for the oversampling of individuals with BMI ≥27 kg/m^2. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality,[24] whose

BMI distribution was similar to the BMI distribution in the general Dutch population.[25] Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.

Pearson correlation coefficients between all body composition measures were calculated. A correlation below 0.4 was considered weak, between 0.4 and 0.7 moderate, and above 0.7 strong. Logistic regression analyses were used to calculate cross-sectional associations of all body compositions measures with hand OA, and were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All continuous variables were standardized by dividing individual values by the standard deviation to be able to compare the ORs, because in this way all ORs describe the effect on the odds of OA of an increase of one standard deviation of the corresponding variable. All analyses have been stratified by sex and adjusted for age. To minimize variation in FM due to differences in body height, additional adjustment for height was performed in the analysis on FM. Furthermore, additional adjustment for FM has been performed in the analyses on visceral and subcutaneous fat in relation to hand OA.

RESULTS

Population characteristics

After exclusion of subjects with missing data of the BIA (n = 25) or physical examination (n = 4), data from 5,284 subjects were analyzed. Table 1 presents the baseline characteristics. Median age was 56 years, and 53% were women. Women had a lower median body weight and WHR but a higher fat percentage and FM than men. Hand OA was present in 8% of men and 20% of women.

Abdominal fat was measured in a random subset of 1,721 participants (46% women). Except for a clinically nonrelevant difference in WHR in men (0.980 vs. 0.982), this subgroup did not differ from the total group (data not shown).

The median amount of VAT was lower than the median amount of SAT, and this difference was most apparent in women (Table 1).

Table 1. Baseline characteristics of the total Netherlands Epidemiology of Obesity study population and stratified by sex

	Total population (n= 5,284)	**Men (n= 2,490)**	**Women (n= 2,794)**
Age (years)	56 (51 to 61)	57 (51 to 61)	56 (51 to 61)
BMI (kg/m^2)	29.9 (27.8 to 32.8)	29.6 (27.9 to 32.0))	30.3 (27.8 to 33.5)
Weight (kg)	90.6 (80.6 to 100.8)	96.6 (89.2 to 106.0)	84.0 (75.8 to 94.2)
Fat percentage (%)	37.5 (29.0 to 43.7)	29.0 (25.9 to 32.7)	43.3 (39.9 to 46.4)
Fat mass (kg)	32.4 (26.1 to 40.0)	28.1 (23.6 to 34.0)	36.4 (30.4 to 43.1)
WHR	0.93 (0.87 to 0.99)	0.98 (0.94 to 1.03)	0.88 (0.84 to 0.92)
VAT (cm^2)*	122.1 (85.4 to 166.3)	142.1 (108.1 to 185.5)	97.2 (67.8 to 138.2)
SAT (cm^2)*	308.3 (242.3 to 388.4)	262.4 (210.3 to 324.2)	359.4 (298.7 to 434.0)
Hand osteoarthritis	746 (14.1)	188 (7.6)	558 (20.0)

Numbers represent medians (interquartile ranges) or number (percentage).

*n = 923 men, n = 798 women.

BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.

Correlations between body composition measures

First, we calculated Pearson's correlation coefficients between all measures of body composition (Table 2). Besides body weight, BMI was strongly correlated with fat percentage and FM in both men and women. BMI, body weight, fat percentage an FM were strongly correlated with SAT in both sexes. The correlations of these body composition measures with VAT were somewhat lower, and were slightly stronger in women as compared with men. Moreover, WHR correlated more strongly with VAT than with SAT in both sexes. The WHR showed a stronger correlation with all measurements of fat (FM, SAT and VAT) in men as compared with women.

The differences between men and women underscored the need for stratified analyses in the sexes.

Table 2. Correlations between body composition measures in 2,490 men (right upper corner) and 2,794 women (left lower corner) of the Netherlands Epidemiology of Obesity study

	BMI (kg/m^2)	**Weight (kg)**	**Fat percentage (%)**	**Fat mass (kg)**	**WHR**	**VAT* (cm^2)**	**SAT * (cm^2)**
BMI (kg/m^2)		0.864	0.859	0.920	0.608	0.667	0.802
Weight (kg)	0.919		0.727	0.893	0.480	0.564	0.787
Fat percentage (%)	0.871	0.890		0.949	0.656	0.696	0.753
Fat mass (kg)	0.927	0.981	0.951		0.612	0.679	0.825
WHR	0.490	0.462	0.526	0.493		0.683	0.512
VAT* (cm^2)	0.738	0.691	0.720	0.727	0.595		0.479
SAT* (cm^2)	0.873	0.849	0.846	0.878	0.448	0.623	

All correlations were statistically significant. Numbers represent Pearson correlation coefficients.

*n = 923 men, n = 798 women.

BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.

Associations of body composition measures with hand osteoarthritis

We next investigated the associations of all body composition measures with hand OA (Table 3).

The fat percentage was associated with hand OA in both men (OR 1.34 (95% CI 1.11 to 1.61)) and women (OR 1.26 (1.05 to 1.51)), meaning that one standard deviation increase in fat percentage (men 6.22%, women 6.88%) is associated with a 34% higher risk of having hand OA in men and a 26% higher risk in women. FM was also associated with hand OA in both sexes (men: OR 1.24 (1.05 to 1.47); women: OR 1.22 (1.07 to 1.39)). Additional adjustment for height in the analysis on FM resulted in comparable ORs (men: OR 1.29 (1.10 to 1.51); women: OR 1.25 (1.10 to 1.42)).

When focusing on the distribution of adipose tissue, we observed the WHR to be associated with hand OA in men (OR 1.45 (1.13 to 1.85)) and to a lesser extent in women (OR 1.17 (1.00 to 1.36)).

Table 3. Associations of body composition measures and hand osteoarthritis

	SD		Adjusted OR (95% CI)	
	Men	**Women**	**Men (n= 2,490)**	**Women (n= 2,794)**
Fat percentage (%)	6.22	6.88	1.34 (1.11 to 1.61)	1.26 (1.05 to 1.51)
Fat mass (kg)	9.39	10.76	1.24 (1.05 to 1.47)	1.22 (1.07 to 1.39)
WHR	0.07	0.07	1.45 (1.13 to 1.85)	1.17 (1.00 to 1.36)
BMI (kg/m^2)	4.01	5.19	1.29 (1.08 to 1.55)	1.25 (1.11 to 1.41)
Weight (kg)	14.49	14.73	1.15 (0.92 to 1.45)	1.20 (1.06 to 1.36)

All ORs express the increase in odds of osteoarthritis per standard deviation and are adjusted for age.

BMI, body mass index; CI, confidence interval; SD, standard deviation; OR, odds ratio; WHR, waist-to-hip ratio.

Abdominal adipose tissue

Since both the amount of adipose tissue and its distribution are of importance, we investigated the associations of VAT and SAT with hand OA in a subgroup who underwent MRI of the abdomen (Table 4). No association was observed between SAT and hand OA. VAT, on the other hand, showed a statistically significant association with hand OA in men (OR 1.33 (1.01 to 1.75)) but was not associated with hand OA in women.

Since VAT and SAT are associated with the total amount of body fat, we also assessed their association with hand OA independent of total body fat by additional adjustment for FM. As a result, the association of VAT with hand OA in men increased (OR 1.51 (1.13 to 2.03)). In women, again no association between VAT and hand OA was observed (OR 0.91 (0.69 to 1.20)).

Table 4. Associations of abdominal adipose tissue and hand osteoarthritis

	SD		Adjusted OR (95% CI)	
	Men	**Women**	**Men (n = 923)**	**Women (n = 798)**
VAT (cm^2)	61.3	50.0	1.33 (1.01 to 1.75)	1.10 (0.85 to 1.44)
SAT (cm^2)	91.7	117.6	1.05 (0.74 to 1.50)	1.22 (0.92 to 1.63)

All ORs express the increase in odds of osteoarthritis per standard deviation and are adjusted for age.

CI, confidence interval; SAT, subcutaneous adipose tissue; SD, standard deviation; OR, odds ratio; VAT, visceral adipose tissue.

DISCUSSION

In this study we aimed to gain insight into the association between adiposity and hand OA. Since both the fat percentage and FM were associated with hand OA in men and women, the amount of adipose tissue seems to be important. The association between WHR and hand OA indicates that the fat distribution is also of importance. When assessing the abdominal distribution of adipose tissue, VAT was shown to be associated with hand OA in men, suggesting involvement of visceral fat in hand OA.

To our knowledge, this study is the first to show an association between the amount of fat and its abdominal distribution with hand OA. Other studies showed associations between OA of the hands and obesity-related co-morbidities: Jonsson and colleagues demonstrated that hand OA and atherosclerosis were associated in older women; both carotid plaques and coronary calcifications showed a linear association with hand OA

severity.[26] Hoeven and colleagues confirmed this observation in a population aged 55 years and older; they showed an association of atherosclerosis and OA of the DIP and MCP joints in women, independent of cardiovascular risk factors.[27] Finally, Haara and colleagues showed that symmetrical DIP OA predicted mortality in women and that OA in any finger joint predicted cardiovascular mortality in men, suggesting an underlying common metabolic factor.[28]

A possible common underlying explanation could be an effect of adipose tissue, especially the visceral component. Visceral fat has been shown previously to be associated with coronary calcifications and carotid atherosclerosis.[29,30] The amount of visceral fat has also been associated with other obesity-related co-morbidities such as diabetes mellitus and metabolic risk factors such as elevated blood pressure, impaired fasting glucose and elevated triglycerides.[15,31,32] Our study shows that visceral fat is also associated with hand OA, implying that adipose tissue and its products can be involved in hand OA.

Visceral fat has been suggested to secrete bioactive cytokines, acting as a unique pathogenic fat depot.[14] The involvement of visceral fat in the pathogenesis of hand OA might thus be explained by its secretion of cytokines, which have been suggested to act locally in joint tissues.[17] Leptin, known especially for its proinflammatory effect, has been shown to affect human cartilage.[17-19] Adiponectin appears to counteract the effect of leptin by anti-inflammatory actions.[17] In vitro studies suggest that adiponectin affects chondrocyte function and modulates cartilage destruction, which might indicate a protective role for adiponectin in OA.[33] This suggestion has been confirmed in an observational follow-up study in patients with hand OA, showing that a higher level of adiponectin is associated with a lower risk for hand OA progression.[34] Knowledge on other adipose-derived cytokines in relation to OA is scarce.

Differences between both sexes regarding body compositions are well known and were also observed in this study. Women had a lower WHR, more subcutaneous fat and less visceral fat than men. The WHR was more strongly correlated to all measurements of fat in men than in women. This is in accordance with previous studies describing sex differences in body composition measures.[35,36] Because of these differences between men and women regarding most body composition measures, all analyses were stratified by sex.

The greater amount of overall fat and lower susceptibility to accumulate visceral fat in women as compared with men might explain the lower ORs of WHR and VAT for hand OA in women. A similar gender difference regarding VAT has been described previously in a study on cardiometabolic risk; VAT was observed to be of greater relevance in men, whereas total FM was of most importance in women.[37] In addition, VAT was observed to be associated with insulin resistance and inflammatory markers primarily in men.[38,39] Another explanation for the lower ORs of WHR and VAT in women might be the importance of unmeasured or unknown risk factors such as hormonal status or genetic effects, overshadowing a possible relatively minor effect of visceral fat.

There are some potential limitations of this study. Hand OA could only be diagnosed based on clinical criteria since no imaging data of the hands were available. However, the ACR clinical criteria are well validated and have a high sensitivity and specificity in diagnosing hand OA.[22]

Furthermore, the fat percentage and FM were measured using a foot-to-foot BIA system, and not with a hand-to-foot BIA. Although it has been suggested that foot-to-foot BIA might overestimate the amount of FM,[40] a study comparing body fat percentages pro-

vided by foot-to-foot BIA with those obtained by hand-to-foot BIA observed a strong correlation between the two methods (r = 0.84).[21] In a study comparing resistance measurements obtained from foot-to-foot BIA with those from underwater weighing and dual-energy X-ray absorptiometry, a strong correlation (r = 0.89) with both methods was also reported.[41]

We investigated all body composition measures in relation to hand OA per standard deviation to be able to compare the different ORs observed in this study. However, whereas the fat percentage and FM involve whole body fat, the amounts of VAT and SAT apply to a small region of the abdominal fat depot. The ORs for fat percentage and FM therefore cannot be compared directly with the ORs for VAT and SAT.

The amount of VAT and SAT were measured in a random 30% of the total study population. Although individuals with a body circumference of 170 cm or higher were not eligible for MRI, body composition measures of the MRI subgroup were not significantly different as compared with the total study population. However, since individuals with extremely high body circumference could not be assessed, the described association between VAT and hand OA might be underestimated.

CONCLUSION

This study showed that both the amount of adipose tissue and its distribution are of importance in hand OA. Assessment of abdominal distribution of adipose tissue showed an association between VAT and hand OA in men, suggesting involvement of visceral fat in hand OA. More research is necessary to gain more insight into the role of adipose tissue in OA, aiming at abdominal fat distribution and secretion of cytokines in relation to OA. Longitudinal studies could help to better understand how visceral fat plays a role in OA development. Furthermore, research towards treatment aiming at the inflammatory effect of adipose tissue may lead to potential new treatment targets in OA.

REFERENCES

1. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
2. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van OG et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-5.
3. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008;16:232-40.
4. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis 2007;66:1244-8.
5. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992;116:535-9.
6. Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998;25:2181-6.
7. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. Osteoarthritis Cartilage 2008;16:367-72.
8. Hochberg MC, Lethbridge-Cejku M, Plato CC, Wigley FM, Tobin JD. Factors associated with osteoarthritis of the hand in males: data from the Baltimore Longitudinal Study of Aging. Am J Epidemiol 1991;134:1121-7.
9. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. Obesity (Silver Spring) 2006;14:1274-81.
10. Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. Osteoarthritis Cartilage 2011;19:37-43.
11. Davis MA, Neuhaus JM, Ettinger WH, Mueller WH. Body fat distribution and osteoarthritis. Am J Epidemiol 1990;132:701-7.
12. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Plato CC, Tobin JD. Obesity and osteoarthritis of the hands in women. Osteoarthritis Cartilage 1993;1:129-35.
13. Kalichman L and Kobyliansky E. Age, body composition, and reproductive indices as predictors of radiographic hand osteoarthritis in Chuvashian women. Scand J Rheumatol 2007;36:53-7.
14. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev 2006;2:367-73.
15. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the

Framingham Heart Study. Circulation 2007;116:39-48.
16. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234-41.
17. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-5.
18. Tilg H and Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-83.
19. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;48:3118-29.
20. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
21. Ritchie JD, Miller CK, Smiciklas-Wright H. Tanita foot-to-foot bioelectrical impedance analysis system validated in older adults. J Am Diet Assoc 2005;105:1617-9.
22. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-10.
23. Korn EL and Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health 1991;81:1166-73.
24. Lumley T. Analysis of complex survey samples. 2004. http://www.jstatsoft.org/ v09/i08/paper
25. Ministerie van VWS. Hoeveel mensen hebben overgewicht? 2013. http://www.rivm.nl/ nldemaat
26. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Ingvarsson T et al. Hand osteoarthritis in older women is associated with carotid and coronary atherosclerosis: the AGES Reykjavik study. Ann Rheum Dis 2009;68:1696-700.
27. Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco O et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis 2012;72:646-51.
28. Haara MM, Manninen P, Kroger H, Arokoski JP, Karkkainen A, Knekt P et al. Osteoarthritis of finger joints in Finns aged 30 or over: prevalence, determinants, and association with mortality. Ann Rheum Dis 2003;62:151-8.
29. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke 2007;38:2422-9.
30. Ditomasso D, Carnethon MR, Wright CM, Allison MA. The associations between visceral fat and calcified atherosclerosis are stronger in women than men. Atherosclerosis 2010;208:531-6.
31. Indulekha K, Anjana RM, Surendar J, Mohan V. Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). Clin Biochem 2011;44:281-7.

32. Hanley AJ, Wagenknecht LE, Norris JM, Bryer-Ash M, Chen YI, Anderson AM et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. Diabetologia 2009;52:2079-86.
33. Chen TH, Chen L, Hsieh MS, Chang CP, Chou DT, Tsai SH. Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta 2006;1762:711-8.
34. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 2011;70:1282-4.
35. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity (Silver Spring) 2011;19:402-8.
36. Carroll JF, Chiapa AL, Rodriquez M, Phelps DR, Cardarelli KM, Vishwanatha JK et al. Visceral fat, waist circumference, and BMI: impact of race/ethnicity. Obesity (Silver Spring) 2008;16:600-7.
37. Onat A, Ugur M, Can G, Yuksel H, Hergenc G. Visceral adipose tissue and body fat mass: predictive values for and role of gender in cardiometabolic risk among Turks. Nutrition 2010;26:382-9.
38. Onat A, Ayhan E, Hergenc G, Can G, Barlan MM. Smoking inhibits visceral fat accumulation in Turkish women: relation of visceral fat and body fat mass to atherogenic dyslipidemia, inflammatory markers, insulin resistance, and blood pressure. Metabolism 2009;58:963-70.
39. Onat A and Can G. Enhanced Proinflammatory State and Autoimmune Activation: a Breakthrough to Understanding Chronic Diseases. Curr Pharm Des 2013. Epub ahead of print.
40. Gagnon C, Menard J, Bourbonnais A, Ardilouze JL, Baillargeon JP, Carpentier AC et al. Comparison of foot-to-foot and hand-to-foot bioelectrical impedance methods in a population with a wide range of body mass indices. Metab Syndr Relat Disord 2010;8:437-41.
41. Nunez C, Gallagher D, Visser M, Pi-Sunyer FX, Wang Z, Heymsfield SB. Bioimpedance analysis: evaluation of leg-to-leg system based on pressure contact footpad electrodes. Med Sci Sports Exerc 1997;29:524-31.

CHAPTER 4

The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study

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ABSTRACT

Objective
To investigate if the amount of fat mass (FM) or skeletal muscle mass (SMM) is more strongly associated with knee osteoarthritis (OA), in both men and women.

Methods
The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort aged 45 to 65 years, including 5,313 participants (53% female, median body mass index (BMI) 29.9 kg/m^2). FM (kg), fat percentage, SMM (kg) and skeletal muscle (SM) percentage were estimated using bioelectrical impedance analysis (BIA). Clinical OA was defined following the ACR criteria. Structural OA was defined based on magnetic resonance imaging (MRI) in 1,142 participants. Logistic regression analyses were used to examine the associations of all body composition measures with clinical and structural knee OA per standard deviation (SD), stratified by sex and adjusted for age and height.

Results
Clinical or structural OA was present in 25% and 14% of women and 12% and 13% of men, respectively. FM and fat percentage were positively associated with clinical knee OA in men and women. SMM was positively associated, while the SM percentage was negatively associated with clinical OA in both men and women. The FM/SMM ratio was positively associated with clinical OA. All determinants showed even stronger ORs for structural knee OA. In men, SMM was more strongly associated with knee OA as compared to FM whereas in women, FM was most strongly associated.

Conclusion
Especially a high FM/SMM ratio seems to be unfavorable in knee OA. In men, SMM is most strongly associated with knee OA whereas in women FM seems to be of most importance.

INTRODUCTION

Knee osteoarthritis (OA) is a common musculoskeletal disorder and a major cause of disability, especially in the elderly.[1] Overweight or obesity, usually characterized by body mass index (BMI), is an important risk factor for knee OA.[2] However, BMI does not distinguish between fat mass (FM) and lean body mass. Therefore it remains unclear whether FM or skeletal muscle mass (SMM) is more important in knee OA.

In knee OA biomechanical pathways are thought to play an important role; excessive mechanical stress due to either a decrease in the load-bearing area on the joint surface or an increase in loading leads to a failed repair of damaged joint tissue.[3] Earlier studies showed that body weight is associated with knee OA and that especially persons with a high FM are at risk for knee OA.[4,5] However, inconsistent results have been described regarding FM in relation to knee OA. Where some studies reported a negative association between FM or fat percentage and knee OA or knee cartilage as well,[6-8] other studies did not find an association.[9,10]

Besides FM the body consists of lean body mass, consisting partially of SMM. SMM is important in the distribution of mechanical loading across the joint surface. Decreased muscle forces can alter the mechanical loading and ultimately result in degeneration of the joint. For example, quadriceps weakness has been shown to be associated with knee OA.[11,12] Conroy et al. confirmed this negative association between quadriceps weakness and OA, however they reported a positive association between SMM and knee OA.[7] This is remarkably since muscle mass and strength have been shown to be highly correlated.[13] Other studies on the association of SMM and knee OA show conflicting results; some observed a negative association,[6,12] where others reported a positive association.[5]

The present study investigates whether the amount of FM or SMM is more strongly associated with knee OA in both men and women. To this end we used two OA definitions: the partly subjective clinical criteria of the American College of Rheumatology (depending on the presence of pain) as well as an objective measure of structural OA, assessed by magnetic resonance imaging (MRI).[14,15] We examined the associations of the relative amounts of FM and SMM with both clinical and structural knee OA.

PATIENTS AND METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in lean, overweight and obese individuals aged between 45 and 65 years. The present study is a cross-sectional analysis of the baseline measurements of the 5,313 participants included in the NEO study between September 2008 and January 2012. Detailed information about the study design and data collection has been described previously.[16] Men and women with a self-reported BMI ≥27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate in the NEO study. In addition, in one municipality (Leiderdorp), all inhabitants aged 45 to 65 years were invited, irrespective of their BMI (n = 874).

All participants completed questionnaires on demographic and clinical data and visited the NEO study center for several baseline measurements. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Clinical assessment and clinical OA diagnosis

Self-reported pain and morning stiffness were measured using standardized questionnaires. Physical examination of both knee joints was performed by trained research nurses, using a standardized scoring form. Bony enlargement, tenderness of the bony margins of the joint, palpable warmth, crepitus and movement restriction were scored. Clinical OA was defined according to the clinical criteria of the American College of Rheumatology.[14]

Body composition measures

Measured body weight (kg) and height (cm) were used to calculate the BMI (kg/m^2). The percentage of body fat and amount of FM (kg) were measured by bioelectrical impedance analysis (BIA) using the Tanita foot-to-foot (FF) BIA system TBF-300A Body Composition Analyzer.[17] The percentage of skeletal muscle (SM) and amount of SMM (kg) were calculated based on height, gender, age and resistance measured by the BIA.[18] To test the reliability, repeated measurements were performed in a random sample of the participants (n = 72); the calculated intraclass correlation coefficient was 0.98.
Since FM and SMM are positively correlated, we also calculated the FM/SMM ratio.

MRI

A random sample (about 20%) of the study participants without contraindications (metallic devices, claustrophobia, body circumference ≥170 cm) underwent MRI of the right knee. Imaging was performed using a dedicated knee coil in a 1.5T system (Philips, Medical Systems, Best, the Netherlands). A standardized scanning protocol was used.
The following parameters were identical for the TSE images; a 150-160 mm field of view and a 304 x 512 matrix. Sequences performed were:
(1) coronal proton density (PD) (repetition time (TR)/echo time (TE) 2335/35 ms); (2) fat-suppressed PD TSE images (TR/TE 2334/35 ms; 3 mm slice thickness; 0.6 mm interslice gap); (3) sagittal PD TSE images (TR/TE 2338/35; echo train length 6; 3.5 mm slice thickness; 0.7 mm interslice gap); (4) sagittal frequency selective fat-suppressed T1-weighted 3D gradient echo (GE) sequence (TR/TE 11/5.5; 25° flip angle; 150 mm field of view, 272 x 512 matrix, 2 mm slice thickness with a 1 mm overlap between images; no gap); (5) axial fat-suppressed PD (TSE) images (TR/TE 3225/15; echo train length 6, 4 mm slice thickness; 0.8 mm interslice gap). Total acquisition time, including the initial survey sequence, was 30 min.

MRI scoring and structural knee OA diagnosis

All MR images were analyzed using the validated semi-quantitative knee OA scoring system (KOSS),[19] by a trained reader (AWV), blinded to clinical data. The presence or absence of osteophytes, cartilage loss, subchondral bone marrow lesions (BMLs) and cysts were scored at four anatomic locations: the medial and lateral femoral condyle and medial and lateral tibial plateau.

Osteophytes were defined as focal bony excrescences extending from a cortical surface and measured from base to tip; ≥3 mm was considered a definite osteophyte.
Based on their depth, cartilage defects were classified as full- or partial thickness.
BMLs were defined as ill-defined areas of increased signal intensity in the subchondral bone extending away from the articular surface; cysts as well-defined foci of high signal intensity in the subchondral bone. Both were required not to be associated with meniscal or ligamentous attachments.
The medial and lateral menisci were reviewed for the presence of subluxation, maceration and degenarative tears. Subluxation was defined as protrusion over the egde of the tibial plateau, maceration as an intrameniscal focus of intermediate signal intensity and tears as regions of intermediate signal intensity within the meniscus, communicating with the surface or inner margin on more than one section.
A random ten percent of the MR images (n = 120) were scored twice to test the reproducibility; the calculated intraclass correlation coefficient was 0.61 to 0.97 for the different features (meniscal maceration 0.61, meniscal tear 0.87, meniscal subluxation 0.93, cyst 0.64, BML 0.93, cartilage loss 0.90, osteophyte 0.97).
Structural OA was defined based on the MRI features following the criteria recently suggested by Hunter et al.[15] Structural OA was defined on the presence of a definite osteophyte and full thickness cartilage loss, or one of these features in addition to at least two of the following features: (1) subchondral BML, (2) cyst, (3) meniscal subluxation, maceration or degenerative tear, or (4) partial thickness cartilage loss. In the recommendation by Hunter et al. bone attrition was described as a fifth feature, since this was not scored in the KOSS it was left out of the definition.

Statistical analysis
Data were analyzed using SPSS version 20 and STATA version 12. In the NEO study there is an oversampling of persons with a BMI of 27 kg/m^2 or higher. To correctly represent associations in the general population,[20] adjustments for the oversampling of individuals with a BMI ≥27 kg/m^2 were made. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality,[21] whose BMI distribution was similar to the BMI distribution in the general Dutch population.[22] Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.
Body composition measures were compared between men and women using a t-test, further analyses were stratified by sex because of the observed significant differences for all measures of body composition. Logistic regression analyses were used to calculate cross-sectional associations of BMI and body compositions with clinical and structural knee OA, and were expressed as odds ratios (OR) with 95% confidence intervals (CI). Furthermore, multivariate logistic regression analysis including both FM and SMM was performed to investigate their independent association with knee OA. All continuous variables were standardized by dividing individual values by the standard deviation (SD) to be able to compare ORs, because in this way all ORs describe the effect on the odds of OA of an increase of one SD of the corresponding variable. All analyses have been stratified by sex and adjusted for age and height. Analyses on SMM and SM percentage in relation to OA were additionally adjusted for the total level of physical activity during 1 week (assessed by the validated Short Questionnaire to Assess Health-enhancing physical activity (SQUASH)[23]).

RESULTS

Population characteristics

After exclusion of individuals with missing data of the BIA (n = 25) or physical examination (n = 4) data from 5,284 participants were analyzed. Table 1 shows the baseline characteristics of the total population and stratified by sex. Women had a lower median weight, SMM and SM percentage, but a higher FM, fat percentage and FM/SMM ratio than men (P < 0.001). Clinical OA was present in 25% of women and 12% of men.

MRI of the right knee was performed in a subset of 1,142 participants. Except for a higher median weight in women (86.0 kg (IQR 77.6 to 95.4) and SMM in women (23.3 kg (21.3 to 25.6)) and men (34.3 kg (31.7 to 36.8)), this subgroup did not differ from the total group as well as from the participants without a knee MRI in age, sex or body compositions (data not shown).

Structural OA was present in 14% of women and 13% of men. To compare this prevalence to clinical knee OA, we assessed the presence of clinical OA of only the right knee in the MRI subgroup, showing a prevalence of 18% in women and 10% in men (total group 14%). Of the individuals with structural knee OA, 39% of women and 31% of men also was defined as having clinical OA. Of the individuals with clinical OA, 31% of women and 40% of men also had structural OA.

Table 1. Baseline characteristics of the total NEO study population and stratified by sex

	Total population, n = 5,284	**Men, n = 2,490**	**Women, n = 2,794**
Age (year)	56 (51-61)	57 (51-61)	56 (51-61)
BMI (kg/m^2)	29.9 (27.8-32.8)	29.6 (27.9-32.0))	30.3 (27.8-33.5)
Height (m)	1.73 (1.66-1.80)	1.80 (1.76-1.85)	1.67 (1.62-1.71)
Weight (kg)	90.6 (80.6-100.8)	96.6 (89.2-106.0)	84.0 (75.8-94.2)
FM (kg)	32.4 (26.1-40.0)	28.1 (23.6-34.0)	36.4 (30.4-43.1)
Fat percentage (%)	37.5 (29.0-43.7)	29.0 (25.9-32.7)	43.3 (39.9-46.4)
SMM (kg)	27.7 (22.6-33.5)	33.6 (31.2-36.4)	22.8 (20.8-25.2)
SM (%)	30.7 (26.9-34.9)	34.8 (32.5-37.1)	27.2 (25.1-29.6)
FM/SMM ratio	1.22 (0.83-1.63)	0.83 (0.70-1.00)	1.59 (1.35-1.84)
Clinical knee OA, no. (%)	991 (18.8)	306 (12.3)	685 (24.5)
Structural knee OA, no. (%)*	156 (13.7)	65 (12.8)	91 (14.4)

Numbers represent medians (interquartile ranges) unless stated otherwise.

*n = 1,142 (508 men, 634 women)

BMI, body mass index; FM, fat mass; no., number; OA, osteoarthritis; SM, skeletal muscle; SMM, skeletal muscle mass.

Association of body composition measures with clinical knee OA (n = 5284)

Next, we investigated the associations of body composition measures with clinical knee OA in men and women, adjusted for age and height (Table 2). FM and fat percentage were positively associated with knee OA in both men and women. For example, the OR of 1.34 in men for FM mean that one SD increase in FM (9.39 kg) is associated with a 34% higher odds of having knee OA. SMM was positively associated with knee OA as well. On the contrary, SM percentage was negatively associated with knee OA, this was statistically significant in women only. Additional adjustment for the level of physical activity did not

change the results (data not shown). Finally, the FM/SMM ratio was positively associated with knee OA in both men and women.

Table 2. Associations of body composition measures with clinical knee OA

	SD		OR (95% CI)	
	Men	**Women**	**Men, n = 2,490**	**Women, n = 2,794**
FM (kg)	9.39	10.76	1.34 (1.12-1.59)	1.44 (1.27-1.63)
Fat percentage (%)	6.22	6.88	1.33 (1.08-1.63)	1.47 (1.21-1.77)
SMM (kg)	4.16	3.19	1.28 (1.02-1.60)	1.36 (1.19-1.56)
SM percentage (%)	4.50	4.40	0.80 (0.60-1.06)	0.74 (0.61-0.91)
FM/SMM ratio	0.26	0.40	1.30 (1.09-1.55)	1.39 (1.20-1.61)
BMI (kg/m^2)	4.01	5.19	1.38 (1.14-1.68)	1.43 (1.28-1.61)
Weight (kg)	14.49	14.73	1.42 (1.14-1.78)	1.46 (1.30-1.64)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.
BMI, body mass index; CI, confidence interval; FM, fat mass; no., number; OR, odds ratio; SD, standard deviation; SM, skeletal muscle; SMM, skeletal muscle mass.

Association of body composition measures with structural knee OA (n = 1142)

In addition to the analyses on clinical knee OA, we investigated the associations of measures of body compositions with structural knee OA (Table 3). FM, fat percentage, SMM and SM percentage were even stronger associated with structural OA than with clinical OA in both men and women. However, in structural OA the association of SM percentage was statistically significant in women only. Again, additional adjustment for physical activity did not alter the observed associations of SMM and SM percentage with OA (data not shown).

The FM/SMM ratio was positively associated with structural knee OA. When comparing the ORs of the different body composition measures for knee OA as shown in Table 3, in men the association of SMM (OR 1.94 (95% CI 1.18 to 3.17)) was somewhat stronger than the association of FM (OR 1.50 (1.09 to 2.07)). In women this is different; the association of FM (OR 2.20 (1.41 to 3.43)) was stronger than the association of SMM (OR 1.86 (1.31 to 2.63)).

Table 3. Associations of body composition measures with structural knee OA

	SD		OR (95% CI)	
	Men	**Women**	**Men, n = 508**	**Women, n = 634**
FM (kg)	9.39	10.76	1.50 (1.09-2.07)	2.20 (1.41-3.43)
Fat percentage (%)	6.22	6.88	1.42 (1.01-1.99)	2.36 (1.23-4.51)
SMM (kg)	4.16	3.19	1.94 (1.18-3.17)	1.86 (1.31-2.63)
SM percentage (%)	4.50	4.40	0.74 (0.50-1.09)	0.51 (0.29-0.88)
FM/SMM ratio	0.26	0.40	1.35 (0.99-1.85)	1.92 (1.23-3.00)
BMI (kg/m^2)	4.01	5.19	1.67 (1.15-2.42)	2.17 (1.48-3.20)
Weight (kg)	14.49	14.73	1.77 (1.19-2.65)	2.31 (1.48-3.63)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.
BMI, body mass index; CI, confidence interval; FM, fat mass; no., number; OR, odds ratio; SD, standard deviation; SM, skeletal muscle; SMM, skeletal muscle mass.

Since FM and SMM are positively correlated, we assessed the associations of both parameters with structural knee OA independently of each other in a logistic regression model including both FM and SMM (Table 4). In men, the association between SMM and OA became stronger and was the most important predictor of knee OA (OR 1.67 (1.07 to 2.61)). In contrast, in women the association of FM with knee OA became stronger and was the most important predictor of knee OA (OR 1.93 (1.24 to 3.02)), independently of SMM.

Table 4. Logistic regression analyses including both FM and SMM with

	SD		OR (95% CI)	
	Men	**Women**	**Men, n = 508**	**Women, n = 634**
FM (kg)	9.39	10.76	1.35 (0.99-1.84)	1.87 (1.18-2.95)
SMM (kg)	4.16	3.19	1.67 (1.07-2.61)	1.32 (0.98-1.78)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.

CI, confidence interval; FM, fat mass; OR, odds ratio; SD, standard deviation; SMM, skeletal muscle mass.

DISCUSSION

In this study we aimed to investigate the relative importance of FM and SMM in knee OA. Both FM and fat percentage were positively associated with knee OA in men and women. The same was observed for SMM, whereas the SM percentage was negatively associated with knee OA. This suggests that especially a high FM relative to low SMM is unfavorable. The importance of the relative amounts of FM and SMM has been confirmed by the association between the FM/SMM ratio and knee OA.

In a subpopulation we had the opportunity to assess structural knee OA by MRI, providing a purely objective outcome measure. Of the individuals with clinical or structural OA, about one third did meet both definitions. The discrepancy underscores the difference between the definitions; whereas in clinical OA objective symptoms as pain are of importance, structural OA is based only on MRI features. All parameters associated with clinical OA were observed to be associated even stronger with structural OA, especially in women. In men, this stronger OR for SM percentage was not statistically significant, this might be due to the smaller number of participants included in the analyses on structural OA.

To date, most studies on knee OA examined predominantly or only women.[5-7,10,12,24,25] Since this study comprises a large group of men as well, we were able to investigate the underlying mechanisms mediating the association between BMI and knee OA in both sexes. In men, a higher OR was observed for SMM in relation to OA whereas in women, FM showed the highest OR for knee OA. This might suggest that the pathogenesis of knee OA in men might be more biomechanical whereas the etiology in women might be more inflammatory. Differences in the pathogenesis of knee OA between the sexes have been suggested before.[12,26,27] The risk factors contributing to the development of knee OA could be different. Trauma and occupational stresses for example, which hypothetically could be associated with SMM, have been reported to be related to knee OA more strongly in men than in women.[26] A larger amount of SMM could serve as a surrogate for individuals who have been more active and therefore more prone to injury, supporting the suggestion of a more biomechanical etiology of knee OA in men. Our results stress that in studies aiming to provide insight into the pathogenesis of knee OA, both sexes should be studied and stratified analyses should be performed.

In the present study, we observed a positive association between SMM and knee OA in both women and men, but when assessing the amount of SM as a percentage of the total body weight, we observed a negative association with knee OA.

The positive association between SMM and OA might be explained by differences in physical activity (and perhaps trauma) or joint loading that are associated with SMM. Although adjustment for physical activity did not alter the observed associations between SMM and OA, the questionnaire on physical activity did not assess physical activity during earlier years. However, the opposite associations of SMM and SM percentage with OA suggests that the positive relation of SMM with OA might be due to the increase of SMM in obese individuals as a consequence of increased loading (association of body weight with SMM: men $\beta = 0.19$, women $\beta = 0.15$ ($P < 0.001$)). However, this increase in SMM is not sufficient in relation to the total weight gain since FM increases more with increasing weight (association of body weight with FM: men $\beta = 0.59$, women $\beta = 0.72$ ($P < 0.001$)), resulting in a lower SM percentage in obese individuals.

An alternative explanation for the association of low SM percentage with knee OA is the metabolic syndrome, frequently occurring in individuals with greater adiposity. In obese individuals with the metabolic syndrome, insulin resistance and systemic inflammation might result in changes in striated muscle, causing loss of muscle mass and muscle weakness.[28] This is supported by a study in exercising and sedentary mice, showing that a high-fat diet induces knee OA in association with increased adiposity, glucose intolerance and systemic pro-inflammatory mediators. Exercise improved glucose tolerance and disrupted the co-expression of pro-inflammatory cytokines. Furthermore, exercise was associated with less severe OA.[29]

Since a lower FM/SMM ratio seems to be beneficial, interventions aiming at improvement of SMM in addition to weight reduction might be useful in the prevention and treatment of knee OA.

This is supported by studies on the effect of weight loss and exercise on physical performance, showing that a combination of both interventions provides greater improvement in physical performance than either intervention alone. In these individuals, more FM relative to fat free mass was lost.[30,31] In addition, a study on weight loss alone observed an increase in physical function but a loss of leg muscle tissue and knee muscle strengths, supporting the need to restore or increase muscle mass during weight loss.[32] Other studies on weight reduction showed that specifically a reduction in FM reduces the risk for knee OA and relieves clinical symptoms.[24,25] This greater reduction in FM relative to loss of fat free mass has been shown to be associated with greater gains in muscle quality as well.[33] As a proxy for SMM, an increase in fat free mass has been shown to be positively associated with tibial cartilage volume.[4]

There are some potential limitations of this study. We measured SMM and SM percentage by BIA and did not have information regarding muscle strength or specific lower limb SMM. However, muscle strength has been shown to be highly correlated with SMM.[13] Furthermore, since muscle parameters were measured using a FF-BIA, measurements depend predominantly on the lower limb amount of SMM.

It has been suggested that FF-BIA might overestimate the amount of FM,[34] however comparative studies reported a strong correlation of the FF-BIA to hand-to-foot BIA ($r = 0.84$), and underwater weighing and dual-energy X-ray absorptiometry ($r = 0.89$).[17,35]

Structural knee OA was defined following the definition suggested by Hunter et al.[15]

Since this definition has not been applied frequently and not been validated yet like the ACR criteria for clinical knee OA, further assessment of this definition is required. However, we observed all body composition measures to be associated similarly or even stronger with structural than clinical OA, suggesting that the structural OA definition discriminates knee OA very well.
Furthermore, since this is a cross-sectional study, causal relationships are difficult to identify.
This study suggests that the amount of SM relative to fat is of importance in knee OA and that the underlying mechanisms differ between men and women. More research is necessary to gain more insight into the precise underlying mechanisms. Future research should aim at clarifying the role of insulin resistance and inflammatory cytokines in the development of knee OA. Furthermore, research of interventions aiming at improvement of SMM in addition to weight reduction should be performed, as this may lead to potential new treatment targets in knee OA.

REFERENCES

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91-7.
2. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
3. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin North Am 2009;93:1-24, xv.
4. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis 2007;66:1244-8.
5. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. Osteoarthritis Cartilage 2008;16:367-72.
6. Berry PA, Wluka AE, Davies-Tuck ML, Wang Y, Strauss BJ, Dixon JB et al. The relationship between body composition and structural changes at the knee. Rheumatology (Oxford) 2010;49:2362-9.
7. Conroy MB, Kwoh CK, Krishnan E, Nevitt MC, Boudreau R, Carbone LD et al. Muscle strength, mass, and quality in older men and women with knee osteoarthritis. Arthritis Care Res (Hoboken) 2012;64:15-21.
8. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008;16:232-40.
9. Hochberg MC, Lethbridge-Cejku M, Plato CC, Wigley FM, Tobin JD. Factors associated with osteoarthritis of the hand in males: data from the Baltimore Longitudinal Study of Aging. Am J Epidemiol 1991;134:1121-7.
10. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. Obesity (Silver Spring) 2006;14:1274-81.
11. Brandt KD. Putting some muscle into osteoarthritis. Ann Intern Med 1997;127:154-6.
12. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM et al. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998;41:1951-9.
13. Frontera WR, Hughes VA, Lutz KJ, Evans WJ. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol 1991;71:644-50.
14. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
15. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A et al. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis Cartilage 2011;19:963-9.
16. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et

al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
17. Ritchie JD, Miller CK, Smiciklas-Wright H. Tanita foot-to-foot bioelectrical impedance analysis system validated in older adults. J Am Diet Assoc 2005;105:1617-9.
18. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol 2000;89:465-71.
19. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005;34:95-102.
20. Korn EL and Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health 1991;81:1166-73.
21. Lumley T. Analysis of complex survey samples. 2004. http://www.jstatsoft.org/ c09/i08/paper
22. Misisterie van VWS. Hoeveel mensen hebben overgewicht? 2013. http://www.rivm.nl/ nldemaat
23. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol 2003;56:1163-9.
24. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992;116:535-9.
25. Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998;25:2181-6.
26. KELLGREN JH and LAWRENCE JS. Osteo-arthrosis and disk degeneration in an urban population. Ann Rheum Dis 1958;17:388-97.
27. Davis MA, Ettinger WH, Neuhaus JM, Cho SA, Hauck WW. The association of knee injury and obesity with unilateral and bilateral osteoarthritis of the knee. Am J Epidemiol 1989;130:278-88.
28. Rojas-Rodriguez J, Escobar-Linares LE, Garcia-Carrasco M, Escarcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860-8.
29. Griffin TM, Huebner JL, Kraus VB, Yan Z, Guilak F. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum 2012;64:443-53.
30. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011;364:1218-29.
31. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004;50:1501-10.
32. Henriksen M, Christensen R, Danneskiold-Samsoe B, Bliddal H. Changes in lower extremity muscle mass and muscle strength after weight loss in

obese patients with knee osteoarthritis: a prospective cohort study. Arthritis Rheum 2012;64:438-42.
33. Wang X, Miller GD, Messier SP, Nicklas BJ. Knee strength maintained despite loss of lean body mass during weight loss in older obese adults with knee osteoarthritis. J Gerontol A Biol Sci Med Sci 2007;62:866-71.
34. Gagnon C, Menard J, Bourbonnais A, Ardilouze JL, Baillargeon JP, Carpentier AC et al. Comparison of foot-to-foot and hand-to-foot bioelectrical impedance methods in a population with a wide range of body mass indices. Metab Syndr Relat Disord 2010;8:437-41.
35. Nunez C, Gallagher D, Visser M, Pi-Sunyer FX, Wang Z, Heymsfield SB. Bioimpedance analysis: evaluation of leg-to-leg system based on pressure contact footpad electrodes. Med Sci Sports Exerc 1997;29:524-31.

CHAPTER 5

Bakers' cyst and tibiofemoral are more distinctive MRI features of symptomatic osteoarthritis than patellofemoral abnormalities

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Submitted.

ABSTRACT

Objective
To investigate which structural magnetic resonance (MR) abnormalities discriminate symptomatic knee osteoarthritis (OA), taking co-occurrence of abnormalities in all compartments into account.

Methods
The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort aged 45 to 65 years. In 1,285 participants (median age 56 years, 55% women, median body mass index (BMI) 30 kg/m^2) MR images of the right knee were obtained. Structural abnormalities (osteophytes, cartilage loss, bone marrow lesions (BMLs), subchondral cysts, meniscal abnormalities, effusion, Baker's cyst) at nine patellofemoral and tibiofemoral locations were scored following the knee OA scoring system. Symptomatic OA in the imaged knee was defined following the American College of Rheumatology criteria. Logistic ridge regression analyses were used to investigate which structural abnormalities discriminate best between individuals with and without symptomatic OA, crude and adjusted for age, sex and BMI.

Results
Symptomatic knee OA was present in 177 individuals. Structural MR abnormalities were highly frequent both in individuals with OA and in those without. Baker's cysts showed the highest adjusted regression coefficient (0.293) for presence of symptomatic OA, followed by osteophytes and BMLs in the medial tibiofemoral compartment (0.185-0.279), osteophytes in the medial trochlear facet (0.262), and effusion (0.197).

Conclusion
Baker's cysts discriminate best between individuals with and without symptomatic knee OA. Especially structural MR abnormalities in the medial side of the tibiofemoral joint and effusion add further in discriminating symptomatic OA. The presence of Baker's cysts may present as a target for treatment.

INTRODUCTION

The knee joint is composed of three compartments, the medial and lateral tibiofemoral compartment and the patellofemoral compartment. Research in knee osteoarthritis (OA) focused mainly on the tibiofemoral joint,[1] although OA can occur in all these compartments, isolated or concurrent.[2] OA in all compartments have been related to symptoms as pain and disability.[3,4] However the underlying relationships and attributions of osteoarthritic abnormalities in the different compartments to symptoms in OA are incompletely understood.

The knee joint comprises bone, cartilage, menisci and synovial tissue. Structural abnormalities have been observed in all these joint tissues, increasing with age.[5] These structural abnormalities are not specific for OA, since they have also been observed in persons without OA.[6-9] Clinical or symptomatic OA is classified based on presence of pain, clinical characteristics and abnormalities observed during physical examination,[10] but which structural abnormalities contribute to symptoms and whether and which structural abnormalities can discriminate symptomatic OA is not clear.

Previous studies on the association between structural abnormalities, such as bone marrow lesions (BMLs), synovitis or cartilage defects, and symptoms in OA showed conflicting results; where some studies found an association between these structural abnormalities and OA symptoms, other studies did not.[11-14] These discrepancies could be caused by co-occurrence of structural abnormalities in different tissues, but it may all have resulted from the analyses, which were univariate or limited multivariate analyses, not adjusting for all tissue abnormalities in all joint locations.

Therefore, this study investigates which specific structural abnormalities in all compartments of the knee joint as assessed by magnetic resonance (MR) imaging can best discriminate between individuals with and without symptomatic OA within the same knee, using a model that takes co-occurrence of all structural abnormalities into account.

PATIENTS AND METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study including 6,671 individuals aged 45 to 65 years, with an oversampling of persons with overweight or obesity. Detailed information about the study design and data collection has been described elsewhere.[15] In short, men and women between 45 and 65 years with a self-reported body mass index (BMI) of 27 kg/m^2 or higher living in the greater area of Leiden were eligible to participate. In addition, all inhabitants aged 45 to 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI.

All participants completed questionnaires on demographic and clinical data and visited the NEO study center for several baseline measurements, including measurement of weight (kg) and height (cm) that were used to calculate the BMI (kg/m^2), and an extensive physical examination. A random sample of 1,285 study participants without contraindications (metallic devices, claustrophobia, body circumference >170 cm) underwent MR imaging of the right knee. The present study is a cross-sectional analysis of baseline measurements of these 1,285 participants.

The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

MR imaging

MR imaging was performed using a dedicated knee coil in a 1.5T system (Philips, Medical Systems, Best, The Netherlands). Our standardized scanning protocol consisted of (1) Coronal proton density (PD) turbo spin echo (TSE), repetition time (TR)/echo time (TE) 2335/35 ms; echo train length (ETL) 6, (2) coronal frequency selective fat-suppressed PD TSE (TR/TE 2334/35 ms; ETL 6, 3 mm slice thickness); (3) sagittal PD TSE (TR/TE 2338/35; ETL 6; 3.5 mm slice thickness); (4) sagittal frequency selective fat-suppressed T1-weighted 3D gradient echo (GE) sequence (TR/TE 11/5.5; 25° flip angle; 150 mm field of view, 272x512 acquisition matrix, 2 mm slice thickness with a 1 mm overlap between images); (5) axial frequency selective fat-suppressed PD TSE (TR/TE 3225/15; ETL 6, 4 mm slice thickness). In all TSE sequences we used a 150-160 mm field of view and a 304x512 acquisition matrix. Total acquisition time, including the initial survey sequence, was 30 min.

Scoring of MR images

A trained reader (AWV, supervised by JLB), used the validated semi-quantitative knee OA scoring system blinded to clinical data.[16] Presence or absence of osteophytes, cartilage loss, subchondral BMLs and subchondral cysts was scored at the following locations: patellar crest, medial and lateral patellar facet, medial and lateral trochlear articular facet, medial and lateral femoral condyle and medial and lateral tibial plateau.

Osteophytes were defined as focal bony excrescences, extending from a cortical surface and measured from base to tip, graded as 0 (absent), 1 (<3 mm), 2 (3-5 mm) or 3 (5 mm). Cartilage loss was graded as 0 (absent), 1 (<50% reduction), 2 (≥50% reduction) or 3 (full-thickness cartilage loss).

BMLs were defined as ill-defined areas of increased signal intensity on T2-weighted images in the subchondral bone extending away from the articular surface and graded 0 (absent), 1 (diameter <5mm), 2 (5 mm-2cm) or 3 (>2 cm).

Subchondral cysts were defined as well-defined foci of high signal intensity on T2-weighted images in the subchondral bone and graded based on their measured greatest dimension as 0 (absent), 1 (<3 mm), 2 (3-5 mm) or 3 (>5 mm). Both BMLs and cysts were required not to be associated with meniscal or ligamentous attachments.

The menisci were reviewed for presence of subluxation, maceration and degenerative tears. Subluxation was defined as protrusion over the tibial plateau edge and graded 0 (absent), 1 (<1/3 meniscal width bulging), 2 (1/3-2/3 bulging) or 3 (>2/3 involved). Maceration was defined as an intrameniscal focus of intermediate signal intensity and graded 0 (absent), 1 (small, central focus in meniscus), 2 (intrameniscal focus surrounded by broad, hypointense peripheral rim) or 3 (thin, hypointense peripheral rim outlining the intrameniscal focus). Tears were defined as regions of intermediate signal intensity within the meniscus, communicating with the surface or inner margin on more than one section, graded 0 (absent) or 1 (present).

Joint effusion was graded 0 (small, physiological sliver of synovial fluid), 1 (small amount of fluid distended 1 or 2 joint recesses), 2 (>2 joint recesses partially distended), or 3 (full, marked distention of all joint recesses).

A Baker's cyst was defined when a circumscribed mass with intermediate signal intensity on PD-weighted and high signal intensity on T2-weighted dual SE sequences was observed, originating from the dorsomedial tibiofemoral joint space. Baker's cysts were graded 0 (absent), 1 (minimal), 2 (moderate) or 3 (severe).
A random 10% of the MR images (n = 120) were scored twice to test the reproducibility; intraclass correlation coefficients were for meniscal maceration 0.61, meniscal tear 0.87, meniscal subluxation 0.93, cyst 0.64, BML 0.93, cartilage loss 0.90, osteophyte 0.97.

Symptomatic knee OA
Self-reported pain and morning stiffness were measured using standardized questionnaires. Physical examination of both knee joints was performed by trained research nurses, using a standardized scoring form. OA was defined based on the clinical criteria of the American College of Rheumatology as presence of pain on most days of the prior month and at least three of the following criteria: (1) age >50 years, (2) stiffness <30 minutes duration, (3) crepitus on active motion, (4) bony tenderness, (5) bony enlargement, (6) no palpable warmth.[10]

Statistical analysis
Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL), Matlab version R2014a (MathWorks, Natick, MA) and R version 3.0.1 (R foundation; www.r-project.org).
The prevalence of structural abnormalities was analyzed in the total study population and stratified by symptomatic OA status. The relation between different structural abnormalities was visualized by network graphs, constructed using R (package 'glasso'), by estimating a sparse inverse covariance matrix using a lasso (L1) penalty. The basis for the graphical lasso calculation was the pooled variance-covariance matrix across both outcome groups (individuals with and without symptomatic OA).
To investigate which specific abnormalities discriminate best between individuals with and without symptomatic OA, the following analyses were performed including all structural abnormalities graded 0 to 3 (only meniscal tears were graded 0/1).
As the number of individuals without symptomatic OA was much higher than the number of OA cases, we split the set of individuals without OA into three parts and repeated the subsequently described model analysis for each of these three parts to assess stability of computations. Individuals without OA were randomly assigned to three mutually exclusive sets, each of these sets was then combined with the OA cases, rendering three calibration sets. The subsequently described discriminant analysis was then applied (repeated) for each of these sets. A logistic ridge regression model (see Hastie et al., 2007 for description) was fit to each of the above constructed calibration sets using a double cross-validatory approach.[17,18] The double cross-validatory approach provides unbiased class probabilities for each individual in each of the above three calibration sets. Cross-validated deviances were used to select optimal models within the double cross-validatory assessment. ROC curves, AUC and classification statistics were used to summarize the double cross-validatory classifications. Double cross-validation uses a separate model fit for each left-out datum to generate unbiased classification summaries. For model parameter interpretation, we therefore refitted the logistic ridge regression model to the calibration data, using the optimum shrinkage (penalty) term identified in the preceding double cross-validatory calculation. Regression coefficients for all as-

sessed structural abnormalities in the different locations within the joint were calculated based on this final fitted model. Penalized estimates such as those provided by the ridge regression reduce variance of estimation by allowing for bias in the estimation of effects, which implies that classical estimates of the variance of these estimates can no longer be meaningfully interpreted.
Both crude analyses and analyses adjusted for age, sex and BMI were performed. Higher regression coefficients reflect better discrimination between presence or absence of symptomatic OA, taking co-occurrence of all abnormalities in different locations within the joint into account.

RESULTS

Population characteristics
After exclusion of individuals with missing data of physical examination (n = 1) data from 1,284 participants were analyzed. Of the studied individuals, 55% were women. Median age was 56 years (interquartile range 50 to 61), median BMI 30.0 kg/m^2 (27.9 to 33.0). Symptomatic OA in the imaged knee was present in 177 individuals. The 1,107 individuals without symptomatic OA were divided in three mutually exclusive sets of 369 individuals for further analyses.

Prevalence of structural MR abnormalities
The prevalence of structural abnormalities in the total study population is presented in Table 1. All assessed structural abnormalities except for subchondral cysts were observed frequently. However, the prevalence differed across locations within the joint.
In the tibiofemoral and patellofemoral compartment osteophytes were commonly observed, especially in the medial tibiofemoral compartment (medial femoral condyle 86%, medial tibial plateau 38%) and the medial patellar facet (59%). Cartilage defects were also frequently observed in both compartments, especially medially (medial femoral condyle 58%, medial tibial plateau 68%, medial patellar facet 65%, medial trochlear facet 53%) and in the patellar crest (65%). BMLs were observed less frequently, mostly located in the patellar crest (22%).
Meniscal abnormalities were observed most commonly in the medial meniscus, maceration was most prevalent (35%), followed by tears (23%) and subluxation (15%).
As presented in Table 2, a higher prevalence of osteophytes, cartilage defects, BMLs and meniscal abnormalities were seen in individuals with symptomatic OA as compared to individuals without.
Effusion was also highly prevalent (80%), both in individuals with and without symptomatic OA. Especially higher grades of effusion were observed more often in individuals with symptomatic OA than in those without. The same was observed for Baker's cysts (overall prevalence 30%); especially grade 2 and 3 were observed most often in individuals with OA.

Table 1. Prevalence of structural abnormalities as assessed on magnetic resonance imaging on different locations in the knee in the total NEO study population

	n = 1284			
	Grade 0 (n (%))	**Grade 1 (n (%))**	**Grade 2 (n (%))**	**Grade 3 (n (%))**
Baker's cyst	894 (70)	245 (19)	100 (8)	45 (4)
Effusion	253 (20)	848 (66)	163 (13)	20 (2)
Tibiofemoral compartment:				
Osteophytes				
- femoral condyle medial / lateral	186 (14) / 293 (23)	946 (74) / 882 (69)	122 (10) / 88 (7)	30 (2) / 21 (2)
- tibial plateau medial / lateral	801 (62) / 929 (72)	436 (34) / 310 (24)	41 (3) / 36 (3)	6 (0) / 9 (1)
Cartilage defects				
- femoral condyle medial / lateral	544 (42) / 1031 (80)	563 (44) / 180 (14)	142 (11) / 65 (5)	35 (3) / 8 (1)
- tibial plateau medial / lateral	409 (32) / 1077 (84)	733 (57) / 102 (8)	129 (10) / 88 (7)	13 (1) / 17 (1)
Bone marrow lesions				
- femoral condyle medial / lateral	1078(84) / 1185(92)	109 (8) / 49 (4)	95 (7) / 48 (4)	2 (0) / 2 (0)
- tibial plateau medial / lateral	1136(88) / 1199(93)	61 (5) / 36 (3)	82 (6) / 45 (4)	5 (0) / 4 (0)
Cysts				
- femoral condyle medial / lateral	1268(99) / 1268(99)	15 (1) / 12 (1)	0 (0) / 4 (0)	1 (0) / 0 (0)
- tibial plateau medial / lateral	1251(97) / 1257(98)	18 (1) / 15 (1)	11 (1) / 6 (0)	4 (0) / 6 (0)
Patellofemoral compartment:				
Osteophytes				
- patellar crest	1270 (99)	7 (1)	5 (0)	2 (0)
- patellar facet medial / lateral	527 (41) / 1057 (82)	642 (50) / 200 (16)	103 (8) / 27 (2)	12 (1) / 0 (0)
- trochlear facet medial / lateral	897 (70) / 1006 (78)	325 (25) / 241 (19)	42 (3) / 28 (2)	19 (1) / 9 (1)
Cartilage defects				
- patellar crest	448 (35)	393 (31)	275 (21)	168 (13)
- patellar facet medial / lateral	445 (35) / 770 (60)	346 (27) / 336 (26)	332 (26) / 126 (10)	161 (13) / 52 (4)
- trochlear facet medial / lateral	607 (47) / 837 (65)	513 (40) / 362 (28)	149 (12) / 58 (5)	15 (1) / 27 (2)
Bone marrow lesions				
- patellar crest	1005 (78)	109 (8)	170 (13)	0 (0)
- patellar facet medial / lateral	1173(91) / 1218(95)	69 (5) / 41 (3)	42 (3) / 24 (2)	0 (0) / 1 (0)

Table 1. *Continued*

	n = 1284			
	Grade 0 (n (%))	**Grade 1 (n (%))**	**Grade 2 (n (%))**	**Grade 3 (n (%))**
- trochlear facet medial / lateral	1208(94) / 1210(94)	45 (4) / 27 (2)	30 (2) / 45 (4)	1 (0) / 2 (0)
Cysts				
- patellar crest	1244 (97)	35 (3)	5 (0)	0 (0)
- patellar facet medial / lateral	1269(99)/1280(100)	14 (1) / 4 (0)	1 (0) / 0 (0)	0 (0) / 0 (0)
- trochlear facet medial / lateral	1274(99) / 1274(99)	9 (1) / 8 (1)	1 (0) / 2 (0)	0 (0) / 0 (0)
Menisci:				
- subluxation medial / lateral	1092(85) / 1112(87)	171 (13) / 156 (12)	19 (1) / 16 (1)	2 (0) / 0 (0)
- maceration medial / lateral	837 (65) / 955 (74)	341 (27) / 262 (20)	102 (8) / 63 (5)	4 (0) / 4 (0)
- tear medial / lateral	985 (77) / 1090 (85)	299 (23) / 194 (15)	na	na

Numbers (%, rounded to whole numbers).
na = not applicable.

Table 2. Prevalence of structural abnormalities as assessed on magnetic resonance imaging on different locations in the knee stratified by symptomatic knee osteoarthritis (OA) status

	No symptomatic OA (n = 1107)	**Symptomatic OA (n = 177)**
	Grade 0-1-2-3 (%)	**Grade 0-1-2-3 (%)**
Baker's cyst	71-19-7-2	60-17-11-12
Effusion	21-68-10-1	14-52-29-6
Tibiofemoral compartment:		
Osteophytes		
- femoral condyle medial / lateral	16-76-8-1 / 24-70-5-1	8-59-20-12 / 16-59-19-6
- tibial plateau medial / lateral	66-32-2-0 / 76-22-2-1	38-47-12-3 / 53-36-9-2
Cartilage defects		
- femoral condyle medial / lateral	44-44-10-2 / 82-13-4-0	30-42-20-8 / 70-18-10-2
- tibial plateau medial / lateral	33-58-9-1 / 85-7-7-1	28-53-15-5 / 76-12-9-2
Bone marrow lesions		
- femoral condyle medial / lateral	87-8-6-0 / 93-3-3-0	67-15-19-np / 88-6-6-np
- tibial plateau medial / lateral	91-5-4-0 / 94-3-3-0	75-5-19-2 / 88-4-7-2
Cysts		
- femoral condyle medial / lateral	99-1-np-0 / 99-1-0-np	98-2-np-np / 98-2-1-np
- tibial plateau medial / lateral	98-1-1-0 / 98-1-1-0	96-3-1-1 / 97-1-1-1
Patellofemoral compartment:		
Osteophytes		
- patellar crest	99-0-0-0	96-2-2-0
- patellar facet medial / lateral	44-49-7-0 / 85-14-1-np	25-54-17-6 / 68-25-7-np
- trochlear facet medial / lateral	74-24-2-1 / 81-17-1-0	46-36-11-7 / 61-28-8-3
Cartilage defects		
- patellar crest	37-30-21-12	22-32-25-22
- patellar facet medial / lateral	36-28-25-12 / 62-26-9-3	27-24-32-18 / 50-29-12-9
- trochlear facet medial / lateral	48-40-11-1 / 66-28-5-1	42-37-16-5 / 59-29-5-7
Bone marrow lesions		
- patellar crest	80-8-12-np	71-10-20-np
- patellar facet medial / lateral	91-5-4-np / 95-3-2-0	93-6-1-np / 92-5-3-np
- trochlear facet medial / lateral	94-4-2-0 / 95-2-3-0	94-3-3-np / 88-5-7-np
Cysts		
- patellar crest	97-3-1-np	97-3-np-np
- patellar facet medial / lateral	99-1-0-np / 100-0-np-np	100-np-np-np / 99-1-np-np
- trochlear facet medial / lateral	99-1-0-np / 99-1-0-np	98-2-np-np / 99-1-np-np
Menisci:		
- subluxation medial / lateral	87-12-1-0 / 87-12-1-np	75-19-6-1 / 83-16-1-np
- maceration medial / lateral	66-27-7-0 / 75-20-5-0	63-23-14-1 / 71-21-6-2
- tear medial / lateral	78-22-na-na / 86-14-na-na	71-29-na-na / 79-22-na-na

Numbers are rounded to percentages as whole numbers.

np = not present, na = not applicable.

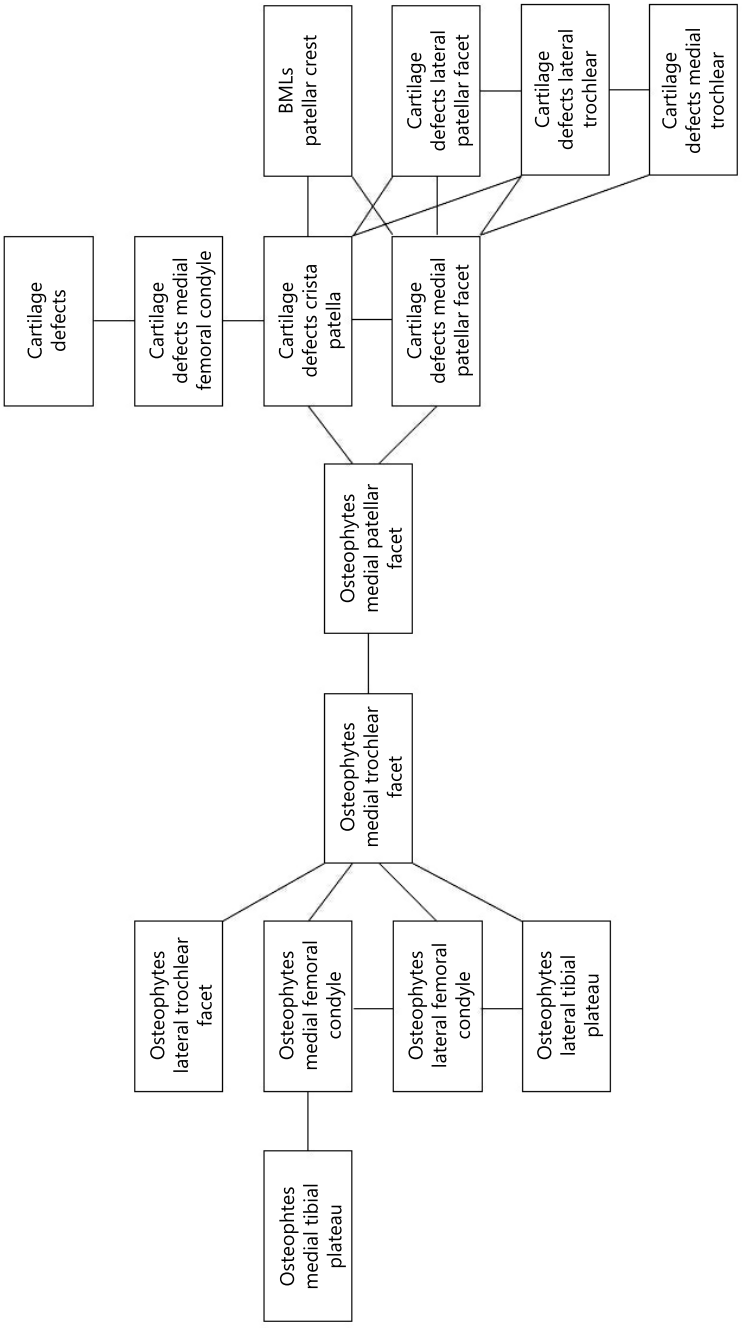

Figure 1. Network graph illustrating the relation between the assessed structural abnormalities on different locations within the knee joint in the total NEO study population. Lines represent a relation between presence of two abnormalities.

Relation between structural abnormalities

In the total study population, including individuals with and without symptomatic OA, the relation between structural abnormalities was visualized by network graphs, showing multiple relations between abnormalities on different locations within the joint. A number of network graphs was performed, the number of relations shown in the graph depending on the used lasso penalty. All network graphs showed relations between osteophytes on different locations within all compartments of the knee and between cartilage defects on different locations. Furthermore, osteophytes and cartilage defects within the same compartment were also related. Figure 1 shows 15 structural abnormalities with 22 relations between them. Besides osteophytes and cartilage defects on different locations within the joint, BMLs in the patellar crest were also present in the network graph, related to cartilage defects in the patellar crest and medial patellar facet.

Structural abnormalities discriminating symptomatic OA

Next, we investigated which specific abnormalities could best discriminate between individuals with and without symptomatic OA, taking co-occurrence of all structural abnormalities into account.

Regression coefficients of the assessed structural abnormalities for presence of OA as obtained by logistic ridge regression analyses are listed in Table 3. Depicted are regression coefficients for all three analyses sets and a mean regression coefficient for these sets. The higher the regression coefficient, the better the corresponding structural abnormality discriminates symptomatic OA, adjusted for co-occurrence of other structural abnormalities. The regression coefficients for subchondral cysts were all below 0.030.

Baker's cysts showed the highest regression coefficient for OA, followed by osteophytes in the medial tibial plateau and medial trochlear facet. The next strongest regression coefficient was found for effusion, followed by BMLs in the medial tibiofemoral compartment and osteophytes in the medial femoral condyle.

The three separate analyses sets were comparable. After adjustment for age, sex and BMI, the same structural abnormalities were observed to discriminate symptomatic OA best. The area under the curve for the three sets were 0.719, 0.698 and 0.693 (Figure 2). Figure 3 illustrates the structural abnormalities best discriminating symptomatic knee OA.

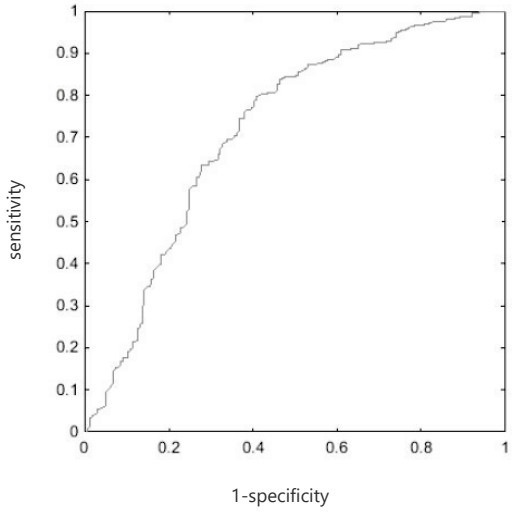

Figure 2. ROC curve of one of the three analyses sets (set 1, AUC = 0.7189). The ROC curves of set 2 and set 3 were comparable (AUC set 2 = 0.698, AUC set 3 = 0.693).

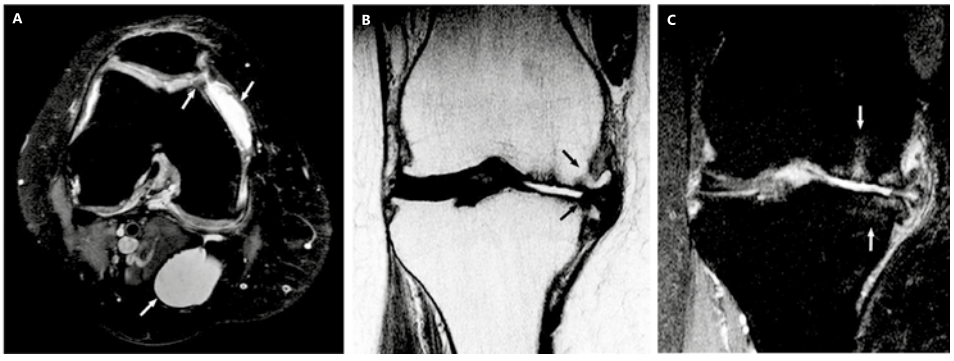

Figure 3. Magnetic resonance (MR) images in individuals with symptomatic knee osteoarthritis illustrating the structural abnormalities that discriminate symptomatic knee osteoarthritis best.

A. Axial fat suppressed proton density (PD) MR image showing a Baker's cyst, effusion and an osteophyte in the medial trochlear facet

B. Coronal PD MR image showing osteophytes in the medial femoral condyle and medial tibial plateau

C. Coronal fat suppressed PD MR image showing BMLs in the medial femoral condyle and medial tibial plateau.

Table 3. Regression coefficients for presence of symptomatic knee osteoarthritis (OA) as obtained by logistic ridge regression analyses

	Set 1	Set 2	Set 3	Mean coeff.
Baker's cyst	0.391	0.235	0.254	**0.293**
Effusion	0.255	0.220	0.116	**0.197**
Tibiofemoral compartment:				
Osteophytes				
- medial femoral condyle	0.184	0.205	0.166	**0.185**
- lateral femoral condyle	0.008	0.066	0.123	0.065
- medial tibial plateau	0.314	0.250	0.273	**0.279**
- lateral tibial plateau	0.019	0.081	0.149	0.083
Cartilage defects				
- medial femoral condyle	0.245	0.075	0.154	0.158
- lateral femoral condyle	0.038	0.074	0.130	0.081
- medial tibial plateau	-0.054	0.046	0.041	0.011
- lateral tibial plateau	-0.119	-0.028	-0.018	-0.055
Bone marrow lesions				
- medial femoral condyle	0.211	0.138	0.230	**0.193**
- lateral femoral condyle	0.003	0.013	-0.053	-0.012
- medial tibial plateau	0.101	0.179	0.283	**0.188**
- lateral tibial plateau	0.175	0.056	0.034	0.088
Patellofemoral compartment:				
Osteophytes				
- patellar crest	0.033	0.009	0.024	0.022
- medial patellar facet	0.135	0.170	0.124	0.143
- lateral patellar facet	0.158	0.037	0.099	0.098
- medial trochlear facet	0.275	0.258	0.252	**0.262**
- lateral trochlear facet	0.047	0.048	0.135	0.077
Cartilage defects				
- patellar crest	0.188	0.123	0.127	0.146
- medial patellar facet	0.184	0.133	0.011	0.109
- lateral patellar facet	0.073	0.095	0.120	0.096
- medial trochlear facet	0.078	0.117	0.021	0.072
- lateral trochlear facet	-0.035	0.105	0.020	0.030
Bone marrow lesions				
- patellar crest	0.070	0.179	0.149	0.133
- medial patellar facet	-0.077	-0.061	-0.097	-0.078
- lateral patellar facet	0.071	0.000	0.014	0.029
- medial trochlear facet	-0.026	-0.024	-0.062	-0.037
- lateral trochlear facet	0.016	0.039	-0.017	0.012
Menisci:				
- subluxation medial / lateral	0.053 / 0.050	0.035 / -0.021	0.016 / -0.021	0.035 / 0.003
- maceration medial / lateral	0.202 / 0.090	0.052 / -0.013	0.070 / 0.109	0.108 / 0.062
- tear medial / lateral	0.004 / 0.092	0.009 / 0.014	0.050 / 0.034	0.021 / 0.047

In bold within the gray rows the strongest mean regression coefficients for presence of symptomatic knee OA. All three sets include all individuals with symptomatic OA in the imaged knee and a random 1/3 of individuals without symptomatic OA.

DISCUSSION

This large population-based study investigates which structural abnormalities as assessed on MR imaging discriminates symptomatic OA within the same knee best, taking co-occurrence of all structural abnormalities on different locations within the joint into account. In the entire study population, comprising individuals with and without symptomatic OA, structural abnormalities were highly frequent in both the tibiofemoral and patellofemoral compartments, most prominent at the medial side. Presence of osteophytes and cartilage defects in different locations were related to each other. The structural abnormalities that discriminates best between individuals with and without symptomatic OA were general abnormalities as Baker's cysts and effusion, in addition to osteophytes and BMLs in the medial tibiofemoral compartment. In the patellofemoral joint only osteophytes in the medial trochlear facet seemed of importance.

This is not the first study associating structural abnormalities with symptomatic knee OA or symptoms as pain, but it is the first investigating this relationship involving structural abnormalities in all patellofemoral and tibiofemoral locations, using a model taking co-occurrence of all abnormalities into account.

Baker's cysts showed the highest regression coefficient for symptomatic OA. The relationship between Baker's cysts and OA symptoms has been assessed in a few studies, showing conflicting results.[11,19-21] Bakers' cysts have not been studied before to discriminate symptomatic OA. Inflammation seems to play a role in development of Baker's cysts since presence and grade of synovial inflammation has been associated with Baker's cysts.[22] Although grade of synovial inflammation has not been assessed in this study, effusion also discriminated symptomatic OA. The prevalence of grade 2 and 3 Baker's cysts was 23% in individuals with symptomatic OA compared to 9% in those without. Perhaps, treatment of knee OA has to focus on prevention of development of Baker's cysts by treatment of synovial inflammation. Studies on treatment of Baker's cysts by steroid injections showed significant reduction of symptoms after intra-articular infiltration, and even more after direct injection into the cyst.[23,24]

As described in a systematic review on structural abnormalities in relation to symptoms in OA, the discriminative role of effusion and BMLs found in this study is in accordance with previous literature.[14] Osteophytes and cartilage defects does not show a clear relation with OA symptoms.[14] This study, taking co-occurrence of structural abnormalities into account, showed osteophytes especially in the medial tibiofemoral joint to discriminate symptomatic OA. Although a high prevalence of cartilage defects was observed, they were found to discriminate symptomatic OA less good. This can be understood when looking at the network graph presented in Figure 1, showing relations between structural abnormalities that co-occur frequently within the total study population. Since cartilage defects co-occur frequently with osteophytes, only one of these abnormalities will discriminate symptomatic OA when taking this co-occurrence into account.

The Baker's cyst, found to discriminate individuals with symptomatic OA best, was not present in the network graph. This is probably due to the lower prevalence of Baker's cysts. Although also Baker's cysts co-occur with other structural abnormalities in the knee, they especially discriminate symptomatic OA.

Although research on knee OA has been focusing increasingly on the patellofemoral compartment during last years,[1,3] this study shows that most of the abnormalities discriminating symptomatic OA are general abnormalities (Baker's cysts and effusion) and structural abnormalities located within the medial tibiofemoral compartment. In current literature on patellofemoral OA, it has been suggested that abnormalities in the patellofemoral compartment may represent an early stage of OA and precede tibiofemoral OA.[25-27] This is in contrast with the minor role of the patellofemoral compartment in discriminating symptomatic OA found in this study.

Strength of this study are the size of the study population, extensive assessment of structural abnormalities using MR imaging and analyses accounting for co-occurrence of all structural abnormalities on different locations within the joint. Symptoms as pain, assessed by self-report, may be influenced by unknown determinants or causes other than OA. Therefore we used symptomatic OA defined by highly sensitive and specific criteria10 instead of only pain as outcome measure.

Because of the large number of individuals without symptomatic OA, the logistic ridge regression analyses were performed in three sets of data, consisting of a random one third of individuals without symptomatic OA in addition to the individuals with symptomatic OA. Analyses of these three sets prevents loss of information due to the high proportion of individuals without OA. Furthermore, structural abnormalities that were found to discriminate symptomatic OA in all three sets supports the importance of especially these abnormalities. The AUC of the three analyses (around 0.7) showed that assessment of all structural abnormalities results in fair discrimination of symptomatic OA.[28]

This study suggests that Baker's cysts discriminate symptomatic knee OA best, followed by effusion and structural abnormalities as osteophytes and BMLs especially in the medial side of the tibiofemoral joint. More research is necessary to gain more insight into the precise underlying mechanisms, longitudinal research will be of help. Especially the role of Baker's cysts in symptomatic OA may provide potential targets for treatment of knee OA.

REFERENCES

1. Crossley KM and Hinman RS. The patellofemoral joint: the forgotten joint in knee osteoarthritis. Osteoarthritis Cartilage 2011;19:765-7.
2. Stefanik JJ, Niu J, Gross KD, Roemer FW, Guermazi A, Felson DT. Using magnetic resonance imaging to determine the compartmental prevalence of knee joint structural damage. Osteoarthritis Cartilage 2013;21:695-9.
3. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. Arthritis Res Ther 2012;14:R63.
4. Stefanik JJ, Neogi T, Niu J, Roemer FW, Segal NA, Lewis CE et al. The diagnostic performance of anterior knee pain and activity-related pain in identifying knees with structural damage in the patellofemoral joint: the Multicenter Osteoarthritis Study. J Rheumatol 2014;41:1695-702.
5. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
6. Beattie KA, Boulos P, Pui M, O'Neill J, Inglis D, Webber CE et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. Osteoarthritis Cartilage 2005;13:181-6.
7. Baranyay FJ, Wang Y, Wluka AE, English DR, Giles GG, Sullivan RO et al. Association of bone marrow lesions with knee structures and risk factors for bone marrow lesions in the knees of clinically healthy, community-based adults. Semin Arthritis Rheum 2007;37:112-8.
8. Guymer E, Baranyay F, Wluka AE, Hanna F, Bell RJ, Davis SR et al. A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women. Osteoarthritis Cartilage 2007;15:1437-42.
9. Hayashi D, Felson DT, Niu J, Hunter DJ, Roemer FW, Aliabadi P et al. Pre-radiographic osteoarthritic changes are highly prevalent in the medial patella and medial posterior femur in older persons: Framingham OA study. Osteoarthritis Cartilage 2014;22:76-83.
10. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
11. Kornaat PR, Bloem JL, Ceulemans RY, Riyazi N, Rosendaal FR, Nelissen RG et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 2006;239:811-7.
12. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541-9.
13. Lo GH, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2009;17:1562-9.
14. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis?

A systematic review. Ann Rheum Dis 2011;70:60-7.
15. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
16. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005;34:95-102.
17. Hastie T, Tibshirani R, Friedman J. The elements of statistical learning. 2007.
18. Mertens BJ, de Noo ME, Tollenaar RA, Deelder AM. Mass spectrometry proteomic diagnosis: enacting the double cross-validatory paradigm. J Comput Biol 2006;13:1591-605.
19. Guermazi A, Hayashi D, Roemer FW, Niu J, Yang M, Lynch JA et al. Cyst-like lesions of the knee joint and their relation to incident knee pain and development of radiographic osteoarthritis: the MOST study. Osteoarthritis Cartilage 2010;18:1386-92.
20. Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. J Rheumatol 2001;28:1330-7.
21. Hill CL, Gale DR, Chaisson CE, Skinner K, Kazis L, Gale ME et al. Periarticular lesions detected on magnetic resonance imaging: prevalence in knees with and without symptoms. Arthritis Rheum 2003;48:2836-44.
22. Chatzopoulos D, Moralidis E, Markou P, Makris V, Arsos G. Baker's cysts in knees with chronic osteoarthritic pain: a clinical, ultrasonographic, radiographic and scintigraphic evaluation. Rheumatol Int 2008;29:141-6.
23. Handy JR. Popliteal cysts in adults: a review. Semin Arthritis Rheum 2001;31:108-18.
24. Bandinelli F, Fedi R, Generini S, Porta F, Candelieri A, Mannoni A et al. Longitudinal ultrasound and clinical follow-up of Baker's cysts injection with steroids in knee osteoarthritis. Clin Rheumatol 2012;31:727-31.
25. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. Ann Rheum Dis 2011;70:1944-8.
26. Schiphof D, van Middelkoop M, de Klerk BM, Oei EH, Hofman A, Koes BW et al. Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). Osteoarthritis Cartilage 2014;22:631-8.
27. Lankhorst NE, Damen J, Oei EH, Bierma-Zeinstra SM, van Middelkoop M. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis; data of cohort hip and cohort knee study. Osteoarthritis & Cartilage 2015;23:Supplement2:A42-A43.
28. Hanley JA. Receiver operating characteristic (ROC) methodology: the state of the art. Crit Rev Diagn Imaging 1989;29:307-35.

CHAPTER 6

Do knee osteoarthritis and fat-free mass interact in their impact on health-related quality of life in men? Results from a population-based cohort

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ABSTRACT

Objective
To investigate whether obesity and other risk factors interact with knee osteoarthritis (OA) in its adverse impact on health-related quality of life (HRQOL).

Methods
In 1,262 participants of the Netherlands Epidemiology of Obesity study, a population-based cohort (age 45 to 65 years, 53% women, and median body mass index (BMI) 27 kg/m^2), knee OA was defined following modified American College of Rheumatology criteria. BMI and fat-free mass (FFM) (as proxy for muscle mass) were assessed by bioelectrical impedance analysis, and comorbidities by self-report. HRQOL was assessed using the Short Form 36 physical component summary (PCS) score. Linear regression analyses were performed to examine associations between knee OA and PCS score, adjusting for age and sex and stratified for BMI, FFM, and comorbidities.

Results
Knee OA (prevalence 16%) was associated with a 7.2-points lower PCS score (95% confidence interval -9.5 to -4.8). PCS score was also negatively associated with obesity and comorbidities; however, no interaction with knee OA was seen. Low FFM was associated with a lower PCS score and interacted with knee OA in men. Interaction between concurring OA and low FFM attributed to 64% of the decrease in PCS score, as compared with men without OA and with high FFM.

Conclusion
Knee OA was associated with a lower HRQOL, as were its risk factors, obesity, comorbidities, and low FFM. In men, FFM interacted with knee OA, leading to an additional decrease of HRQOL in the case of concurrence. Especially in the former, improvement of FFM may improve HRQOL in knee OA patients.

INTRODUCTION

Of the musculoskeletal disorders, osteoarthritis (OA) is the second largest contributor to disability. Knee OA has been shown to account for 83% of the global years lived with disability that were due to the presence of any OA.[1] In addition, knee OA has been associated with an impaired health-related quality of life (HRQOL).[2-4]

Several risk factors for knee OA are known;[5,6] some of these risk factors are not only associated with development of OA but also with a decreased HRQOL. It is possible that presence of knee OA together with a risk factor that is also associated with HRQOL results in strengthening of both adverse associations with HRQOL. The latter will be especially important when it concerns risk factors that can either be prevented or treated, as interventions aimed at prevention or treatment of these factors could then result in additional improvement of HRQOL in knee OA patients.

Modifiable risk factors for OA that also decrease HRQOL could be potential targets for interventions. Obesity may be one of those factors; it has been related both to development of knee OA and to impaired HRQOL.[7-9] Another risk factor for knee OA that may be a target for intervention is muscle weakness.[10] Although no studies related muscle weakness or the actual amount of muscle mass to HRQOL, physical frailty (associated with low fat-free mass (FFM), a proxy for muscle mass) has been related to decreased HRQOL.[11] A preventable risk factor is the presence of comorbidities, such as cardiovascular diseases and diabetes mellitus. Such comorbidities have been associated both with presence of knee OA and decreased HRQOL.[12-14]

Obesity, exercise (related to muscle mass), and comorbidities have been related to HRQOL, not only in the general population but also within knee OA patients.[15-18] However, the relative contributions of knee OA and these risk factors to HRQOL, as well as a possible interaction when they concur, are not clear.

To gain insight into possible targets for improvement or prevention of HRQOL in knee OA patients, we aimed to evaluate the impact of the presence of knee OA and its modifiable or preventable risk factors: obesity, FFM (as proxy for muscle mass), and comorbidities on HRQOL. In addition, we aimed to examine the presence of interaction between knee OA and these risk factors in relation to HRQOL.

PATIENTS AND METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study including 6,673 individuals aged 45 to 65 years, with an oversampling of persons with overweight or obesity (members of the NEO Study Group are listed in Appendix A). Detailed information about the study design and data collection has been described previously.[19] In short, men and women between ages 45 to 65 years with a self-reported body mass index (BMI) of ≥27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate. In addition, all inhabitants aged 45 to 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI.

All participants completed questionnaires on demographic and clinical data, in addition to the Short Form 36 (SF-36) Health Survey, and visited the NEO study center between September 2008 and September 2012 for an extensive physical examination, including anthropometry and blood sampling. All medication that was used in the month preceding the study visit was recorded. A random sample of 1,285 study participants without contraindications (metallic devices, claustrophobia, body circumference >170 cm) underwent magnetic resonance (MR) imaging of the right knee. The present study is a cross-sectional analysis of baseline measurements of these 1,285 participants. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Data collection

Highest level of education was reported in categories according to the Dutch education system and grouped into low, medium, or high education. Reported professions were categorized into non-, light- and heavy physically demanding work, based on a classification scheme of physical work demands by De Zwart et al.[20]

MR imaging

MR imaging was performed using a dedicated knee coil in a 1.5T system (Philips, Medical Systems). Our standardized scanning protocol consisted of (1) coronal proton density (PD) turbo spin-echo (TSE), repetition time (TR)/echo time (TE) 2,335/35 msec; echo train length (ETL) 6; (2) coronal frequency selective fat-suppressed PD TSE (TR/TE 2,334/ 35 msec, ETL 6, 3 mm slice thickness); (3) sagittal PD TSE (TR/TE 2,338/35 msec, ETL 6; 3.5 mm slice thickness); (4) sagittal frequency selective fat-suppressed T1-weighted 3-dimensional gradient echo sequence (TR/TE 11/5.5, 25° flip angle, 150 mm field of view, 272 x 512 acquisition matrix, 2 mm slice thickness with a 1 mm overlap between images); and (5) axial frequency selective fat-suppressed PD TSE (TR/TE 3,225/15 msec, ETL 6, 4 mm slice thickness). In all TSE sequences we used a 150-160 mm field of view and a 304 x 512 acquisition matrix. Total acquisition time, including the initial survey sequence, was 30 minutes.

Definition of OA

Knee OA was defined, based on modified criteria of the American College of Rheumatology (ACR), as presence of osteophytes, knee pain on most days of the prior month, and at least 1 of the following criteria: age >50 years, stiffness <30 minutes duration, and crepitus on active motion.[21] Instead of the presence of radiographic osteophytes as described in the original ACR criteria, osteophytes were assessed with MR imaging.

Assessment of the MR imaging was done by a trained reader (AWV, supervised by JLB), using the validated semiquantitative knee OA scoring system, blinded to clinical data. Osteophytes were defined as focal bony excrescences extending from a cortical surface and measured from base to tip. Osteophytes were either absent (grade 0), or present (grade 1 (<3 mm), grade 2 (3-5 mm), or grade 3 (>5 mm)).[22] A random 10% of the MR images (n = 120) were scored twice to test the reproducibility; the calculated intraclass correlation coefficient was 0.97.

Physical examination of the knees was performed by trained research nurses, using a standardized scoring form. Self-reported knee pain and morning stiffness were measured using standardized questionnaires.

Body composition

Height was measured with a calibrated tape measure. Body weight, fat mass, and body fat percentage were measured using the Tanita foot-to-foot bio impedance balance (TBF-310, Tanita International Division).[23] BMI was calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2). According to the classification of the World Health Organization, BMI was categorized into normal weight (BMI <25 kg/m^2), overweight (BMI 25-30 kg/m^2), and obesity (BMI ≥30 kg/m^2).

The percentage of FFM was calculated as 100 minus the percentage of body fat measured by bioelectrical impedance analysis using the Tanita balance.[23] Percentage of FFM was divided in tertiles separately in men and women because of the major difference in FFM between the sexes.[24] Low FFM was defined as the lowest tertile of percentage FFM.

Comorbidities

The presence of cerebrovascular disease, lung disease, cardiovascular diseases (myocardial infarction, angina, congestive heart failure, stroke, peripheral vascular disease), and diabetes was self-reported using a standardized questionnaire. In addition, use of glucose-lowering therapy or a measured fasting plasma glucose of ≥7.0 mmol/liter at the time of the study visit were also defined as diabetes mellitus.

HRQOL

HRQOL was assessed using the physical component summary (PCS) score of the generic SF-36. The SF-36 PCS and mental component summary scores were derived using norm-based data from the Dutch population, standardized to a mean of 50 and SD of 10.[25] The total scores range from 0 to 100, and higher scores indicate better HRQOL.26 The minimal clinical important difference is 2.5 to 5.0 points.[27]

Statistical analysis

Data were analyzed using STATA, version 12. In the NEO study there is an oversampling of persons with a BMI ≥27 kg/m^2. To correctly represent associations in the general population, adjustments for the oversampling of individuals with a BMI ≥27 kg/m^2 were made.[28] This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality (n = 1,671),[29] whose BMI distribution was similar to the BMI distribution in the general Dutch population.[30] Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.

First, we performed linear regression analyses to examine the association of knee OA with the SF-36 PCS score. Regression coefficients with 95% confidence intervals (95% CI) were reported and can be interpreted as the mean difference in PCS score of participants with knee OA as compared with participants without knee OA. Adjustments were made for age, sex, BMI, FFM, and presence of comorbidities.

Second, we examined the presence of interaction of knee OA with obesity, low percentage FFM, or comorbidities in relation to HRQOL by including interaction terms between knee OA and BMI, knee OA and percentage FFM, and knee OA, and presence of comorbidities in the model. These regression analyses were performed separately for the 3 interaction terms. Interaction was considered present when the interaction term was significant ($P < 0.05$).

Finally, for a transparent presentation of the joint associations, we stratified all analyses by knee OA and categories of BMI, FFM and comorbidities to report all associations compared with the unexposed group as a joint reference category.[31,32]
For example, the adjusted difference in PCS scores were calculated for each stratum of BMI, using individuals without knee OA and with normal weight as reference. Similar analyses were performed with tertiles of FFM and presence/absence of comorbidities.
Since BMI is a cumulative measure of fat, muscle, and bone, we performed sensitivity analyses including fat mass as specific measure of adiposity instead of BMI as robust measure of obesity. Furthermore, since MR imaging is a very sensitive tool for detection of osteophytes, sensitivity analyses excluding small osteophytes (grade 1) from the knee OA definition were performed.

RESULTS

Population characteristics
After exclusion of individuals with missing SF-36 data (n = 23), data from 1,262 participants were analyzed. The unweighted baseline characteristics, i.e. without taking oversampling of BMI ≥27 kg/m^2 into account, are shown in Supplementary Table 1. Table 1 shows the weighted baseline characteristics of the total study population and stratified by knee OA. These characteristics represent the population to which all subsequent results apply. Median (25th to 75th percentiles) age of the total study population was 56 years (51 to 61 years), BMI 27 kg/m^2 (24 to 29 kg/m^2), and 56% were women.
The prevalence of knee OA, including osteophytes of at least grade 1 as assessed on MR imaging, was 16% (95% CI 13% to 19%). The prevalence of knee OA when including only osteophytes of at least grade 2 was 5% (95% CI 4% to 7%). Median age and percentage of women were higher in individuals with knee OA. Furthermore, individuals with knee OA had a higher median BMI and more comorbidities as compared with participants without knee OA. Mean SF-36 PCS score was lower in individuals with knee OA than in those without (Table 1).

Knee OA in relation to HRQOL
First, we investigated the association between knee OA and PCS score (Table 2). The crude mean PCS score in individuals with knee OA was 7.4 points lower (95% CI -9.3 to -5.4) than in individuals without knee OA. After adjustment for age, sex, and the assessed risk factors, the mean difference in PCS score between individuals with and without OA was -6.2 points (95% CI -8.0 to -4.4).
Sensitivity analysis, including fat mass as specific measure of adiposity instead of BMI as robust measure of obesity, provided the same mean difference in PCS score between individuals with and without OA (-6.2 points (95% CI -8.1 to -4.4)). Sensitivity analyses, including knee OA based on osteophytes of at least grade 2 instead of all observed osteophytes, yielded similar results.

Table 1. Baseline characteristics of the NEO study population

		Total population	Knee OA (prevalence 16%)	No knee OA (prevalence 84%)
Age (years)		56 (51-61)	57 (53-61)	56 (50-61)
Sex (% women)		56	61	55
Education (high)		38	34	39
Profession (high physically demanding)		10	10	9
BMI (kg/m^2)		26.7 (23.8-29.4)	27.1 (24.8-30.7)	26.6 (23.4-29.2)
FFM (kg)	Men	74.7 (71.2-79.3)	74.7 (71.4-79.0)	74.8 (71.2-79.3)
	Women	61.6 (57.2-66.7)	59.8 (55.2-63.7)	61.7 (57.4-67.3)
Comorbidities		14	24	13
- Cardiovascular disease		6	8	5
- Cerebrovascular accident		3	2	3
- Diabetes		7	12	6
- Lung disease		4	9	2
SF-36 MCS score		51.5 ± 8.7	51.2 ± 9.9	51.5 ± 8.5
SF-36 PCS score		53.0 ± 8.6	46.9 ± 9.5	54.2 ± 7.9

Values are the percentage, median (25th to 75th percentiles), or mean ± SD. Results are based on weighted analyses of the study population (n = 1,262).

BMI, body mass index; FFM, fat-free mass; MCS, mental component summary; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary; SF-36, Short Form 36 health survey.

Table 2. Association of knee OA with PCS score in 1,262 participants of the NEO study

	Mean difference PCS score	95% CI
Crude	-7.4	-9.3, -5.4
Adjusted for age and sex	-7.2	-9.1, -5.3
Adjusted for age, sex, and BMI	-6.5	-8.3, -4.7
Adjusted for age, sex, and FFM	-6.7	-8.4, -4.9
Adjusted for age, sex, and comorbidities	-6.6	-8.5, -4.8
Adjusted for age, sex, BMI, FFM, and comorbidities	-6.2	-8.0, -4.4

Results are based on weighted analyses of the study population.

BMI, body mass index; FFM, fat-free mass; CI, confidence interval; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary.

Interaction between knee OA and its risk factors in relation to HRQOL

Next, we investigated whether knee OA interacts with obesity, low FFM, or comorbidities in relation to HRQOL. In men, a significant interaction term (P = 0.002) was observed between the presence of knee OA and low FFM in relation to HRQOL. There was no interaction between knee OA and obesity and knee OA and comorbidities. When performing a sensitivity analysis including fat mass instead of BMI, again no interaction with presence of knee OA was observed in relation to HRQOL. Sensitivity analyses including knee OA based on osteophytes of at least grade 2 instead of all observed osteophytes provided similar results.

Table 3 shows the mean PCS score stratified by presence of knee OA and BMI categories, as well as the adjusted mean difference in PCS score between the strata, using individuals with a normal weight and without knee OA as reference. The adjusted mean difference in PCS score due to the presence of only knee OA (within normal weight individuals) was -5.3 points (95% CI -9.9 to -0.6), the difference in PCS score due to presence of obesity within individuals without knee OA was -2.6 points (95% CI -5.2 to -0.02). When knee OA and obesity concurred, the mean PCS score was -9.4 (95% CI -12.3 to -6.4).

Table 3. PCS mean score and difference, stratified by knee OA and BMI category

	PCS score (mean ± SD)		**Mean difference PCS score (95%CI)***	
BMI	No knee OA	Knee OA	No knee OA	Knee OA
< 25 kg/m^2	56.1 ± 6.4	50.4 ± 8.7	reference	-5.3 (-9.9, -0.6)
25-30 kg/m^2	54.2 ± 8.0	46.8 ± 9.3	-0.9 (-2.8, 1.0)	-7.5 (-10.4, -4.6)
>30 kg/m^2	50.8 ± 9.2	43.4 ± 9.7	-2.6 (-5.2, -0.02)	-9.4 (-12.3, -6.4)

Results are based on weighted analyses of the study population (n = 1,262).

* As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, sex, comorbidities, and percentage FFM.

BMI, body mass index; CI, confidence interval, OA, osteoarthritis; PCS, physical component summary.

Table 4 shows the mean PCS score and adjusted difference stratified by presence of knee OA and tertiles of percentage FFM, separately in men and women. In men with knee OA in the lowest tertile of FFM the mean PCS score was 10.2 (95% CI -14.6 to -5.8) points lower than in the reference category. If no interaction would have been present we would expect a lower PCS score of 3.7 points in men with knee OA (-0.7 points) and in the lowest tertile of FFM (-3.0 points). However, as illustrated in Figure 1, the decrease in mean PCS score between men with concurring knee OA and low FFM as compared with the reference category is higher (-10.2 points) than the summed decreases due to only knee OA or low FFM (-3.7 points). In absence of bias, the additional 64% (6.5 of 10.2 points) of the decrease in PCS score can be attributed to interaction between knee OA and low percentage FFM. No such association was observed in women.

Table 4. PCS mean score and difference, stratified by knee OA and percentage fat-free mass separately in men and women

	PCS score (mean ± SD)		Mean difference PCS score (95%CI)*	
FFM (%)	No knee OA	Knee OA	No knee OA	Knee OA
Men#				
Highest tertile	57.3 ± 6.1	56.3 ± 3.6	reference	-0.7 (-2.9, 1.5)
Middle tertile	54.7 ± 7.5	44.6 ± 8.3	-2.7 (-5.2, -0.1)	-11.8 (-17.1, -6.6)
Lowest tertile	53.2 ± 8.0	45.2 ± 10.7	-3.0 (-5.8, -0.2)	-10.2 (-14.6, -5.8)
Women§				
Highest tertile	55.4 ± 7.1	46.2 ± 9.8	reference	-9.5 (-18.0, -1.0)
Middle tertile	55.1 ± 7.3	48.9 ± 8.8	1.5 (-1.1, 4.2)	-4.4 (-9.1, 0.3)
Lowest tertile	51.2 ± 9.2	44.5 ± 9.5	0.7 (-2.3, 3.6)	-5.0 (-8.8, -1.3)

Results are based on weighted analyses of the study population (n = 568 for men, n = 694 for women).

* As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, comorbidities, and BMI.

Men: highest tertile ≥73.2%, middle tertile 68.7-73.1%, lowest tertile <68.7%.

§ Women: highest tertile ≥58.7%, middle tertile 54.5-58.6%, lowest tertile <54.5%.

BMI, body mass index; CI, confidence interval; FFM, fat-free mass; OA, osteoarthritis; PCS, physical component summary.

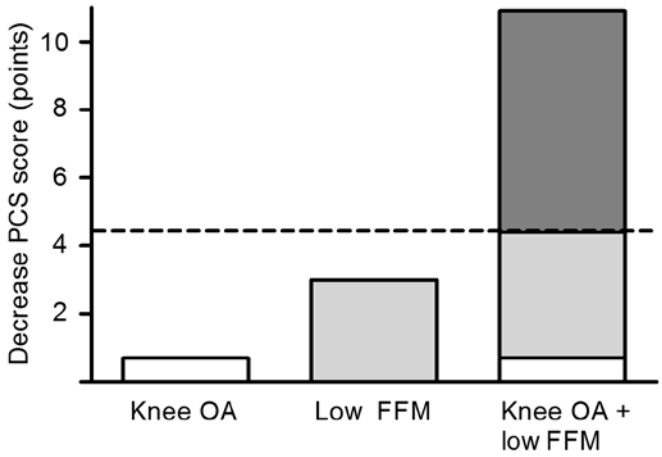

Figure 1. Adjusted decrease in mean physical component summary (PCS) score in men with knee osteoarthritis (OA), low FFM (FFM), or both, compared with men without knee OA and high FFM: decrease due to knee OA (white), decrease due to low FFM (gray), and additional decrease in PCS score due to interaction between concurring knee OA and low FFM (dark gray). The broken line indicates exact additivity of effects. Results are based on weighted analyses of the study population, adjusted for age, sex, comorbidities, and body mass index.

Finally, Table 5 shows the PCS score stratified by presence of knee OA and presence of comorbidities. The adjusted difference in mean PCS score was -6.6 points (95% CI -8.7 to -4.5) due to presence of knee OA and -4.4 points (95% CI -6.2 to -2.7) due to comorbidities. When knee OA and comorbidities concurred, mean PCS score was 9.1 points lower (95% CI -12.6 to -5.7) as compared with the reference category.

Table 5. PCS mean score and difference, stratified by knee OA and comorbidities

	PCS score (mean ± SD)		**Mean difference PCS score (95%CI)***	
Comorbidities	No knee OA	Knee OA	No knee OA	Knee OA
Absent	54.9 ± 7.5	47.7 ± 9.1	reference	-6.6 (-8.7, -4.5)
Present	49.4 ± 9.0	44.1 ± 10.5	-4.4 (-6.2, -2.7)	-9.1 (-12.6, -5.7)

Results are based on weighted analyses of the study population (n = 1,262). Comorbidities include cardiovascular disease, cerebrovascular accident, diabetes and lung disease.

*As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, sex, percentage FFM, and BMI.

CI, confidence interval; OA, osteoarthritis; PCS, Physical Component Summary.

DISCUSSION

This study aimed at evaluating the interaction between knee OA and its risk factors obesity, low percentage FFM (as proxy for muscle mass), and comorbidities in their association with HRQOL, measured by the PCS score. After adjusting for age and sex, the mean PCS score was observed to be 6.2 points lower in individuals with knee OA than in those without. Because 2.5 to 5.0 points difference in PCS score has been described as the minimum clinically important difference in arthritis patients,[27] the observed decrease is clinically relevant.

When knee OA concurred with obesity, low FFM, and comorbidities, interaction was observed between knee OA and low percentage FFM in men, but not with the other risk factors.

Although knee OA and its assessed risk factors have been related to impairment of HRQOL before, this study is the first showing that knee OA may interact with FFM in its relation with HRQOL in a population-based cohort. To our knowledge, an interaction of knee OA with low FFM in relation to HRQOL has not been described before.

The presence of knee OA together with low FFM was associated with a larger impairment of HRQOL than would be expected on the basis of the separate associations of knee OA and low FFM with HRQOL. This observation suggests that concurrence of knee OA and low FFM may result in strengthening of their separate adverse associations with HRQOL. Therefore, it will be of importance to increase FFM in knee OA patients. Although disease-modifying treatment is not yet available for knee OA, the decreased HRQOL in knee OA patients may be prevented by interventions aiming at obesity and the amount of FFM (i.e., reducing weight and strengthening of muscle). Although to a lesser extent, prevention, but also strict control and treatment of comorbidities may maintain or improve HRQOL in knee OA patients.

Our results are supported by a recent study of Messier et al., showing that reducing weight and performing exercises improved HRQOL within knee OA patients.[18] The knowledge that exercising reduces pain and improves physical function in knee OA patients

may provide an explanation.[33] The effect of prevention or treatment of comorbidities on HRQOL in knee OA patients has not been evaluated in a longitudinal study.

In the present study, analyses on FFM were stratified by sex because of the large differences in amount of FFM between men and women. Although previous studies on proxies for muscle mass in relation to HRQOL did not assess men and women separately, our study underscores the utility of sex-stratified analyses. Different results were observed for men and women, as percentage FFM was associated with impaired HRQOL only in men. Within women, the most impaired HRQOL was observed in individuals with knee OA in the highest tertile of FFM. The underlying mechanism for the observed difference is not clear. The amount and intensity of physical activity, probably related to the amount of muscle mass and to HRQOL, may be higher in men than in women. However, additional adjustment for physical activity did not change the results (data not shown). In addition to the observed importance of FFM for HRQOL in men, we observed a stronger association between the amount of muscle mass and presence of knee OA in men than in women in a previous study.[34] Perhaps, the role of muscle mass in both the pathogenesis of knee OA and HRQOL is different between men and women.

A strength of this study is the size of the study population. However, since this is an observational cross-sectional study, residual confounding may still be present. Since the direction of associations cannot be determined, reverse causation may be present. Although several determinants have been measured in this study, not all determinants that may affect quality of life in knee OA patients could be accounted for. An example of such a determinant is the presence and severity of chronic pain.

Knee OA was defined based on the presence of osteophytes assessed by MR imaging instead of, as incorporated in the original ACR criteria, by radiography. Since MR imaging is a more sensitive tool for detection of osteophytes,[35] it could be that we observed more osteophytes than would be detected by radiography, leading to a higher prevalence of knee OA. Therefore, we repeated all analyses including knee OA based on the presence of osteophytes of at least 3 mm (defined as grade 2 and 3) instead of all observed osteophytes. These analyses did not change the results.

We did have MR images of the right knee only. The presence of OA of the left knee (or presence of bilateral knee OA) could therefore not be assessed.

Another limitation is that we did not have information regarding the actual amount of muscle mass or muscle strength. However, FFM consists for a substantial part of muscle mass and has been shown to be correlated with both muscle mass and muscle strength.36 Therefore the percentage FFM is a valuable proxy for muscle mass.

Although we mentioned low muscle mass as a risk factor for knee OA in this study, it may also be a consequence of knee OA because of disuse of muscles due to OA associated knee pain. However, the association between low FFM and impaired HRQOL within knee OA patients applies to all men with knee OA, independent of having low muscle mass as cause or consequence of their knee OA. We also did not have information on history of knee injury, which may act as a confounder in the association between muscle mass and knee OA.

Finally, the presence of comorbidities was based on self-report; unfortunately we did not have information of medical records to check the reliability of the reported comorbidities. However, studies on agreement of self-report and medical record data showed substantial agreement for most of the assessed comorbidities.[37-39]

In conclusion, this study confirms that knee OA is associated with impaired HRQOL. Additional impairment of HRQOL was observed in men because of interaction between concurring knee OA and low FFM. No such interaction with obesity was seen. Interventions aiming at prevention or treatment of obesity or comorbidities could maintain HRQOL in knee OA patients, and interventions aiming at increasing the percentage FFM may result in additional improvement of HRQOL in men with knee OA. Longitudinal research could help to confirm and quantify the beneficial effect of these interventions on HRQOL in knee OA patients.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163-96.
2. Alkan BM, Fidan F, Tosun A, Ardicoglu O. Quality of life and self-reported disability in patients with knee osteoarthritis. Mod Rheumatol 2014;24:166-71.
3. Woo J, Lau E, Lee P, Kwok T, Lau WC, Chan C et al. Impact of osteoarthritis on quality of life in a Hong Kong Chinese population. J Rheumatol 2004;31:2433-8.
4. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res 2005;17:255-63.
5. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133:635-46.
6. Zhang Y and Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355-69.
7. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
8. Anandacoomarasamy A, Caterson ID, Leibman S, Smith GS, Sambrook PN, Fransen M et al. Influence of BMI on health-related quality of life: comparison between an obese adult cohort and age-matched population norms. Obesity (Silver Spring) 2009;17:2114-8.
9. de Zwaan M, Petersen I, Kaerber M, Burgmer R, Nolting B, Legenbauer T et al. Obesity and quality of life: a controlled study of normal-weight and obese individuals. Psychosomatics 2009;50:474-82.
10. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP et al. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med 1997;127:97-104.
11. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. Obes Res 2004;12:913-20.
12. Hoeven TA, Kavousi M, Clockaerts S, Kerkhof HJ, van Meurs JB, Franco O et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. Ann Rheum Dis 2013;72:646-51.
13. Nieves-Plaza M, Castro-Santana LE, Font YM, Mayor AM, Vila LM. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. J Clin Rheumatol 2013;19:1-6.
14. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA 1989;262:907-13.
15. van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95.
16. Ackerman IN and Osborne RH. Obesity and increased burden of hip and knee joint disease in Australia: results from

a national survey. BMC Musculoskelet Disord 2012;13:254.
17. Tuominen U, Blom M, Hirvonen J, Seitsalo S, Lehto M, Paavolainen P et al. The effect of co-morbidities on health-related quality of life in patients placed on the waiting list for total joint replacement. Health Qual Life Outcomes 2007;5:16.
18. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263-73.
19. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
20. de Zwart BC, Broersen JP, van der Beek AJ, Frings-Dresen MH, Van Dijk FJ. Occupational classification according to work demands: an evaluation study. Int J Occup Med Environ Health 1997;10:283-95.
21. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
22. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005;34:95-102.
23. Ritchie JD, Miller CK, Smiciklas-Wright H. Tanita foot-to-foot bioelectrical impedance analysis system validated in older adults. J Am Diet Assoc 2005;105:1617-9.
24. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985) 2000;89:81-8.
25. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.
26. Ware JE, Jr. and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
27. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE, Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43:1478-87.
28. Korn EL and Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health 1991;81:1166-73.
29. Lumley T. Analysis of complex survey samples. 2004. http://www.jstatsoft.org/v09/i08/paper
30. Misisterie van VWS. Hoeveel mensen hebben overgewicht? 2013. http://www.rivm.nl/ nldemaat
31. Vandenbroucke JP, Von EE, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4:e297.
32.

33. de Mutsert R, de Jager DJ, Jager KJ, Zoccali C, Dekker FW. Interaction on an additive scale. Nephron Clin Pract 2011;119:c154-c157.
34. Fransen M and McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2008;CD004376.
35. Visser AW, de Mutsert R, Loef M, le Cessie S, den Heijer M, Bloem JL et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. Osteoarthritis Cartilage 2014;22:197-202.
36. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). BMJ 2012;345:e5339.
37. Lafortuna CL, Maffiuletti NA, Agosti F, Sartorio A. Gender variations of body composition, muscle strength and power output in morbid obesity. Int J Obes (Lond) 2005;29:833-41.
38. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. Am J Epidemiol 1997;145:762-9.
39. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol 2004;57:1096-103.
40. Machon M, Arriola L, Larranaga N, Amiano P, Moreno-Iribas C, Agudo A et al. Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study. J Epidemiol Community Health 2013;67:71-5.

Supplementary table. Unweighted baseline characteristics of 1,262 participants of the NEO study with an over-sampling of BMI ≥ 27 kg/m^2

		Total population n = 1,262	**Knee OA n = 229**	**No knee OA n = 1,033**
Age (year)		56 (50-61)	57 (53-61)	56 (50-61)
Sex (% women)		55	66	52
Education (% high)		32	31	32
Profession (% high physically demanding)		12	11	12
BMI (kg/m^2)		30.0 (27.9-33.0)	31.0 (28.3-34.3)	29.9 (27.8-32.6)
FFM (kg)	Men	71.3 (67.6-74.5)	70.6 (67.4-73.8)	71.5 (67.8-74.5)
	Women	56.6 (53.5-59.9)	55.8 (52.4-58.7)	56.8 (53.7-60.1)
Comorbidities (%)		20	30	18
- Cardiovascular disease		7	8	6
- Cerebrovascular accident		2	2	2
- Diabetes		11	15	10
- Lung disease		7	15	4
SF-36 MCS score		50.5 ± 9.5	50.8 ± 10.2	50.4 ± 9.4
SF-36 PCS score		51.2 ± 9.4	44.9 ± 9.7	52.6 ± 8.7

Values are the percentage, median (25th to 75th percentiles), or mean ± SD.

BMI, body mass index; FFM, fat-free mass; MCS, mental component summary; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary; SF-36, Short Form 36 health survey.

PART II

Identification of appropriate outcome measurements for hand OA research

CHAPTER 7

Instruments measuring pain, physical function or patient global assessment in hand osteoarthritis – a systematic literature search

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ABSTRACT

Objective
Description of use and metric properties of instruments measuring pain, physical function or patient global assessment in hand osteoarthritis (OA).

Methods
Medical literature databases up to January 2014 were systematically reviewed for studies reporting on instruments measuring pain, physical function or patient global assessment in hand OA. The frequency of the use of these instruments were described, as well as their metric properties, including discrimination (reliability, sensitivity to change), feasibility and validity.

Results
In 66 included studies, various questionnaires and performance- or assessor-based instruments were applied for evaluation of pain, physical function or patient global assessment. No major differences regarding metric properties were observed between the instruments although the amount of supporting evidence varied. The most frequently evaluated questionnaires were the Australian/Canadian Hand OA Index (AUSCAN) pain subscale and visual analogue scale (VAS) pain for pain assessment and the AUSCAN function subscale and Functional Index for Hand OA (FIHOA) for physical function assessment. Excellent reliability was shown for the AUSCAN and FIHOA and good sensitivity to change for all mentioned instruments; additionally the FIHOA had good feasibility. Good construct validity was suggested for all mentioned questionnaires. The most commonly applied performance- or assessor-based instrument were grip and pinch strength for assessment of physical function, in addition to assessment of pain by palpation. For these measures good sensitivity to change and construct validity were established.

Conclusion
The AUSCAN, FIHOA, VAS pain, grip and pinch strength and pain on palpation were most frequently tested and provided most supporting evidence for good metric properties. More research has to be performed to compare the different instruments to each other.

INTRODUCTION

Hand osteoarthritis (OA) is a highly prevalent disorder, characterized by bony enlargements and deformities.[1-3] Most studies on individuals with OA are based on the general population. Individuals with hand OA can experience symptoms as pain, decreased grip strength and disability, leading to a high clinical burden.[4-6] In clinical practice, treatment for patients with hand OA (individuals with hand OA seeking health care) is administrated to decrease symptoms and improve function, however the evidence to support these treatments is limited since few high-quality clinical trials have been performed in hand OA.[7,8]

An important problem in the lack of high-quality clinical trials in hand OA is the lack of standardization of outcome measures.[8] Therefore, the Outcome Measures in Rheumatology (OMERACT) and Osteoarthritis Research Society International Task Force on Clinical Trials Guidelines defined core domains to describe outcomes in clinical trials on symptom modification, comprising pain, physical function and patient global assessment.[9-12]

For assessment of these domains, several patient reported outcome (PRO) measures are available. Hand OA specific questionnaires as the Functional Index for Hand OA (FIHOA) and Australian/Canadian Hand OA Index (AUSCAN),[13,14] but also hand disorder or arthritis specific questionnaires as the Michigan Hand Outcomes Questionnaire (MHQ), Arthritis Impact Measurement Scale-2 (AIMS-2) and Health Assessment Questionnaire (HAQ) have been developed to assess one or more of these domains.[15-17] In addition, physical function can be assessed using performance-based measures such as grip or pinch strength or the Arthritis Hand Function Test (AHFT). In addition to self-report and performance-based instruments, assessor-based measures such as joint tenderness upon palpation are used for assessment of pain.[18,19] Besides the above mentioned questionnaires and assessor- or performance-based measures, several other instruments, which will be described in this manuscript, are used for clinical assessment of hand OA. Although most available instruments have been shown to be reliable for measurement of pain, physical function or patient global assessment, a systematic comparison of the different instruments for assessment of hand OA has not been performed.

Our study was conducted in the framework of the OMERACT hand OA working group, aiming to identify instruments for measurement of pain, physical function and patient global assessment in hand OA which can be recommended for use in clinical trials on OA. Therefore, insight into available instruments and their metric properties is needed. To this end, we performed a systematic literature review aiming to describe the frequency of use of available instruments measuring pain, physical function or patient global assessment in studies on hand OA, and to describe the metric properties of these instruments.[20] Metric properties were described using the OMERACT filter,[21] focusing on aspects of discrimination (reliability and sensitivity to change), feasibility and truth (validity).

METHODS

Study design and identification of studies

The study design and performance followed the PRISMA guidelines.[20] In cooperation with a medical librarian (JWS), a systematic literature search was performed to obtain all man-

uscripts reporting on instruments measuring pain, physical function or patient global assessment in hand OA. Medical literature databases (PubMed, Embase, Web of Science, COCHRANE, CINAHL, Academic Search Premier and ScienceDirect) were searched from the date of their inception up to January 2014, using all variations of the following key words 'hand', 'osteoarthritis', 'outcome assessment', 'reliability', 'sensitive', 'feasibility' and 'validity' (see supplementary file for exact search strings).

Inclusion and exclusion criteria

First all retrieved titles were screened, subsequently selected abstracts were reviewed and finally full text articles of the remaining references were read by one reviewer (AWV). A random sample of 200 titles (9% of the titles identified by literature search) was also reviewed by a second reviewer (MK). Because of the similar selection of titles further extraction was done by a single reviewer but in case of uncertainties, these were discussed and solved by consensus.

Studies reporting on metric properties of instruments assessing pain, physical function and patient global assessment in hand OA were included. The metric properties of the studied instruments were described according to four items: reliability, sensitivity to change, feasibility and validity, inclusion criteria differed per item:

- Reliability was described based on studies evaluating the reliability of one or more instruments performed more than once in the same group of patients, either by the same performer over time or by different performers during one study visit. Both cross-sectional and longitudinal studies were included.
- Sensitivity to change was described based on longitudinal studies evaluating change of pain, physical function or patient global assessment in hand OA measured by one or more instruments.
- Feasibility was described based on studies evaluating this item of one or more instruments.
- Validity was described based on studies comparing different instruments assessing pain, physical function or patient global assessment in the same patients. Again, both cross-sectional and longitudinal studies were included.

Studies that fulfilled the requirements for at least one of these four items were included in this review. In order to be able to generalize the description of metric properties of the applied instruments to different populations, evaluation by only one study was considered as insufficient evidence to draw conclusions. Therefore, only instruments that were assessed by at least two studies were included in the description of metric properties.

Studies reporting on surgical interventions, less than 25 patients having hand OA or on diseases other than hand OA were excluded, as well as animal studies, reviews, abstracts, letters to the editor and studies in languages other than English. Because of the recently published systematic literature review on outcome measures in trapeziometacarpal OA by Marks et al.,[22] studies reporting only on trapeziometacarpal OA were also excluded.

Data extraction

A self-made standardized form was used to extract information on the following data: (1) Study population (population size, setting, age, sex), (2) Instruments and assessed domains, (3) Study design and follow-up duration, (4) Results concerning: measures of

reliability (intraclass correlation coefficient (ICC), kappa-value, percentage of agreement, smallest detectable difference (SDD)), sensitivity to change (percentage of change, amount of change, standardized response mean (SRM)), feasibility (time needed to perform outcome measure), validity (correlation, association and measures of agreement between different instruments assessing the same domain). From 6 random studies data were also extracted by MK, resulting in similar extracted data. All extracted results were discussed by both reviewers to avoid missing information.

Statistical analyses

Because of the heterogeneity of the studies with respect to the evaluated instruments it was not possible to perform a meta-analysis. Therefore, we performed a descriptive review.

RESULTS

Literature flow

In total 4,351 titles were identified, 2,244 unique references were left for screening after removing duplicate references (Figure 1). During the screening, 2,008 references could be removed based on title. After reviewing 236 abstracts and 92 full-text articles, 66 studies satisfied the inclusion criteria (Table 1).

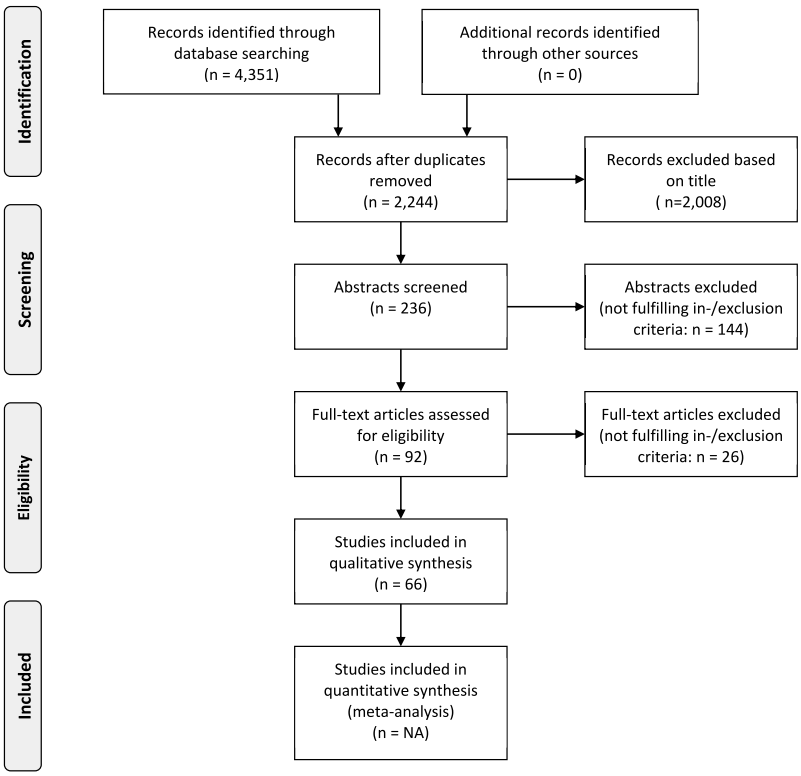

Figure 1. Overview of literature research

Table 1. Overview of included studies (n = 66)

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Allen, 2006[23]	GOGO study (familial OA), 531 (80), 68	Bony enlargement, KL≥2 in ≥1 DIP	Observational, mean FU 4 years	- AUSCAN (Likert) - Grip/pinch strength
Allen, 2006[24]	GOGO study, 878 (80), 69	Bony enlargement, KL≥2 in ≥1 DIP	Observational, cross-sectional	- AUSCAN (Likert) - Self-reported pain (0-3) - Grip/pinch strength
Altman, 2009[45]	Secondary care, 385 (77), 64	ACR criteria	RCT (intervention >control)* duration 8 weeks	- AUSCAN (VAS) - VAS pain, global
Backman, 1997[18]	Secondary care, 26 (88), 67	OA ≥2 joints, rheumatologist confirmed	Observational, test-retest after 2 weeks	- OMFAQ - AHFT
Barthel, 2010[46]	Secondary care, 783 (80), 64	ACR criteria,KL≥1, symptoms ≥1 year	RCT (intervention > control), duration 8 weeks	- AUSCAN (VAS) - VAS pain, global
Bellamy, 2002[25]	Study 1: secondary care, 50 (80), 60 Study 2: secondary care, 44 (86), 60	ACR criteria	Study 1: Observational, test-retest after 1 week Study 2: Intervention, duration 6 weeks	Study 1 and 2: - AUSCAN (Likert, VAS) - FIHOA (original, Likert, VAS) Study 1 only: - HAQ, HAQ pain scale - Global pain/function(0-4) - Modified Doyle Index - Grip/pinch strength
Bijsterbosch, 2010[19]	GARP study (familial polyarticular OA), 260 (84), 65	ACR criteria	Observational, cross-sectional	- AUSCAN (Likert) - Doyle index
Bijsterbosch, 2011[82]	GARP study, 289 (83), 60	ACR criteria	Observational, FU 6 years	- AUSCAN (Likert)
Botha-Scheepers, 2008[83]	GARP study, 289 (83), 60	ACR criteria	Observational, FU 2 years	- AUSCAN (Likert) - Pain intensity score (pain on pressure, 0-60)
Brosseau, 2005[47]	Secondary care, 88 (78), 65	ACR criteria, radiographic OA	RCT (intervention=control)# duration 6 weeks	- AUSCAN (Likert) - VAS pain - Grip/pinch strength
Dilek, 2013[48]	Secondary care, 56 (89), 59	ACR criteria, bilateral	RCT (intervention > control), duration 3 weeks	- AUSCAN (not specified) - FIHOA - VAS pain rest/during ADL - Grip/pinch strength - No. painful/tender joints
Dreiser, 1993[49]	Secondary care, 60 (85), 59	Radiographic OA	RCT (intervention > control), duration 2 weeks	- FIHOA - VAS pain - Pain movement/pressure (1-5)
Dreiser, 1995[13]	Secondary care, 200 (84), 66	Radiographic OA	Observational, cross-sectional	- FIHOA - VAS pain

Table 1. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Dreiser, 2000[26]	Not specified, 261 (92), 61	ACR criteria, radio-graphic OA≥2 joints bilateral, symptoms	RCT (effect not specified), duration 6 months	- FIHOA - VAS pain - Grip strength
Dziedzic, 2007[27]	Primary care, 55 (60), 67	Hand problems (symptoms, nodes)	Observational, test-retest after 1 month	- AUSCAN (Likert) - Grip/pinch strength, GAT
Dziedzic, 2013[50]	Primary care, 257 (66), 66	ACR criteria	RCT (intervention > control), duration 6 months	- AUSCAN (not specified) - ASES pain - Average pain severity (0-10) - Satisfaction hand function (0-10) - Severity functional problem (0-10) - Grip/pinch strength, GAT
Fernandes, 2012[28]	Secondary care, 211 (95), 63	ACR criteria	Observational, FU 3 months	- AUSCAN (Likert) - ASES pain - COPM - MAP-hand - Modified HAQ - Grip strength, GAT
Fioravanti, 2014[51]	Primary care, 60 (87), 71	ACR criteria, symptomatic	RCT (intervention > control), duration 2 weeks	- FIHOA - HAQ - VAS pain
Flynn, 1994[52]	Secondary care, 26 (88), range 52-82	ACR criteria	RCT (intervention > control), duration 2 months	- Disease severity (1-10) - Global assessment (1-6) - Grip strength - No. painful/tender joints
Gabay, 2011[53]	Secondary care, 162 (74), 63	ACR criteria, radio-graphic OA≥2 joints ≥2 flares finger OA	RCT (intervention > control), duration 6 months	- FIHOA - VAS pain - Grip strength
Garfinkel, 1994[54]	Not specified, 25 (56), range 52-79	ACR criteria	RCT (intervention > control), duration 10 weeks	- Pain rest/activity (not specified) - Hand function (not specified) - Grip strength - Tenderness
Grifka, 2004[55]	Secondary care, 594 (83), 62	ACR criteria, symptomatic ≥3 months	RCT (intervention > control), duration 4 weeks	- AUSCAN (Likert) - HAQ - VAS pain, global - Grip strength
Haugen, 2009[29]	Secondary care, 83 (93), 60	ACR criteria,KL≥2, ≥1 swollen/tender joint, VAS pain ≥30	RCT (intervention > control), duration 42 days	- AUSCAN (not specified) - VAS pain, global - No. tender joints
Haugen, 2011[30]	Secondary care (Oslo hand OA cohort), 209 (91), 62	ACR criteria	Observational, FU 7 years	- AIMS-2 - FIHOA - AUSCAN (Likert)

Table 1. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Haugen, 2013[84]	Oslo hand OA cohort, 209 (91), 62	ACR criteria	Observational, FU 7 years	- AUSCAN - Grip strength - No. tender joints
Hirsch, 1999[31]	Women's Health and Aging Study, 919 (100), age ≥65	ACR criteria	Observational, cross-sectional	- Pain/tenderness (no./intensity (0-3)) - Grip/pinch strength
Horvath, 2011[56]	Secondary care, 63 (81), 63	ACR criteria, radiographic OA, pain ≥3 months	RCT (intervention > control), duration 3 weeks	- HAQ - VAS pain (rest/exertion), global - Grip/pinch strength - No. tender joints
Kanat, 2013[57]	Not specified, 50 (100), 63	ACR criteria	RCT (intervention > control), duration 10 days	- AUSCAN (not specified) - Cochin scale - Pain rest/motion (0-10) - Grip/pinch strength
Keen, 2010[58]	Secondary care, 36 (86), 58	ACR criteria or radiographic OA	Intervention, FU 4 weeks (after injection)	- AUSCAN (VAS) - VAS pain (most painful/all), global
Kjeken, 2011[59]	Secondary care, 70 (97), 61	ACR criteria	RCT (intervention = control), duration 3 months	- AUSCAN (Likert) - COPM (0-10) - Modified HAQ - VAS pain, global
Kovacs, 2012[60]	Secondary care, 45 (93), 59	ACR criteria, KL≥2 in ≥2 joints, VAS pain ≥30	RCT (intervention > control), duration 3 weeks	- AUSCAN (Likert) - HAQ - VAS pain - Grip strength
Kvien, 2007[61]	Secondary care, 83 (93), 60	ACR criteria,KL≥2, ≥1 swollen/tender joint, VAS pain ≥30	RCT (intervention > control), duration 42 days	- AUSCAN (not specified) - VAS pain, global - No. tender joints
Kwok, 2011[62]	Secondary care, 195 (87), 59	Diagnosed by rheumatologist	Observational, FU 3 months	- AUSCAN (Likert)
MacIntyre, 2009[32]	Community-dwelling, 99 (80), 67	ACR criteria (dominant hand)	Observational, cross-sectional	- AIMS-2 - Dexterity - Grip strength
MacIntyre, 2010[33]	Community-dwelling, 104 (81), 68	ACR criteria (dominant hand)	Observational, cross-sectional	- PRWHE - Dexterity - Grip/pinch strength
Marshall, 2013[85]	Primary care, 1076 (60), 65	Hand symptoms	Observational, FU 3 years	- AUSCAN (Likert)
Moe, 2010[34]	Secondary care (Oslo hand OA cohort), 128 (91), 69	ACR criteria	Observational, test-retest after 1 week	- AIMS-2 - AUSCAN (not specified) - FIHOA - HAQ - VAS pain - Grip strength - MPUT
Moratz, 1986[63]	Population/secondary care, 77 (73), 69	Not specified	Intervention, duration 12 weeks	- Disability (0-3) - Grip/pinch strength

Table 1. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Myers, 2011[35]	Primary care, 55 (60), 66	Hand pain/problems	Observational, test-retest after 1 month	- Interview on hand problems - Pain (0-10) - Grip/pinch strength, GAT - Pain/tenderness palpation
Myrer, 2011[64]	Volunteers, 35 (77), 64	ACR criteria, FIHOA >5	RCT (intervention > control), duration 4 weeks	- FIHOA - VAS pain (rest/movement)
Pastinen, 1988[65]	Secondary care, 29 (79), 58	Clinical/radio-graphic finger OA	RCT (intervention > control), duration 14 weeks	- VAS pain (during grip/pinch) - Grip/pinch strength
Poiraudeau, 2001[36]	Secondary care, 89 (91), 63	ACR criteria	Observational, FU 6 months	- Cochin scale - FIHOA - Revel functional index - Ritchie articular index - VAS pain, handicap
Poole, 2010[37]	Population based (senior centres), 40 (60), 63	Diagnosis of OA (not specified), symptoms	Observational, test-retest 1 week	- Cochin scale - FIHOA - MHQ - AHFT - HFI, HAMIS
Reeves, 2000[66]	Not specified, 27 (59), 64	Radiographic OA, pain	RCT (intervention > control), FU 6 months (after injection)	- VAS pain (rest/movement/grip) - Flexion motion
Rintelen, 2009[38]	Secondary care, 71 (91), 60	ACR criteria	Observational, cross-sectional	- Short Form-SACRAH - Modified-SACRAH
Rogers, 2007[67]	Secondary care, 55 (80), 72	KL≥2	Intervention, duration 2 years	- AIMS-2 - Pain (0-10) - Grip strength
Rogers, 2009[68]	Community-based, 46 (87), 75	KL≥2	RCT (intervention = control), duration 6 weeks	- AUSCAN (VAS) - Dexterity - Grip/pinch strength
Romero -Cerecero, 2013[69]	Not specified, 113 (95), 62	ACR criteria, radio-graphic OA≥2 joints VAS≥40, FIHOA≥5	RCT (intervention = control), duration 4 weeks	- FIHOA - VAS pain
Rothacker, 1994[70]	Not specified, 49 (84), 66	Physician/ radio-graphic confirmed OA, symptoms	RCT (intervention > control), FU 45 minutes (after cream)	- Pain 0-5
Rothacker, 1998[71]	Secondary care, 81 (74), 61	Physician confir-med OA, symptoms	RCT (intervention > control), FU 45 minutes (after cream)	- Pain 0-5

Table 1. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Sautner, 2004[39]	Secondary care, 60 (73), 62	ACR criteria	Observational, cross-sectional	- SACRAH, modified-SACRAH - VAS global
Sautner, 2008[40]	Secondary care, 66 (77), 58	ACR criteria	Observational, cross-sectional	- AUSCAN (VAS) - SACRAH, modified-SACRAH - VAS global
Saviola, 2012[72]	Secondary care, 38 (95), 61	Radiographic erosive OA ≥2 joints, VAS ≥40	RCT (intervention 1 > intervention 2), duration 2 years (intervention 2 only 1y)	- FIHOA - VAS pain, global - Grip strength - No. tender joints
Schnitzer, 1994[73]	Not specified, 59 (68), 68	Radiographic/ physical OA findings	RCT (intervention > control), duration 9 weeks	- HAQ - VAS pain - Grip strength - Joint tenderness (by dolorimeter)
Seiler, 1983[74]	Secondary care, 41 (90), median 63	Radiographic OA, ≥3 painful/tender joints, ≥1 inflamed Heberden node	RCT (intervention > control), duration 4 weeks	- No. painful joints - Grip strength - Pain index (no./intensity (0-3))
Shin, 2013[75]	Secondary care, 86 (97), 58	ACR criteria	RCT (intervention = control), duration 12 weeks	- AUSCAN (not specified) - HAQ - VAS global - No. tender joints
Stamm, 2007[41]	Secondary care, 100 (87), 61	Bony swelling ≥1 DIP/PIP, pain/ bony swelling ≥1 CMC1	Observational, cross-sectional	- AIMS-2 - AUSCAN (not specified) - Cochin scale - FIHOA - HAQ - SACRAH, modified-SACRAH - Grip strength - JTHFT, MPUT, button Test
Stamm, 2002[76]	Secondary care, 40 (88), 60	ACR criteria	RCT (intervention > control), duration 3 months	- HAQ - VAS pain, global - Grip strength
Stange -Rezende, 2006[77]	Secondary care, 45 (93), 60	ACR criteria	RCT (intervention = control), duration 3 weeks	- AUSCAN (Likert) - VAS pain (general/hands), global - Grip strength - MPUT
Stukstette, 2013[78]	Secondary care, 151 (83), 59	ACR criteria	RCT (intervention = control), duration 3 months	- AUSCAN (Likert) - COPM - Grip/pinch strength
Tubach, 2012[42]	Secondary care, 249 (88), 64	ACR criteria	Intervention, FU 4 weeks	- VAS pain, global, functional disability

Table 1. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Definition of hand OA	Study design	Applied instruments
Verbruggen, 2011[79]	Secondary care, 60 (85), 61	ACR criteria	RCT (intervention = control), duration 1 year	- AUSCAN (not specified) - Grip strength - No. tender joints
Wenham, 2012[80]	Not specified, 70 (81), 61	ACR criteria	RCT (intervention = control), duration 4 weeks	- AUSCAN (VAS) - VAS pain (average/worst joint), global - No. tender joints
Widrig, 2007[81]	Primary and secondary care, 204 (74), 64	ACR criteria, radio-graphic OA≥2 joints VAS≥40, FIHOA≥5	RCT (intervention = control), duration 3 weeks	- FIHOA - VAS pain - No. tender joints
Wittoek, 2009[43]	Secondary care, 72 (89), 62	ACR criteria	Observational, cross-sectional	- AUSCAN (Likert) - FIHOA - VAS pain
Ziv, 2008[44]	Not specified, 32 (100), 70	ACR criteria	Observational, test-retest after 1 week	- Gip/pinch strength

*Intervention group performed better than control group, according to primary outcome measure.
Intervention group did not perform better than control group, according to primary outcome measure.
ADL, activities of daily living; AHFT, Arthritis hand function test; AIMS-2, Arthritis Impact Measurement Scale; ASES, Arthritis Self Efficacy Scale; AUSCAN, Australian/Canadian Hand OA Index; ACR, American College of Rheumatology; CMC1, 1st carpometacarpal joint; COPM, Canadian Occupational Performance Measure; DIP, distal interphalangeal joint; FIHOA, Functional Index for Hand Osteoarthritis; FU, follow-up; GARP, Genenetics osteoArthritis and Progession; GAT, grip ability test; GOGO, Genetics of Generalized Osteoarthritis; HAQ, Health Assessment Questionnaire; JTHFT, Jebsen-Taylor Hand Function Test; KL, Kellgren-Lawrence; MAP-hand, Measure of Activity Performance; MHQ, Michigan Hand Outcomes Questionnaire; MPUT, Moberg Picking Up Test; no., number; OA, osteoarthritis; OMFAQ, OARS (Older Americans' Resources and Services) Multidimensional Functional Assessment Questionnaire; PIP, proximal interphalangeal joint; PRWHE, Patient-Rated Wrist/Hand Evaluation; RCT, randomized controlled trial; SACRAH, Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; VAS, visual analogue scale.

Clinical outcome measures

The instruments that were used for assessment of the OMERACT core domains pain, physical function and patient global assessment in the 66 identified studies are specified in Table 2. Different instruments were applied, comprising twelve questionnaires, one interview and a number of rating scales (visual analogue scale (VAS), numeric rating scale (NRS) or Likert). Furthermore, nine different performance- or assessor-based measures were applied for assessment of physical function; pain was assessed by palpation, using the number of painful or tender joints, the Doyle index or Ritchie articular index.

The AUSCAN was most frequently applied (n = 34), followed by the VAS pain (n = 30), VAS global (n = 16), FIHOA (n = 14) and HAQ (n = 12). The AIMS-2 was applied in five studies, the Cochin scale and Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (SACRAH) in four studies, the Canadian Occupational Performance Measure (COPM) in three studies and the Arthritis Self Efficacy Scale (ASES) in two studies. The Measure of Activity Performance (MAP-hand), MHQ, Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire (OMFAQ), Patient-Rated Wrist/Hand Evaluation (PRWHE) and Revel functional index were all used in only one study each.

Of the performance- or assessor-based measures, grip strength was applied most frequently (n = 35), followed by pain or tenderness on palpation (n = 21). Other applied performance- or assessor-based measures were pinch strength (n = 17), the grip ability test (GAT) (n = 4), Moberg Pickup Test (MPUT) (n = 3), Arthritis Hand Function Test (AHFT) (n = 2), evaluation of dexterity (n = 3), button test (n = 1), Hand Mobility in Scleroderma Test (HAMIS) (n = 1), Hand Functional Index (HFI) (n = 1) and the Jebsen-Taylor Hand Function Test (JTHFT) (n = 1).

Table 2. Instruments measuring pain, physical function or patient global assessment applied in the included studies

	Domain	Specifications	No. studies applied
Questionnaires			
AIMS-2[16]	Physical function	78 items, rated on 5 point scale. Transformed into 12 scales, score range 0 - 10 (worst possible). 1 scale for hand/finger function.	5
ASES[89]	Pain, physical function	20 items, scored 10 (very uncertain) – 100 (very certain to can do). 3 subscales: pain/function /other symptoms, scored by taking mean of subscale items (range 10-100).	2
AUSCAN[14]	Pain, physical function, global assessment	15 items, Likert (0, none - 4, extreme) / VAS version. Summed into 3 subscales: pain (Likert range 0-20 / VAS range 0-100), stiffness (0-4 / 0-100), function (0-36 / 0-100).	34
Cochin scale[90]	Physical function	18 items, rated on Likert scale (0, without difficulty – 5, impossible). Summed to final score, range 0-90.	4
COPM[91]	Physical function	Interview on most important activities. Five most important activities scored for performance /satisfaction (1-10). Subscale scores range 0 (not able to do/satisfied) – 10 (extremely able to do/satisfied).	3
FIHOA[13]	Physical function	10 items, range 0 (no difficulty) – 3(impossible). Total score range 0-30. Original, VAS, Likert version.	15
HAQ[17]	Physical function	20 items. Total score range 0 to 3 (higher score indicates poorer functioning).	12
MAP-hand[92]	Physical function	18 items, range 0 (no difficulty) – 4 (not able to do). Total mean score calculated.	1
MHQ[15]	Pain, physical function,	37 items, rated on 5 point Likert (1,very good – 5, very poor). Scores normalized to 0-100 scale.	1
OMFAQ[93]	Physical function	5 domains of functioning, scored 1 (excellent) – 6 (total impaired). Total score range 5-30. Physical / instrumental ADL scale.	1
PRWHE[94]	Physical function	15 item scale, rated on 0-10 NRS. Summed to subscales: pain (0-50), disability (0- 60).	1
Revel functional index[95]	Physical function	10 questions, rated 0 (without difficulty) – 2 (impossible). Total score range 0-20.	1
SACRAH[96]	Pain, physical function	23 questions, rated on VAS scale. 3 domains: functional status, stiffness, pain. Original, Short-Form, Modified version.	4
VAS[97] / NRS / Likert	Pain, physical function, global assessment	Used for assessment of pain, patient global assessment, functioning, perceived strength, etcetera.	43

Table 2. *Continued*

	Domain	Specifications	No. studies applied
Performance- or assessor-based instruments			
AHFT[18]	Physical function	11-item test, 4 subscales: grip/pinch strength, dexterity, applied dexterity, applied strength. Score per subscale.	2
Button Test[98]	Physical function	Unbutton and button 5 buttons, using a standard board. Score recorded in seconds.	1
Dexterity	Physical function	Assessed using dexterity/purdue pegboard	2
GAT[99]	Physical function	Modification of Grip Function Test. 3 items, timed (sec) and summed to total GAT score. GAT score <20 sec = normal.	4
Grip strength	Physical function	Measured in mmHg or in kg.	35
HAMIS[100]	Physical function	9 items rated 0 (no problems performing the motion) – 3 (unable). Total score range 0-27	1
HFI[101]	Physical function	9 wrist/hand items from Keitel Function Test, measuring motion patterns. Items ranged 0 (no difficulties) – 3 (much difficulties). Total score 0-52 (0-26 for each upper extremity)	1
JTHFT[102]	Physical function	7 items, timed in seconds. Summed to total score.	1
MPUT[103]	Physical function	Picking up 10 items and placing in container, timed in seconds.	3
Pinch strength	Physical function	Measured in mmHg or in kg.	17
Tenderness/ Pain on palpation, Doyle[104] / Ritchie articular index[105]	Pain	Tenderness on palpation. Score range Doyle total 0-144, Doyle hand 0-72 Score range Ritchie articular index 0-60	21

AHFT, Arthritis hand function test; AIMS-2, Arthritis Impact Measurement Scale; ADL, activities of daily living; OARS, Older Americans' Resources and Services; ASES, Arthritis Self Efficacy Scale; AUSCAN, Australian/Canadian Hand OA Index; COPM, Canadian Occupational Performance Measure; FIHOA, Functional Index for Hand OA; GAT, Grip ability test; HAQ, Health Assessment Questionnaire; HAMIS, Hand Mobility in Scleroderma Test; HFI, hand functional index; JTHFT, Jebsen-Taylor Hand Function Test; MAP-hand, Measure of Activity Performance; MHQ, Michigan Hand Outcomes Questionnaire; MPUT, Moberg Picking Up Test; NRS, numeric rating scale; OMFAQ, OARS (Older Americans' Resources and Services) Multidimensional Functional Assessment Questionnaire; PRWHE, Patient-Rated Wrist/ Hand Evaluation; ROM, Range of motion; SACRAH, Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; VAS, Visual Analogue Scale.

Table 3. Metric properties of instruments measuring pain, physical function or patient global assessment – reliability*

	First author	Relevant results
Questionnaires		
AUSCAN	Bellamy[25]	ICC (Likert / VAS):
		- pain: 0.70 / 0.84
		- function: 0.86 / 0.90
	Dziedzic[27]	ICC:
		- pain: 0.88
		- function: 0.87
	Haugen[30]	ICC
		- pain: 0.93
		- function: 0.94
		- total: 0.96
	Moe[34]	ICC, SDD:
		- pain: 0.80, 1.06
		- function: 0.92, 0.80
		- total: 0.87, 0.76
Cochin scale	Poiraudeau[36]	Interrater ICC: 0.96
	Poole[37]	ICC: 0.94
FIHOA	Dreiser[13]	ICC: 0.95, mean difference 0.17 ± 1.64
	Haugen[30]	ICC: 0.88
	Moe[34]	ICC: 0.94, SDD 5.55
	Poole[37]	ICC: 0.74
	Wittoek[43]	ICC: 0.96
Performance- or assessor-based instruments		
Grip strength	Myers[35]	Inter-/intra-observer ICC: range per hand 0.91-0.94 / 0.90-0.92
	Ziv[44]	SDD (right, left): 2.48, 1.94
Pinch strength	Myers[35]	Inter-/intra-observer ICC: range per test/hand 0.87-0.94 / 0.89-0.96
	Ziv[44]	SDD (right, left): range per test 0.40-0.54, 0.42-0.63
Tenderness/pain on palpation	Bijsterbosch[19]	Inter-/intrarater ICC of Doyle index: 0.88 / range per rater 0.94-0.97
	Myers[35]	Inter-/intra-observer κ (% agreement): 0.64 / 0.69 (95 / 96)

* Only instruments assessed in ≥2 studies were included in this table.

AUSCAN, Australian/Canadian Hand OA Index; FIHOA, Functional Index for Hand; ICC, intraclass correlation coefficient; κ, kappa; SDD, smallest detectable difference; VAS, visual analogue scale.

Study characteristics

The characteristics of the 66 included studies are described in Table 1. The source populations were predominantly secondary care (n = 41), in addition to primary care (n = 6), population-based (n = 6) and familial OA studies (n = 5). All studies included more women than men and the mean age was >50 years in almost all studies. Different study designs were included; 26 observational studies, 35 randomized controlled trials and four intervention studies.

Of the included studies, 25 studies primarily aimed at evaluation of metric properties of one or more instruments measuring pain, physical function or patient global assessment.[13,18,19,23-44] The remaining studies applied these instruments to evaluate the effect of a treatment or intervention (n = 37),[45-81] or to evaluate disease course over time (n = 4).[82-85]

Metric properties of clinical outcome measures

Discrimination: Reliability

Only eleven studies provided data on measures of reliability, including seven instruments.[13,19,25,27,30,34-37,43,44] The FIHOA and AUSCAN were most frequently evaluated (see Table 3). The AHFT and GAT were evaluated in only one study each.[18,35] The reported measures of reliability of instruments that were assessed in at least two studies are listed in Table 3.

In general, all evaluated instruments showed good measures of reliability. Three studies evaluated two questionnaires for assessment of physical function, enabling direct comparison of these measures.[34,37] Haugen et al. reported excellent reliability for both the AUSCAN function subscale and FIHOA,[30] Moe et al. reported the same in addition to comparable SDDs for both questionnaires.[34] Poole et al. evaluated the FIHOA in addition to the Cochin scale, reporting the highest ICC for the Cochin scale.[37]

Performance- or assessor-based measures were assessed less frequent but showed good measures of reliability.

In summary, only two instruments (AUSCAN and FIHOA) were extensively tested, showing excellent measures of reliability for both questionnaires. Other instruments, whilst showing good measures of reliability, had only been tested in one or two studies. Therefore, only tentative conclusions can be drawn for these instruments.

Discrimination: Sensitivity to change

Of the 45 studies assessing change over time in pain, physical function or patient global assessment,[25,26,29,36,42,45,47-85] seven studies did not demonstrate any significant change (one observational study, six RCTs).[62,69,75,78-81] Six studies only observed a statistically significant change in pain or patient global assessment (one observational study, five RCTs),[29,50,54,60,61,77] and five studies only observed change in physical function (all RCTs).[45,47,59,65,76]

The studies that detected change in at least one instrument assessing the corresponding domain are summarized in Table 4. The results of these studies regarding measured change over time are described in the online supplementary table.

Pain was most frequently assessed using the VAS or NRS, detecting change in 88% of these studies. Other applied instruments were the AUSCAN pain scale and pain/tenderness assessed on palpation, detecting change in 78 and 92% of the studies, respectively (see Table 4).[29,36,48,49,52,54,56,61,72-74,83,84] The ASES pain scale was applied in only one study and therefore not included in the table.[50]

Physical function was most frequently assessed by measured grip strength, detecting change in 75% of these studies. Other commonly applied instruments were the AUSCAN function scale (82% detecting change), FIHOA (67% detecting change), HAQ (50% detecting change) and grip strength (57% detecting change). The Cochin scale and VAS or NRS were less frequently used (see Table 4). The AIMS-2,[67] COPM,[59] dexterity,[68] GAT,[50] and MPUT77 were all assessed in only one study each.
Patient global assessment was assessed using the VAS global, detecting change in 60% of these studies. The 40% that did not detect change over time did measure change in AUSCAN function, COPM or the number of tender joints. A few number of studies assessed change in patient global assessment using the AUSCAN total (see Table 4).
In summary, the VAS pain was by far the most frequently applied instrument for assessment of change over time of pain in hand OA, followed by the AUSCAN pain subscale and pain on palpation. For assessment of change of physical function, the AUSCAN function subscale, FIHOA and grip strength assessment were commonly used. Change in patient global assessment was most frequently evaluated using the VAS global. The majority of studies that reported change in pain, physical function or patient global assessment detected this change by all applied instruments assessing the corresponding domain, suggesting good sensitivity to change for all evaluated instruments.

Feasibility
The number of items of the different applied instruments is described in Table 2. Although most of these instruments are available in the public domain, payment is required for use of the AUSCAN.
Only four of the included studies reported data on time needed to apply the used instruments.[13,19,37,39] Two studies reported the completion time of a questionnaire: for completion of the modified SACRAH, a median of 95 seconds was measured (range 80-175 seconds),[39] and for completion of the FIHOA, a mean of 165 seconds (standard deviation (SD) 119 seconds, range 50-600) was measured in patients with painful OA whereas inactive OA patients needed on average 136 seconds (SD 97 seconds, range 20-240).[13] The other two studies reported the time required to administer one or two assessor-/performance-based measures: for the Doyle index, a mean time of 5.1 minutes (range 2.4-7.8) was reported,[19] and the AHFT and HAMIS were reported to require 20-25 and 5 minutes, respectively.[37]
In summary, questionnaires took less time than assessor-/performance-based measures. The completion time of both assessed questionnaires was short, so both the FIHOA and modified SACRAH are highly feasible.

Validity
Eighteen studies correlated different instruments (mostly questionnaires), providing information on construct validity. The reported correlations between instruments assessing either pain or physical function or patient global assessment are presented in Table 5. Most of the studies (n = 16) reported cross-sectional correlations, whereas correlations or associations between assessed change over time were reported in only three studies.[23,28,46]

Table 4. Metric properties of instruments measuring pain, physical function or patient global assessment - sensitivity to change.* Only studies demonstrating significant change in pain, physical function or patient global assessment by at least one of the applied instruments are shown.

	No. of studies reporting change in corresponding instrument	**No. of studies not reporting change, discordant with other instruments assessing corresponding domain**	**Percentage of studies that detected change**
RCTs/intervention studies			
Questionnaires			
AUSCAN function	5 [25,45,48,55,58]	2 [47,59]	71%
AUSCAN pain	6 [25,29,55,58,61,77]	2 [48,60]	75%
AUSCAN total	2 [55,57]	0	100%
Cochin scale	1 [57]	0	100%
FIHOA	6 [26,49,51,53,64,72]	3 [25,36,48]	67%
HAQ	3 [51,56,73]	3 [55,59,76]	50%
VAS/NRS pain	21 [26,29,42,48,49,51,53-58,60,61,64,66,67,70-72]	3 [36,73,77]	88%
VAS global	6 [29,42,55,61,72,76]	4 [45,52,56,59]	60%
VAS/NRS function	2 [42,63]	0	100%
Performance- or assessor-based instruments			
Grip strength	11 [26,47,56,63,65,67,68,72,74,76]	4 [48,53,55,57]	73%
Pinch strength	4 [56,63,65,68]	3 [47,48,57]	57%
Tenderness/pain on palpation	9 [48,49,52,54,56,61,72-74]	1 [29]	90%
Observational studies			
Patient reported instruments			
AUSCAN function	4 [82-85]	0	100%
AUSCAN pain	4 [82-85]	1 [50]	80%
Cochin scale	1 [36]	0	100%
VAS pain	1 [50]	0	100%
Performance- or assessor-based measures:			
Grip strength	1 [84]	0	100%
Tenderness/pain on palpation	3 [36,83,84]	0	100%

* Only instruments assessed in ≥2 studies were included in this table.

AUSCAN, Australian/Canadian Hand OA Index; FIHOA, Functional Index for Hand OA; HAQ, Health Assessment Questionnaire; no., number; NRS, numeric rating scale; VAS, visual analogue scale.

The AUSCAN, grip strength and FIHOA scores were compared with other outcome measures most frequently (see Table 5). Correlations of the ASES pain scale, COPM and MAP-hand with other clinical outcome measures were evaluated in only one study,[28] as were the JTHFT,[41] Revel functional index,[36] PRWHE,[33] MHQ, HFI and HAMIS.[37] These studies were therefore not included in Table 5.

Varying correlation coefficients were reported among the different studies. In general, correlations between different questionnaires were stronger than correlations of performance-based measures with other performance-based measures or with questionnaires. Correlations between different instruments assessing physical function ranged from 0.52 to 0.89 between questionnaires, from 0.05 to 0.67 between questionnaires and performance-based measures and from 0.25 to 0.96 between performance-based measures. For assessment of pain, correlations between 0.55 and 0.81 were observed between questionnaires, and correlations between 0.47 and 0.65 between questionnaires and pain on palpation. However, only few correlation coefficients above 0.90 were observed, suggesting that different instruments catch different aspects of the assessed domain.

Two of the three studies associating change over time by different instruments presented correlation coefficients, which were in line with the results described above.[28,46] The third study calculated beta coefficients for the association of change of the AUSCAN and grip and pinch strength with global assessment of change, adjusted for age, gender, number of osteoarthritic hand joints and time between assessments. The strongest association with global assessment of change was observed for the AUSCAN.[23]

In summary, construct validity of various instruments measuring pain, physical function or patient global assessment has been assessed in multiple cross-sectional studies but only few longitudinal data are available. Moderate to good correlations were observed, especially between questionnaires, suggesting good construct validity.

Table 6 summarizes the available information of metric properties per domain for the six most frequently applied instruments for assessment of pain, physical function and patient global assessment. Information of metric properties was considered established when supporting results were observed in at least three studies. The non-availability of the AUSCAN in the public domain is included as negative evidence regarding the feasibility.

Table 5. Metric properties of instruments measuring pain, physical function or patient global assessment – validity.* Correlations between different instruments as observed in cross-sectional and longitudinal studies are shown.

	First author	Correlation with:
Cross-sectional studies		
Questionnaires		
AIMS-2	MacIntyre[32]	- Dexterity small/large objects: r range per item 0.23 to 0.40 / 0.14 to 0.31# - Grip strength: r range per item -0.23 to -0.37#
	Moe[34]	AIMS-2 physical / arm / hand: - AUSCAN function: r 0.83 / 0.70 / 0.77*** - FIHOA: r 0.80 / 0.71 / 0.69***
AUSCAN function	Stamm[41]	- JTHFT: r 0.67****
	Allen[24]	- Grip strength right, left: r -0.42,-0.40*** - Pinch strength right, left: r -0.23,-0.16***
	Bellamy[25]	Likert, VAS: - Global function (0-4): r 0.72, 0.74** - FIHOA (original): r 0.78, 0.86**- HAQ: r 0.65, 0.68** - Grip strength: r -0.39, -0.45** - Pinch grip: r -0.31, -0.36**
	Dziedzic[27]	- GAT: r 0.54** - Grip strength: r -0.56** - Pinch strength: r -0.60**
	Fernandes[28]	- MAP-hand: r 0.76#
	Moe[34]	- AIMS-2 physical: r 0.83, arm: r 0.70, hand: r 0.77*** - FIHOA: r 0.88*** - HAQ: r 0.80*** - Grip strength: r -0.62*** - MPUT right, left: r 0.58,0.63***
	Sautner[40]	- VAS global: r 0.55****
	Stamm[41]	- JTHFT: r 0.386****
	Wittoek[43]	- FIHOA: r 0.81***
AUSCAN pain	Allen[24]	- Pain severity right, left: r 0.58,0.55***
	Bellamy[25]	Likert, VAS: - Global pain (0-4): r 0.57, 0.64** - HAQ pain: r 0.57, 0.66** - Doyle: r 0.56, 0.47**
	Bijsterbosch[19]	- Doyle hand, total: r 0.65, 0.61***
	Moe[34]	- VAS pain: r 0.77***
	Wittoek[43]	- VAS pain: r 0.79***
Cochin scale	Poiraudeau[36]	- FIHOA: r 0.87# - Revel functional index: r 0.86 - VAS handicap: r 0.67
	Poole[37]	- FIHOA: r 0.89** - MHQ: r -0.82** - AHFT: r range per item -0.64 to 0.57** - HFI: r 0.55, HAMIS: r 0.49**

Table 5. *Continued*

	First author	Correlation with:
	Stamm[41]	- JTHFT: r 0.369**
FIHOA	Bellamy[25]	Original / Likert / VAS: - AUSCAN function (Likert, VAS): r 0.78, 0.86 / 0.80, 0.85 / 0.80, 0.88**
	Moe[34]	- AIMS-2 physical / arm / hand: r 0.80 / 0.71 / 0.69*** - AUSCAN function: r 0.88*** - HAQ: r 0.73*** - Grip strength: r -0.5*** - MPUT right / left: r 0.55 / 0.59***
	Poiraudeau[36]	- Cochin scale: r 0.87#
	Poole[37]	- Cochin: r 0.89** - MHQ: r -0.86** - AHFT: r range per item -0.57 to 0.46** - HFI: r 0.53, HAMIS: r 0.50**
	Stamm[41]	- JTHFT: r 0.387****
	Wittoek[43]	- AUSCAN function: r 0.81***
HAQ	Bellamy[25]	- AUSCAN function (Likert, VAS): r 0.65, 0.68**
	Fernandes[28]	Modified HAQ with MAP-hand: r 0.46#
	Moe[34]	- AUSCAN function: r 0.80*** - FIHOA: r 0.73***
	Stamm[41]	- JTHFT: r 0.424****
SACRAH	Rintelen[38]	Short Form-SACRAH with Modified-SACRAH: r 0.699***
	Sautner[39]	Modified-SACRAH: - SACRAH: r 0.978 (range subscales 0.912-0.958)**** - VAS global: r 0.64****
	Sautner[40]	Modified-SACRAH function / total with VAS global: r 0.55 / 0.65****
	Stamm[41]	SACRAH / M-SACRAH: - JTHFT: r 0.436 (range per scale 0.371-0.437) / 0.388****
VAS global	Sautner[39]	- Modified-SACRAH: r 0.64****
	Sautner[40]	- Function AUSCAN / modified-SACRAH: r 0.55 / 0.55**** - Pain AUSCAN / modified-SACRAH: r 0.59 / 0.56**** - Total modified-SACRAH: r 0.65****
VAS pain	Moe[34]	- AUSCAN pain: r 0.77***
	Wittoek[43]	- AUSCAN pain: r 0.79***
Performance- or assessor-based instruments		
AHFT	Backman[18]	- OMFAQ instrumental ADL scale: range per item r -0.75 to 0.75*** - OMFAQ physical ADL scale: range per item r -0.67 to 0.68***
	Poole[37]	- Cochin scale: r range per item -0.64 to 0.57** - FIHOA: r range per item -0.57 to 0.46** - MHQ: r range per item -0.48 to 0.65**
Dexterity	MacIntyre[32]	Large / small objects: - AIMS-2: r range per item 0.14 to 0.31 / 0.23 to 0.40#

Table 5. *Continued*

	First author	Correlation with:
	MacIntyre[33]	Large / small objects: - Grip strength: r -0.32 (range digits -0.25 to -0.30) / -0.28 (-0.10 to -0.41)# - Pinch (tripod, narrow, wide key): r -0.37, -0.30, -0.34 / -0.34, -0.25, -0.25#
GAT	Dziedzic[27]	- AUSCAN function: r 0.54**
	Fernandes[28]	- MAP-hand: r 0.43#
Grip strength	Allen[24]	- AUSCAN function (right, left): r -0.42,-0.40***
	Bellamy[25]	- AUSCAN function (Likert, VAS): r -0.39, -0.45**
	Dziedzic[27]	- AUSCAN function: r -0.56**
	Fernandes[28]	- MAP-hand: r -0.32#
	MacIntyre[32]	- AIMS-2: r range per item -0.23 to -0.37#
	MacIntyre[33]	- PRWHE activities: r -0.23# - Dexterity large: r - 0.32, small: -0.28# - Pinch strength (range per test): r 0.76 to 0.78#
	Moe[34]	- AUSCAN function: r -0.62*** - FIHOA: r -0.50***
	Stamm[41]	- JTHFT: r -0.395****
MPUT	Moe[34]	- AUSCAN function (right, left): r 0.58, 0.63*** - FIHOA (right, left): r 0.55, 0.59***
	Stamm[41]	- JTHFT: r 0.690****
Pinch strength	Allen[24]	- AUSCAN function (right, left): r -0.23, -0.16***
	Bellamy[25]	- AUSCAN function (Likert, VAS): r -0.31, -0.36**
	Dziedzic[27]	- AUSCAN function: r -0.60**
	MacIntyre[33]	- PRWHE activities (range per test): r -0.22 to -0.26# - Dexterity (range per test) large: r -0.30 to -0.37, small: r -0.25 to -0.34# - Grip strength (range per test): r 0.75 to 0.96#
Tenderness/pain on palpation	Bellamy[25]	Doyle with AUSCAN (Likert, VAS) pain: r 0.56, 0.47**
	Bijsterbosch[19]	Doyle hand / total with AUSCAN pain: r 0.65 / 0.61***
	Longitudinal studies	
Questionnaires		
AUSCAN total	Allen[23]	Association global assessment of change (right, left) with AUSCAN total: β 0.29, 0.27 (P < 0.001). Stronger among greater radiographic OA severity.
AUSCAN function	Fernandes[28]	- Change MAP-hand: r 0.52#
AUSCAN pain	Barthel[46]	- Change VAS pain: r 0.81***
VAS global	Barthel[46]	- Change AUSCAN function: r 0.71***, pain: r 0.75*** - Change VAS pain: r 0.76***
VAS pain	Barthel[46]	- Change AUSCAN pain: r 0.81***
Performance- or assessor-based instruments		
GAT	Fernandes[28]	- Change MAP-hand: r 0.06#
Grip strength	Allen[23]	- Global assessment of change (right, left): β -0.16, -0.13 (P 0.003, 0.015) Stronger associations among greater radiographic OA severity.
	Fernandes[28]	- Change MAP-hand: r -0.05#

Table 5. *Continued*

	First author	Correlation with:
Pinch strength	Allen[23]	- Global assessment of change (right, left): β -0.13, -0.11 (P 0.022, 0.060) Stronger associations among greater radiographic OA severity.

* Only instruments assessed in ≥2 studies were included in this table.

No p-values provided. ** p-value < 0.05. *** p-value < 0.001. **** p-value < 0.0001.

AHFT, Arthritis hand function test; AIMS-2, Arthritis Impact Measurement Scale; ADL, activities of daily living; ASES, Arthritis Self Efficacy Scale; AUSCAN, Australian/Canadian Hand OA Index; β, beta coefficient; CI, confidence interval; COPM, Canadian Occupational Performance Measure; FIHOA, Functional Index for Hand OA; GAT, Grip ability test; HAQ, Health Assessment Questionnaire; JTHFT, Jebsen-Taylor Hand Function Test; MPUT, Moberg Picking Up Test; P, p-value; r, correlation coefficient; SACRAH, Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; VAS, Visual Analogue Scale.

Table 6. Available information of metric properties from at least 3 studies for the most frequently applied instruments (in at least 15 clinical studies) for evaluation of pain, physical function or patient global assessment

	Reliability	Sensitivity to change	Feasibility	Validity
Questionnaires				
AUSCAN	+	+	- #	+
FIHOA	+	+	+**	+
VAS pain		+		+
Performance- or assessor-based instruments				
Grip strength	+*	+		+
Pinch strength	+*	+		+
Tenderness/pain on palpation	+*	+		+*

+ = established evidence

* supporting evidence in only 2 studies

** supporting evidence in only 1 study

not available in public domain

AUSCAN, Australian/Canadian Hand OA Index; FIHOA, Functional Index for Hand OA; VAS, visual analogue scale.

DISCUSSION

The most frequently applied and evaluated instruments for assessment of pain were the AUSCAN pain subscale, VAS pain and pain on palpation. The AUSCAN function subscale, FIHOA and grip and pinch strength were most frequently applied and evaluated for assessment of physical function. Patient global assessment was most frequently evaluated using the VAS global.

In the description of discrimination, the reliability of the AUSCAN and FIHOA were found to be extensively tested and shown to be excellent. The reliability of other instruments was suggested to be good, but only scarce evidence was available.

The VAS pain was by far the most commonly used instrument for assessment of change of pain, followed by the AUSCAN pain subscale and pain on palpation. The AUSCAN function subscale, FIHOA and assessment of grip and pinch strength were regularly applied for assessment of change of physical function. Change of patient global assessment was most often evaluated by the VAS global. The majority of studies detected change by all used instruments, suggesting good sensitivity to change for the evaluated instruments. Change in pain was detected most frequently by the VAS pain or pain on palpation, whereas change in physical function was detected most frequently by the AUSCAN function subscale or measured grip strength.

In the description of feasibility, only few studies reported on time needed to perform instruments. Questionnaires took less time than performance-based measures. Of the frequently applied instruments, only the FIHOA was evaluated and seemed feasible. This is supported by the availability of this questionnaire in the public domain, in contrast with the AUSCAN.

For the description of validity, numerous cross-sectional studies assessed correlations between various instruments but only few longitudinal data was available. The strongest correlations were reported between different questionnaires assessing pain or physical function. Remarkably, the VAS pain, as one of the most frequently applied instruments, was evaluated in only a limited number of studies.

For further evaluation of validity, comparison to an external standard should be performed. However, no external standards for evaluation of pain, physical function and patient global assessment have been agreed upon, perhaps due to varying definitions and measurement of these concepts. For assessment of physical function, observation of the performance of tasks as described by specific instruments assessing physical function may be useful in the evaluation of validity of these instruments.[86]

Based on this review, it is not possible to decide on one instrument that should be recommended for measurement of pain, physical function or patient global assessment in hand OA research. Although no major differences regarding metric properties of the evaluated instruments were observed, the amount of supporting evidence varied extensively between the instruments.

Before consensus can be reached on which instruments should be applied, some aspects need further investigation. The reliability of especially the VAS pain, grip and pinch strength and pain on palpation needs to be further established in a variety of populations. Regarding the sensitivity to change, the minimal clinical important difference of instruments needs to be determined. Only for the AUSCAN a minimal clinically important improvement has been proposed.[87] Validity of instruments assessing physical function

should be further investigated by comparing these instruments to an external standard. Furthermore, future research should evaluate instruments within specific subtypes of hand OA.

This study has some limitations. We intended to include as many available studies as possible that provided information on instruments and their metric properties, not only studies that actually aimed at evaluating this. Because of the large heterogeneity across studies regarding their purpose (primarily aiming at evaluation instruments or applying instruments for other primary aims) and study design, the methodological quality of the included studies was not assessed. Furthermore, the heterogeneity did not enable pooling of data into a meta-analysis and addressing the presence of publication bias.

Limitations regarding the literature search are the included databases, restriction to English language and exclusion of abstracts and unpublished results.

Within all studies assessing the VAS pain or VAS global, different questions were used. The individual questions were observed to be highly variable, especially regarding the type of pain (global pain, overall disease severity, intensity, not specified) and time settings (last 24 or 48 hours, two days, two weeks, not specified). In future research this phrasing should be standardized. Furthermore, the VAS pain score has been shown to be influenced by the information on the disease and its consequences that is given to patients when determining the VAS,[88] which could not be addressed due to lack of information on this topic in the included studies. However, future studies evaluating the VAS should take the effect of patient information into account.

In conclusion, our systematic literature review provides an overview of the instruments that are used for measurement of pain, physical function and patient global assessment in hand OA. Most information on the metric properties of these instruments was available for the questionnaires AUSCAN (assessing pain and function), FIHOA (assessing function) and VAS pain, and for the performance- or assessor-based instruments grip and pinch strength and pain on palpation. To enhance comparability across future studies in hand OA, consensus has to be reached on recommended instruments for measurement of pain, physical function and patient global assessment in hand OA. More research has to be performed to compare the different instruments to each other.

REFERENCES

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
2. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
3. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis 2009;68:8-17.
4. Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002;156:1021-7.
5. Kjeken I, Dagfinrud H, Slatkowsky-Christensen B, Mowinckel P, Uhlig T, Kvien TK et al. Activity limitations and participation restrictions in women with hand osteoarthritis: patients' descriptions and associations between dimensions of functioning. Ann Rheum Dis 2005;64:1633-8.
6. Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. Ann Rheum Dis 2010;69:1784-8.
7. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. Nat Rev Rheumatol 2014;10:242-51.
8. Mahendira D and Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. Osteoarthritis Cartilage 2009;17:1263-8.
9. Kloppenburg M, Boyesen P, Smeets W, Haugen I, Liu R, Visser W et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: Advances and Future Research Priorities. J Rheumatol 2014;41:810-8.
10. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage 1996;4:217-43.
11. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.
12. Maheu E, Altman RD, Bloch DA, Doherty M, Hochberg M, Mannoni A et al. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International. Osteoarthritis Cartilage 2006;14:303-22.

13. Dreiser RL, Maheu E, Guillou GB, Caspard H, Grouin JM. Validation of an algofunctional index for osteoarthritis of the hand. Rev Rhum Engl Ed 1995;62:43S-53S.
14. Bellamy N, Campbell J, Haraoui B, Buchbinder R, Hobby K, Roth JH et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis Cartilage 2002;10:855-62.
15. Chung KC, Pillsbury MS, Walters MR, Hayward RA. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. J Hand Surg Am 1998;23:575-87.
16. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum 1992;35:1-10.
17. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
18. Backman C and Mackie H. Reliability and validity of the arthritis hand function test in adults with osteoarthritis. OCCUP THER J RES 1997;17:55-66.
19. Bijsterbosch J, Wassenaar MJ, le CS, Slagboom PE, Rosendaal FR, Huizinga TW et al. Doyle Index is a valuable additional pain measure in osteoarthritis. Osteoarthritis Cartilage 2010;18:1046-50.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
21. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
22. Marks M, Schoones JW, Kolling C, Herren DB, Goldhahn J, Vliet Vlieland TP. Outcome measures and their measurement properties for trapeziometacarpal osteoarthritis: a systematic literature review. J Hand Surg Eur Vol 2013;38:822-38.
23. Allen KD, Jordan JM, Renner JB, Kraus VB. Relationship of global assessment of change to AUSCAN and pinch and grip strength among individuals with hand osteoarthritis. Osteoarthritis Cartilage 2006;14:1281-7.
24. Allen KD, Jordan JM, Renner JB, Kraus VB. Validity, factor structure, and clinical relevance of the AUSCAN Osteoarthritis Hand Index. Arthritis Rheum 2006;54:551-6.
25. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002;10:863-9.
26. Dreiser RL, Maheu E, Guillou GB. Sensitivity to change of the functional index for hand osteoarthritis. Osteoarthritis Cartilage 2000;8 Suppl A:S25-S28.

27. Dziedzic KS, Thomas E, Myers H, Hill S, Hay EM. The Australian/Canadian osteoarthritis hand index in a community-dwelling population of older adults: reliability and validity. Arthritis Rheum 2007;57:423-8.
28. Fernandes L, Grotle M, Darre S, Nossum R, Kjeken I. Validity and responsiveness of the Measure of Activity Performance of the Hand (MAP-Hand) in patients with hand osteoarthritis. J Rehabil Med 2012;44:869-76.
29. Haugen IK, Slatkowsky-Christensen B, Lessem J, Kvien TK. The responsiveness of joint counts, patient-reported measures and proposed composite scores in hand osteoarthritis: analyses from a placebo-controlled trial. Ann Rheum Dis 2010;69:1436-40.
30. Haugen IK, Moe RH, Slatkowsky-Christensen B, Kvien TK, van der Heijde D, Garratt A. The AUSCAN subscales, AIMS-2 hand/finger subscale, and FIOHA were not unidimensional scales. J Clin Epidemiol 2011;64:1039-46.
31. Hirsch R, Guralnik JM, Leveille SG, Simonsick EM, Ling S, Bandeen-Roche K et al. Severity of hand osteoarthritis and its association with upper extremity impairment in a population of disabled older women: the Women's Health and Aging Study. Aging (Milano) 1999;11:253-61.
32. MacIntyre NJ and Wessel J. Construct validity of the AIMS-2 upper limb function scales as a measure of disability in individuals with osteoarthritis of the hand. Clin Rheumatol 2009;28:573-8.
33. MacIntyre NJ, Wessel J, MacDermid JC, Galea V. Assessment of strength of individual digits in persons with osteoarthritis of the hand. HAND THER 2010;15:39-44.
34. Moe RH, Garratt A, Slatkowsky-Christensen B, Maheu E, Mowinckel P, Kvien TK et al. Concurrent evaluation of data quality, reliability and validity of the Australian/Canadian Osteoarthritis Hand Index and the Functional Index for Hand Osteoarthritis. Rheumatology (Oxford) 2010;49:2327-36.
35. Myers HL, Thomas E, Hay EM, Dziedzic KS. Hand assessment in older adults with musculoskeletal hand problems: a reliability study. BMC Musculoskelet Disord 2011;12:3.
36. Poiraudeau S, Chevalier X, Conrozier T, Flippo RM, Liote F, Noel E et al. Reliability, validity, and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. Osteoarthritis Cartilage 2001;9:570-7.
37. Poole JL, Lucero SL, Mynatt R. Self-Reports and Performance-Based Tests of Hand Function in Persons with Osteoarthritis. Physical & Occupational Therapy in Geriatrics 2010;28:249-58.
38. Rintelen B, Haindl PM, Mai HT, Sautner J, Maktari A, Leeb BF. A tool for the assessment of hand involvement in rheumatic disorders in daily routine--the SF-SACRAH (short form score for the assessment and quantification of chronic rheumatic affections of the hands). Osteoarthritis Cartilage 2009;17:59-63.
39. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the M-SACRAH, a modified, shortened version of SACRAH (Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands). Rheumatology (Oxford) 2004;43:1409-13.
40. Sautner J, Andel I, Rintelen B, Leeb BF. A comparison of the modified score for the assessment of chronic rheumatoid affections of the hands and the australian/canadian osteoarthritis hand index in hand osteoarthritis patients. Int J Rheumatol 2009;2009:249096.

41. Stamm T, Mathis M, Aletaha D, Kloppenburg M, Machold K, Smolen J. Mapping hand functioning in hand osteoarthritis: comparing self-report instruments with a comprehensive hand function test. Arthritis Rheum 2007;57:1230-7.
42. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res (Hoboken) 2012;64:1699-707.
43. Wittoek R, Cruyssen BV, Maheu E, Verbruggen G. Cross-cultural adaptation of the Dutch version of the Functional Index for Hand Osteoarthritis (FIHOA) and a study on its construct validity. Osteoarthritis Cartilage 2009;17:607-12.
44. Ziv E, Patish H, Dvir Z. Grip and pinch strength in healthy subjects and patients with primary osteoarthritis of the hand: a reproducibility study. Open Orthop J 2008;2:86-90.
45. Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol 2009;36:1991-9.
46. Barthel HR, Peniston JH, Clark MB, Gold MS, Altman RD. Correlation of pain relief with physical function in hand osteoarthritis: randomized controlled trial post hoc analysis. Arthritis Res Ther 2010;12:R7.
47. Brosseau L, Wells G, Marchand S, Gaboury I, Stokes B, Morin M et al. Randomized controlled trial on low level laser therapy (LLLT) in the treatment of osteoarthritis (OA) of the hand. Lasers Surg Med 2005;36:210-9.
48. Dilek B, Gozum M, Sahin E, Baydar M, Ergor G, El O et al. Efficacy of paraffin bath therapy in hand osteoarthritis: a single-blinded randomized controlled trial. Arch Phys Med Rehabil 2013;94:642-9.
49. Dreiser RL, Gersberg M, Thomas F, Courcier S. Ibuprofen 800 mg for the treatment of osteoarthritis of the interphalangeal joints of the hand or trapezo metacarpal joint. Revue du Rhumatisme (English Edition) 1993;60:719-24.
50. Dziedzic K, Nicholls E, Hill S, Hammond A, Handy J, Thomas E et al. Self-management approaches for osteoarthritis in the hand: a 2x2 factorial randomised trial. Ann Rheum Dis 2015;74:108-18.
51. Fioravanti A, Tenti S, Giannitti C, Fortunati NA, Galeazzi M. Short- and long-term effects of mud-bath treatment on hand osteoarthritis: a randomized clinical trial. Int J Biometeorol 2014;58:79-86.
52. Flynn MA, Irvin W, Krause G. The effect of folate and cobalamin on osteoarthritic hands. J Am Coll Nutr 1994;13:351-6.
53. Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. Arthritis Rheum 2011;63:3383-91.
54. Garfinkel MS, Schumacher HR, Jr., Husain A, Levy M, Reshetar RA. Evaluation of a yoga based regimen for treatment of osteoarthritis of the hands. J Rheumatol 1994;21:2341-3.
55. Grifka JK, Zacher J, Brown JP, Seriolo B, Lee A, Moore A et al. Efficacy

and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand. Clin Exp Rheumatol 2004;22:589-96.
56. Horvath K, Kulisch A, Nemeth A, Bender T. Evaluation of the effect of balneotherapy in patients with osteoarthritis of the hands: a randomized controlled single-blind follow-up study. Clin Rehabil 2012;26:431-41.
57. Kanat E, Alp A, Yurtkuran M. Magnetotherapy in hand osteoarthritis: a pilot trial. Complement Ther Med 2013;21:603-8.
58. Keen HI, Wakefield RJ, Hensor EM, Emery P, Conaghan PG. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. Rheumatology (Oxford) 2010;49:1093-100.
59. Kjeken I, Darre S, Smedslund G, Hagen KB, Nossum R. Effect of assistive technology in hand osteoarthritis: a randomised controlled trial. Ann Rheum Dis 2011;70:1447-52.
60. Kovacs C, Pecze M, Tihanyi A, Kovacs L, Balogh S, Bender T. The effect of sulphurous water in patients with osteoarthritis of hand. Double-blind, randomized, controlled follow-up study. Clin Rheumatol 2012;31:1437-42.
61. Kvien TK, Fjeld E, Slatkowsky-Christensen B, Nichols M, Zhang Y, Proven A et al. Efficacy and safety of a novel synergistic drug candidate, CRx-102, in hand osteoarthritis. Ann Rheum Dis 2008;67:942-8.
62. Kwok WY, Kloppenburg M, Beaart-van de Voorde LJ, Huizinga TW, Vliet Vlieland TP. Role of rheumatology clinical nurse specialists in optimizing management of hand osteoarthritis during daily practice in secondary care: an observational study. J Multidiscip Healthc 2011;4:403-11.
63. Moratz V, Muncie J, Miranda-Walsh H. Occupational therapy in the multidisciplinary assessment and management of osteoarthritis. Clinical Therapeutics 1986;9:24-9.
64. Myrer JW, Johnson AW, Mitchell UH, Measom GJ, Fellingham GW. Topical analgesic added to paraffin enhances paraffin bath treatment of individuals with hand osteoarthritis. Disabil Rehabil 2011;33:467-74.
65. Pastinen O, Forsskahl B, Marklund M. Local glycosaminoglycan polysulphate injection therapy in osteoarthritis of the hand. A placebo-controlled clinical study. Scand J Rheumatol 1988;17:197-202.
66. Reeves KD and Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. J Altern Complement Med 2000;6:311-20.
67. Rogers MW and Wilder FV. The effects of strength training among persons with hand osteoarthritis: a two-year follow-up study. J Hand Ther 2007;20:244-9.
68. Rogers MW and Wilder FV. Exercise and hand osteoarthritis symptomatology: a controlled crossover trial. J Hand Ther 2009;22:10-7.
69. Romero-Cerecero O, Meckes-Fischer M, Zamilpa A, Enrique Jimenez-Ferrer J, Nicasio-Torres P, Perez-Garcia D et al. Clinical trial for evaluating the effectiveness and tolerability of topical Sphaeralcea angustifolia treatment in hand osteoarthritis. J Ethnopharmacol 2013;147:467-73.
70. Rothacker D, Difigilo C, Lee I. A clinical trial of topical 10% trolamine salicylate in osteoarthritis. CURR THER RES CLIN EXP 1994;55:584-97.

71. Rothacker DQ, Lee I, Littlejohn ITW. Effectiveness of a single topical application of 10% trolamine salicylate cream in the symptomatic treatment of osteoarthritis. Journal of Clinical Rheumatology 1998;4:6-12.
72. Saviola G, Abdi AL, Campostrini L, Sacco S, Baiardi P, Manfredi M et al. Clodronate and hydroxychloroquine in erosive osteoarthritis: a 24-month open randomized pilot study. Modern rheumatology / the Japan Rheumatism Association 2012;22:256-63.
73. Schnitzer T, Morton C, Coker S. Topical capsaicin therapy for osteoarthritis pain: Achieving a maintenance regimen. Semin Arthritis Rheum 1994;23:34-40.
74. Seiler V. Meclofenamate sodium in the treatment of degenerative joint disease of the hand (Heberden nodes). Arzneimittel-Forschung/Drug Research 1983;33:656-9.
75. Shin K, Kim JW, Moon KW, Yang JA, Lee EY, Song YW et al. The efficacy of diacerein in hand osteoarthritis: a double-blind, randomized, placebo-controlled study. Clin Ther 2013;35:431-9.
76. Stamm TA, Machold KP, Smolen JS, Fischer S, Redlich K, Graninger W et al. Joint protection and home hand exercises improve hand function in patients with hand osteoarthritis: a randomized controlled trial. Arthritis Rheum 2002;47:44-9.
77. Stange-Rezende L, Stamm TA, Schiffert T, Sahinbegovic E, Gaiger A, Smolen J et al. Clinical study on the effect of infrared radiation of a tiled stove on patients with hand osteoarthritis. Scand J Rheumatol 2006;35:476-80.
78. Stukstette MJ, Dekker J, den Broeder AA, Westeneng JM, Bijlsma JW, van den Ende CH. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term; results of a randomized controlled trial. Osteoarthritis Cartilage 2013;21:901-10.
79. Verbruggen G, Wittoek R, Vander CB, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. Ann Rheum Dis 2012;71:891-8.
80. Wenham CY, Hensor EM, Grainger AJ, Hodgson R, Balamoody S, Dore CJ et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. Rheumatology (Oxford) 2012;51:2286-94.
81. Widrig R, Suter A, Saller R, Melzer J. Choosing between NSAID and arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study. Rheumatol Int 2007;27:585-91.
82. Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011;70:68-73.
83. Botha-Scheepers S, Riyazi N, Watt I, Rosendaal FR, Slagboom E, Bellamy N et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. Ann Rheum Dis 2009;68:1260-4.
84. Haugen IK, Slatkowsky-Christensen B, Boyesen P, van der Heijde D, Kvien TK. Cross-sectional and longitudinal associations between radiographic features and measures of pain and physical function in hand osteoarthritis. Osteoarthritis Cartilage 2013;21:1191-8.
85. Marshall M, Peat G, Nicholls E, van der Windt D, Myers H, Dziedzic K. Subsets of symptomatic hand osteoarthritis

in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. Osteoarthritis Cartilage 2013;21:1674-84.
86. van den Ende CH, Hazes JM, le CS, Breedveld FC, Dijkmans BA. Discordance between objective and subjective assessment of functional ability of patients with rheumatoid arthritis. Br J Rheumatol 1995;34:951-5.
87. Bellamy N and Wilson C. International estimation of minimally clinically important improvement (MCII75): the Reflect study. 2007;37(Suppl2):A36.
88. Rovetta G, Monteforte P, Molfetta L. Evaluating pain in osteoarthritis of the hands: the effect of patient information. Int J Clin Pharmacol Res 2003;23:61-7.
89. Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis Rheum 1989;32:37-44.
90. Duruoz MT, Poiraudeau S, Fermanian J, Menkes CJ, Amor B, Dougados M et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. J Rheumatol 1996;23:1167-72.
91. Law M, Baptiste S, Carswell A, McColl M, Polatajko H, Pollock N. Canadian Occupational Performance Measure (Manual), 4th edition. Ottawa: CAOT Publications ACE. 2005;
92. Paulsen T, Grotle M, Garratt A, Kjeken I. Development and psychometric testing of the patient-reported measure of activity performance of the hand (MAP-Hand) in rheumatoid arthritis. J Rehabil Med 2010;42:636-44.
93. Fillenbaum GG and Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 1981;36:428-34.
94. MacDermid JC, Turgeon T, Richards RS, Beadle M, Roth JH. Patient rating of wrist pain and disability: a reliable and valid measurement tool. J Orthop Trauma 1998;12:577-86.
95. Revel M and Amor B. Orthopedic treatment of swan-neck deformities of the rheumatoid hand. Rev Rhum Mal Osteoartic 1989;56:93-6.
96. Leeb BF, Sautner J, Andel I, Rintelen B. SACRAH: a score for assessment and quantification of chronic rheumatic affections of the hands. Rheumatology (Oxford) 2003;42:1173-8.
97. Huskisson EC. Measurement of pain. Lancet 1974;2:1127-31.
98. Pincus T, Brooks RH, Callahan LF. Reliability of grip strength, walking time and button test performed according to a standard protocol. J Rheumatol 1991;18:997-1000.
99. Dellhag B and Bjelle A. A Grip Ability Test for use in rheumatology practice. J Rheumatol 1995;22:1559-65.
100. Sandqvist G and Eklund M. Hand Mobility in Scleroderma (HAMIS) test: the reliability of a novel hand function test. Arthritis Care Res 2000;13:369-74.
101. Eberl DR, Fasching V, Rahlfs V, Schleyer I, Wolf R. Repeatability and objectivity of various measurements in rheumatoid arthritis. A comparative study. Arthritis Rheum 1976;19:1278-86.
102. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil 1969;50:311-9.
103. Ng CL, Ho DD, Chow SP. The Moberg pickup test: results of testing with a standard protocol. J Hand Ther 1999;12:309-12.

104. Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. Ann Rheum Dis 1981;40:75-8.
105. Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393-406.

Supplementary table. Results of the studies that detected change in at least one instrument evaluating either pain or physical function of patient global assessment*

	First author	Relevant results
Questionnaires		
AUSCAN function	Altman[45]	Mean change intervention: 26.5, control: 19.2 (P 0.017)
	Bellamy[25]	Mean change (Likert, VAS): -0.32 (p 0.001), -8.97 (P 0.001) Average SRM (Likert, VAS): -0.67, -0.76
	Bijsterbosch[82]	Mean change (95%CI): 2.1 (1.3-2.9) Percentage change: 50% increased limitations, 26% decreased
	Botha-Scheepers[83]	Mean change (95%CI): 1.4 (0.5, 2.3), SRM: 0.23 Percentage change: 53% increased, 12% no change, 36% decrease
	Brosseau[47]	No significant change (in contrast with grip strength)
	Dilek[48]	Median change intervention: -1.65 (P < 0.016), control no significant change.
	Grifka[55]	Mean change intervention (1/2) vs control: -4.3 / -6.0 vs -3.1 (P < 0.01)
	Haugen[84]	Mean change 1.2, SD 6.3
	Keen[58]	Mean change: 159.5 (P < 0.05)
	Kjeken[59]	No significant change (in contrast with COPM)
	Marshall[85]	Increase: range 1-3 in symptomatic OA patients
AUSCAN pain	Bellamy[25]	Mean change (Likert, VAS): -0.34 (P 0.001), -6.46 (P 0.003) Average SRM (Likert, VAS): -0.71, -0.84
	Bijsterbosch[82]	Mean change (95%CI): 0.7 (0.3, 1.2) Percentage change: 40% increased, 26% decreased
	Botha-Scheepers[83]	Mean change (95%CI): 1.0 (0.4, 1.6), SRM: 0.25 Percentage change: 50% increased, 20% no change, 30% decrease
	Dilek[48]	No significant change (in contrast with VAS pain)
	Dziedzic[50]	No significant change (in contrast with ASES pain, average pain)
	Grifka[55]	Mean change intervention (1/2) vs control: -3.0 / -3.9 vs -2.1 (P < 0.01)
	Haugen[29]	Mean change intervention: -20.5, control: -6.2 (P 0.012), SRM 0.68
	Haugen[84]	Mean change 0.8, SD 3.4
	Keen[58]	Mean change: -117.5 (P < 0.05)
	Kovacs[60]	No significant change (in contrast with VAS pain)
	Kvien[61]	Mean change intervention vs control: -20.5 vs -6.2 (P 0.012)
	Marshall[85]	Increase: range 0.5-1.5 in symptomatic OA patients
	Stange-Rezende[77]	Mean change intervention: 0.62, control: -0.33 (P 0.034)
AUSCAN total	Grifka[55]	Mean change intervention (1/2) vs control: -7.7 / -10.5 vs -5.6 (P < 0.005)
	Kanat[57]	Total: mean change intervention: -17, control: -2 (P < 0.001)
Cochin scale	Kanat[57]	Mean change intervention: -12, control: -2 (P < 0.001)
	Poiraudeau[36]	Mean change: -2.35, SRM: -0.26, effect size: -0.17
FIHOA	Bellamy[25]	No significant change (in contrast with AUSCAN function) SRM (original, Likert, VAS): -0.31, -0.28, -0.27
	Dilek[48]	No significant change (in contrast with AUSCAN function)
	Dreiser[49]	Mean change intervention: -5.7, control: -2.8 (P 0.005)
	Dreiser[26]	Mean change: -2.8, SRM: 0.58

Supplementary table. *Continued*

	First author	Relevant results
	Fioravanti[51]	Intervention decreased, control no change (P < 0.001)
	Gabay[53]	Mean change intervention: -2.9, control: -0.7 (P 0.008)
	Myrer[64]	Mean change intervention: 3.42 (P < 0.05), control no significant change
	Poiraudeau[36]	No significant change (in contrast with Cochin scale) SRM: -0.03, effect size:-0.02
	Saviola[72]	Mean change intervention 1 (1/2 year): -51/-41% (P 0.026), intervention 2 no significant change.
HAQ	Fioravanti[51]	Mean change intervention: -0.30, control: -0.02 (P < 0.001)
	Grifka[55]	No significant change (in contrast with AUSCAN function)
	Horvath[56]	Mean change intervention 2: -0.5, control: -0.1 (P < 0.01), intervention 1 no significant change.
	Kjeken[59]	No significant change (in contrast with COPM)
	Schnitzer[73]	Mean change intervention: 1.5, control: 0.09 (p-value not specified)
	Stamm[76]	No significant difference (in contrast with grip strength)
VAS/NRS pain	Dilek[48]	Pain rest: median change intervention: -3.00, control no change (P 0.01) Pain ADL no significant different change
	Dreiser[49]	VAS pain: mean change intervention: -37.6, control: -16.5 (P 0.001) No. joints pain movement grade 4/5: mean change intervention: -24, control: -13 (P 0.009)
	Dreiser[26]	Mean change: -19.5, SRM: 0.87
	Dziedzic[50]	Average pain severity (0-10): mean difference between intervention 2 and control: 0.53. No difference between intervention 1 and control
	Fioravanti[51]	Intervention reduced, control no change (P < 0.001)
	Gabay[53]	Mean change intervention: -20.0, control: -11.3 (P 0.016)
	Garfinkel[54]	Pain during activity: mean change intervention: -4.29, control: -1.00 (P < 0.01). No significant change in pain at rest
	Grifka[55]	Mean change intervention 1/2: -28.0 / -30.0, control: -19.3 (P < 0.001)
	Haugen[29]	Mean change intervention: -23.5, control: -6.3 (P 0.005), SRM: 0.77
	Horvath[56]	Mean change intervention 1/2 vs control: - pain rest: -28.9 / -21.5 (P < 0.05) vs no significant change - pain exertion: -28.2 / -23.2 (P < 0.05) vs no significant change
	Kanat[57]	Pain rest/motion (1-10): mean change intervention: -4 / -7, control no change (P < 0.001)
	Keen[58]	Mean change most painful:-36.0, all joints:-36.0, global:-39.0 (P < 0.001)
	Kovacs[60]	Mean change intervention: -35.7, control: -10.5 (P 0.002)
	Kvien[61]	Mean change intervention: -23.5, control: -6.3 (P 0.005)
	Myrer[64]	Pain rest/movement: mean change intervention: 21.8 / 29.8 (P < 0.05), control no significant change
	Poiraudeau[36]	No significant change (in contrast with no. tender joints) SRM: -0.10, effect size: -0.12
	Reeves[66]	Pain movement: mean change intervention:-1.89, control:-0.62 (P 0.027). No significant change in pain rest/grip
	Rogers[67]	Pain (0-10): mean change in participants with pain ≥3: -2.15 (P < 0.006)

Supplementary table. *Continued*

	First author	Relevant results
	Rothacker[70]	Pain (0-5) decrease after 45 min intervention > control (P 0.046). Intervention vs control: time to pain peak relief 31 vs 48 min (P 0.018)
	Rothacker[71]	Pain (0-5): mean change intervention: -1.3, control: -0.8 (P 0.026)
	Saviola[72]	Mean change intervention 1 (1/2 year): -54/-46% (P 0.001), intervention 2 (1 year): 26% (P 0.018)
	Schnitzer[73]	No significant change (in contrast with no. tender joints)
	Stange-Rezende[77]	No significant change (in contrast with AUSCAN pain)
	Tubach[42]	MCII (95%CI) absolute / relative improvement: 16 (13-19) / 23 (20-25), PASS: 41 (38-43)
VAS global	Altman[45]	No significant change (in contrast with AUSCAN function)
	Flynn[52]	No significant change (in contrast with no. tender joints)
	Grifka[55]	Mean change intervention (1/2): -16.3 / -20.9, control: -9.4 (P < 0.001)
	Haugen[29]	Mean change intervention: 23.4, control: -4.6 (P 0.001), SRM: 0.92
	Horvath[56]	No significant change (in contrast with VAS pain, HAQ, grip/pinch strength, no. tender joints)
	Kjeken[59]	No significant change (in contrast with COPM)
	Kvien[61]	Mean change intervention: -23.4, control: -4.6 (P 0.001)
	Saviola[72]	Mean change intervention 1 (1/2 year): 50/70 (P 0.021), intervention 2 (1year): 10 (P < 0.001)
	Stamm[76]	Intervention: 65% improvement, control: 20% improvement (P < 0.05)
	Tubach[42]	MCII (95%CI) absolute / relative improvement: 15 (12-17) / 20 (16-23), PASS: 42 (40-44)
VAS/NRS function	Moratz[63]	Mean change disability score: -0.5 (P < 0.05)
	Tubach[42]	VAS functional disability: MCII (95%CI) absolute / relative improvement: 12 (9-14) / 18 (16-20), PASS: 42 (38-46)
Performance- or assessor-based instruments		
Grip strength	Brosseau[47]	Improvement in intervention group (P 0.041)
	Dilek[48]	No significant change (in contrast with AUSCAN function)
	Dreiser[26]	Mean change: 4.9, SRM: 0.22
	Gabay[53]	No significant change (in contrast with FIHOA)
	Grifka[55]	No significant change (in contrast with VAS, AUSCAN)
	Haugen[84]	Mean change (SD) right: -0.7 (6.9), left: -1.1 (6.9)
	Horvath[56]	Mean change intervention (1 / 2) vs control: right hand 3.8 / 3.5 vs -0.1 (P < 0.05 / not significant). Left hand not significant different.
	Kanat[57]	No significant change (in contrast with Cochin scale)
	Moratz[63]	Minimal improvement (3 lb)
	Pastinen[65]	Change intervention vs control group: 118 vs 91% (P 0.014)
	Rogers[67]	Mean change: isotonic strength 1.94 (p<0.0003), max. isometric right/ left 3.62 (P < 0.002) / 2.95 (P < 0.0005)
	Rogers[68]	Mean change intervention vs control: range 1.98-2.92 vs no significant change

Supplementary table. *Continued*

	First author	Relevant results
	Saviola[72]	Mean change intervention 1 (1/2 year): right 25/25%, left 22/20% (P < 0.05), intervention 2 (1 year) no significant change
	Schnitzer[73]	Mean change intervention: 32%, control: 3% (P 0.046)
	Seiler[74]	Mean change intervention: 21.82 (18%), control: 6.58 (6%) (P < 0.05)
	Stamm[76]	Mean change right/left intervention: 0.12/0.11, control: 0.03/0.03 (P < 0.0005)
Pinch strength	Brosseau[47]	No significant change (in contrast with grip strength)
	Dilek[48]	No significant change (in contrast with AUSCAN function)
	Horvath[56]	Mean change intervention (1 / 2) vs control: right hand 0.6 / 0.7 vs 0.1 (not significant / P < 0.05). Left hand not significant different.
	Kanat[57]	No significant change (in contrast with Cochin scale)
	Moratz[63]	Minimal improvement (3 lb)
	Pastinen[65]	Change intervention vs control group: 118 vs 98% (P 0.018)
	Rogers[68]	Mean change intervention vs control: range 0.56-1.24 vs no significant change
Tenderness/pain on palpation	Botha-Scheepers[83]	Pain intensity score: mean change 4.2 (95%CI 3.2, 5.1), SRM: 0.67, increase / no change / decrease: 74 / 11 / 15%
	Dilek[48]	No. painful joints: median change intervention: -4 (P < 0.016), control no significant change. No significant change in no. tender joints
	Dreiser[49]	No. painful joints: mean change intervention: -19, control: -10 (P <0.001)
	Flynn[52]	No. tender joints: mean change intervention 1: -1.0, control: -0.7 (P 0.02) No significant change intervention 2
	Garfinkel[54]	Tenderness right/left: mean change intervention: 2.20/2.14, control: 0.40/0.41 (P < 0.01)
	Haugen[29]	No. tender joints: mean change intervention: -4.8, control: -2.5 (P 0.084) SRM: 0.46
	Haugen[84]	Mean change -2, range -5 to 1
	Horvath[56]	No. tender joints: mean change intervention 1/2: -4.2 / -5.1, control: -0.4 (P < 0.01)
	Kvien[61]	No. tender joints: mean change intervention: -5.0, control: -2.6 (P 0.083)
	Poiraudeau[36]	Tenderness: mean change 1.68, SRM: 0.35, effect size: 0.22
	Saviola[72]	No. tender joints: mean change intervention 1 (1/2 year): -83/-50% (P 0.011), intervention 2 (1 year) no significant change.
	Schnitzer[73]	Tenderness: mean change intervention: 21.7%, control: 1.2% (P 0.02)
	Seiler[74]	Mean change intervention vs control: - No. of painful joints: -2.45 (43%) / -0.05 (1%) (P < 0.05) - Pain index: -6.09 (60%) / - 4.10 (30%) (P < 0.05)

* Only instruments assessed in ≥2 studies were included.

AUSCAN, Australian/Canadian Hand OA Index; CI, confidence interval; FIHOA, Functional Index for Hand OA; HAQ, Health Assessment Questionnaire; MCII, minimum clinically important improvement; no., number; OA, osteoarthritis; P, p-value; PASS, patient acceptable symptom state; SRM, standardized response mean; VAS, Visual Analogue Scale; vs, versus.

OVERVIEW OF LITERATURE SEARCH PER DATABASE

Total d.d. 20-01-2014:		2244 references, extracted from the following databases:
•	PubMed:	1843
•	MEDLINE:	840, of which 0 unique
•	Embase:	870, of which 317 unique
•	Web of Science:	344, of which 38 unique
•	COCHRANE:	197, of which 101 unique
•	CINAHL:	149, of which 41 unique
•	Academic Search Premier:	53, of which 11 unique
•	ScienceDirect:	80, of which 17 unique

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CHAPTER 8

Radiographic scoring methods in hand osteoarthritis – a systematic literature search and descriptive review

A.W. Visser, P. Bøyesen, I.K. Haugen, J.W. Schoones, D.M. van der Heijde, F.R. Rosendaal, M. Kloppenburg

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ABSTRACT

Objective
This systematic literature review aimed to evaluate the use of conventional radiography in hand osteoarthritis (OA) and to assess the metric properties of the different radiographic scoring methods.

Design
Medical literature databases up to November 2013 were systematically reviewed for studies reporting on radiographic scoring of structural damage in hand OA. The use and metric properties of the scoring methods, including discrimination (reliability, sensitivity to change), feasibility and validity, were evaluated.

Results
Of the 48 included studies, 10 provided data on reliability, 11 on sensitivity to change, four on feasibility and 36 on validity of radiographic scoring methods. Thirteen different scoring methods have been used in studies evaluating radiographic hand OA. The number of examined joints differed extensively and the obtained scores were analyzed in various ways. The reliability of the assessed radiographic scoring methods was good for all evaluated scoring methods, for both cross-sectional and longitudinal radiographic scoring. The responsiveness to change was similar for all evaluated scoring methods. There were no major differences in feasibility between the evaluated scoring methods, although the evidence was limited. There was limited knowledge about the validity of radiographic OA findings compared with clinical nodules and deformities, whereas there was better evidence for an association between radiographic findings and symptoms and hand function.

Conclusions
Several radiographic scoring methods are used in hand OA literature. To enhance comparability across studies in hand OA, consensus has to be reached on a preferred scoring method, the examined joints and the used presentation of data.

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder, frequently affecting the hands.[1,2] Hand OA is characterized by the formation of bony enlargements and deformities, most frequently occurring in the distal interphalangeal (DIP) joints and first carpometacarpal (CMC1) joints, less often in the proximal interphalangeal (PIP) joints and least prevalent in metacarpaphalangeal (MCP) joints.[3] Currently, no structure modifying treatments are available. To date, few high-quality clinical trials have been performed in hand OA.[4,5] A key problem in the lack of high-quality clinical trials in hand OA is the lack of standardization of outcome measures.[4,6] The Outcome Measures in Rheumatoid Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI) Task Force on Clinical Trials Guidelines defined core domains to describe outcomes in clinical trials. One of these domains for structure modifying trials was imaging.[7-9]

Conventional radiography is commonly used to assess structural damage in hand OA, as they are widely available and relatively cheap. Radiography allows visualization of osteophytes, joint space narrowing (JSN), subchondral cysts, sclerosis and central erosions.

Several standardized scoring methods are available such as the Kellgren-Lawrence (KL),[10] Kessler[11] and Kallmann grading scales,[12] the OARSI scoring atlas,[13] the Verbruggen-Veys anatomical phase score,[14] and the Gent University scoring system (GUSS).[15] These scores differ in the joints that are assessed, the type of scores (composite score or individual feature scores), and the total score ranges.

Most scoring methods have been shown to be reliable instruments for the assessment of structural damage in hand OA as well as its change.[15-17] However, a systematic comparison of the different scoring methods that will help to decide on a recommended method has not been performed.

We performed a systematic review to evaluate the use of conventional radiography in studies on hand OA and to assess the metric properties of the different radiographic scoring methods.[18] To this end we made use of the OMERACT filter,[19] focusing on aspects of discrimination (reliability and sensitivity to change), feasibility and truth (validity) of the radiographic scoring methods available in hand OA.

METHODS

Identification of studies

In cooperation with a medical librarian (JWS), a systemic literature search was performed to obtain all manuscripts reporting on any radiographic scoring methods assessing the nature, severity and progression of structural damage in hand OA. Medical literature databases (PubMed, Embase, Web of Science, COCHRANE and CINAHL) were searched up to November 2013, using all variations of the following key words 'hand', 'osteoarthritis', 'radiography', 'reliability', 'validity', 'sensitive' and 'feasibility' (see Supplementary File for exact search strings).

Inclusion and exclusion criteria

First all retrieved titles were screened, subsequently selected abstracts were reviewed and finally full text articles of the remaining references were read by one reviewer (AWV). A random sample of 150 titles was also reviewed by a second reviewer (MK), resulting in a similar selection of titles. In case of uncertainties in the reviewing process by the single reviewer, these were discussed and solved with MK. The metric properties of the studied radiographic scoring methods were evaluated according to four items: reliability, sensitivity to change, feasibility and validity. Inclusion criteria required for studies to evaluate these items differed per item:

- Reliability was evaluated in studies describing the reliability of two or more scoring methods performed on the same radiographs and by the same reader. Both cross-sectional and longitudinal studies were included.
- Sensitivity to change was evaluated in longitudinal studies of at least one year, in which hand OA was assessed by at least two radiographic scoring methods. Studies with a follow-up duration between one and three years using only one radiographic scoring method were also included.
- Feasibility was evaluated in studies describing the feasibility of one or more scoring methods.
- Validity was evaluated in studies comparing a radiographic scoring method with other measurements of structural damage such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), digital photography, histology or nodes at physical examination. In addition, validity was evaluated in studies comparing radiographic findings to clinical signs such as hand function or symptoms. Both cross-sectional and longitudinal studies were included.

  Studies that fulfilled the requirements for at least one of these four items were included in this review.

  Animal studies, reviews, abstracts, letters to the editor and studies reporting on musculoskeletal diseases other than hand OA or in languages other than English were excluded.

Data extraction

A standardized form was used to extract information about the following data: (1) study population (population size, setting, age, sex), (2) applied radiographic scoring methods, (3) performance of the scoring (number of readers, consensus/independent reading, (4) assessed joints, (5) level of analyses of obtained scores (joint, joint group or patient level) and used definition of outcome (e.g. summed scores (total or per feature), counts of number of affected joints, dichotomized outcome), (6) results concerning: reliability (intraclass correlation coefficient (ICC), kappa-value, percentage of agreement, smallest detectable change (SDC)), sensitivity to change (percentage of change, amount of change, standardized response mean (SRM)), feasibility (time needed to perform scoring), validity (correlations, associations and measures of agreement between radiographic scores and other measures). From a random number of studies data were also extracted by MK and all extracted results were discussed with MK.

Statistical analyses

Due to the heterogeneity of the studies and the difference in outcome measures that were used it was not possible to perform a meta-analysis. Therefore we chose to perform a descriptive review.

RESULTS

Literature flow

After removing duplicate references, 1,873 unique references were identified (Figure 1). After reviewing 133 abstracts and 80 full-text articles, 48 articles were included in this review. Of the included studies, 10 fulfilled the inclusion criteria for evaluation of reliability,[12,16,17,20-26 11] for sensitivity to change,[14,16,17,24-31] four for feasibility, [11,16,17,22] and 36 for validity of radiographic scoring methods.[20-24,32-62]

Evaluation of radiographic scoring methods was the primary aim in 10 of the included studies.[11,12,14,16,17,22,26,27,59,60] The other studies used radiographic scoring to identify prevalence or progression of radiographic OA features (n = 7),[20,25,28-30,33,34] or to compare obtained scores with other outcome measures (other imaging methods, clinical outcomes, histology) (n = 31).[21,23,24,31,32,35-38,40-58,61-63]

The characteristics of the evaluated or applied radiographic scoring methods (except for non-validated methods) are depicted in Table 1.

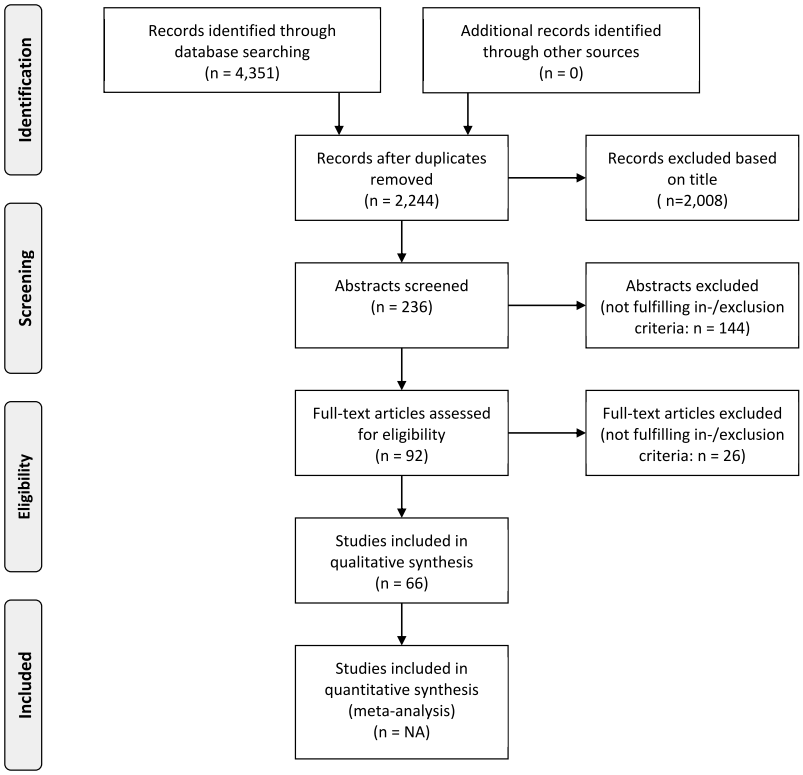

Figure 1. Overview of literature research

Table 1. Radiographic scoring methods for hand osteoarthritis

Scoring method	No. of joints	DIP	PIP	IP1	MCP	CMC1	STT	Scored features	Type of score	Range of total score
Anatomical phases[14]	26	+	+	+	+	-	-	Osteophytes, JSN, erosions, sclerosis	Composite score	0-218.4
Anatomical lesions[14]	24	+	+	-	+	-	-	Osteophytes, JSN, cysts	Composite score	Not specified
Burnett[74]	18	+	+	-	-	+	-	Osteophytes, JSN, sclerosis	Individual features	0-126
Eaton[75]	4	-	-	-	-	+	+	Osteophytes, JSN, erosions, cysts, sclerosis, subluxation	Composite score	Not specified
GUSS[15]	18	+	+	+	-	-	-	Osteolytic areas, bone plate resorption, JSN	Composite score	10-300
Kallman[12]	22	+	+	+	-	+	+	Osteophytes, JSN, cysts, sclerosis, deformity, cortical collapse	Individual features	0-208
Kellgren-Lawrence[10]	30	+	+	+	+	+	-	Osteophytes, JSN, sclerosis, alignment	Composite score	0-120
Kessler[11]	18	+	+	-	-	+	-	Osteophytes, JSN, sclerosis	Composite score	0-18
Lane[76]	22	+	+	+	-	+	+	Osteophytes, JSN, erosions/ cysts, sclerosis, deformity	Individual features	0-182
OARSI[13]	20	+	+	+	-	+	-	Osteophytes, JSN, erosions/ cysts, sclerosis, alignment	Individual features	0-198

CMC1, first carpometacarpal joint; DIP, distal interphalangeal joint; GUSS, Gent University scoring system; IP1, first interphalangeal joint; JSN, joint space narrowing; MCP, metacarpaphalangeal joint; No., number; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal joint; STT, scaphotrapezotrapezoidal joint.

Study characteristics

The characteristics of the 48 included studies are depicted in Table 2. Most studies included more women than men and most of the studied individuals were aged >50 years. As shown in Table 2, a wide variety of scoring methods (n = 13) was used to assess radiographic (signs of) hand OA. The KL scoring method was used most frequently (n = 24), followed by the OARSI scoring method (n = 18). Other scoring methods were the Kallman (n = 9), individual features following non-validated methods (n = 7), anatomical phases (n = 6), anatomical lesions (n = 2) and automatic JSW measurement (n = 3). The GUSS,

Burnett, Kessler, Lane, Eaton and a non-validated global score were all used in only one study. Although the majority of studies used only one radiographic scoring method, 15 studies used more than one method.

The examined joint groups differed between the studies: DIPs and PIPs were assessed most frequently (in 48 and 46 studies, respectively), followed by the CMC1s (n = 34), MCPs (n = 30), IP1s (n = 23) and the scaphotrapezotrapezoidal (STT) joints (n = 8).

The way the analysis of the radiographic scores were executed was quite different across the studies; (1) the score of one joint (the most severely affected) from a joint group, hand or patient[33,36,37,43,46,50], (2) sum score for all joints and features[14,16,17,20-22,24-26,31,34,38,44,45], (3) sum scores per feature[21,22,24,27-29,48], (4) sum scores per joint group[16,24,47,49], (5) mean score per feature[12,30] or per joint[60], (6) scores on joint level (composite score or per feature)[12,20-24,34,35,38,40-44,47,48,51-53,60,61] and (7) presence or absence of radiographic features per joint,[21,22,54,55,57,58] joint group,[32,38,39,45] or on patient level[52,56].

Table 2. Overview of included studies (n = 48)

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Scoring methods	Joints investigated	Analysis of radiographic scores
Addimanda, 2012[20]	Secondary care (50% erosive OA), 446 (93), 68	KL Kallman	DIP, PIP, CMC1 DIP, PIP, CMC1	Score per joint, summed total Score per joint per feature, summed per joint, summed total
Bagge, 1991[33]	General population, 217 (66), 82	KL	DIP, PIP, IP, MCP, CMC1	Score per joint group (most affected joint)
Bijsterbosch, 2011[16]	Familial polyarticular OA (GARP), 90 (78), 60	KL OARSI Anatomical phases	DIP, PIP, IP1, MCP, CMC1 DIP, PIP, IP1, CMC1 DIP, PIP, IP1, MCP	Summed per joint group, summed total Summed per joint group, summed total Summed per joint group, summed total
Botha-Scheepers, 2005[27]	Familial polyarticular OA (GARP), 20 (90), median age 62	OARSI	DIP, PIP, IP1, MCP, CMC1, STT	Summed total per feature
Botha-Scheepers, 2007[29]	Familial polyarticular OA (GARP), 193 (80), 60	OARSI	DIP, PIP, IP1, MCP, CMC1, STT	Summed total per feature
Botha-Scheepers, 2008[28]	Familial polyarticular OA (GARP), 172 (79), 61	OARSI	DIP, PIP, IP1, CMC1	Summed total per feature
Buckland-Wright,1990[30]	Unclear (radiographic OA patients), 32 (91), 62	Stereoscopic measurement	DIP, PIP, MCP	Mean score total per feature, mean score per joint group per feature

Table 2. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Scoring methods	Joints investigated	Analysis of radiographic scores
Caspi, 2001[34]	Secondary care (geriatric patients), 253 (68), 79	Modified OARSI	DIP, PIP, IP1, MCP, CMC1	Score per joint, summed total
Ceceli, 2012[62]	Secondary care, 60 (100), 59	Kallman	Not specified	Summed per hand
Cicuttini, 1998[35]	General population (twin study), 660 (100), 56	Burnett Kallman	DIP PIP, CMC1	Score per joint Score per joint
Dahaghin, 2004[43]	General population (Rotterdam study), 3906 (58), 67	Modified KL	DIP, PIP, MCP, CMC1, STT	Score per joint, score per joint group, score per patient (most affected joint)
Ding, 2007[44]	Finnish dentists/ teachers, 543 (100), range 45-63	KL	DIP, PIP, IP1, MCP	Score per joint, no. of joints scored ≥2, summed total
Dominick, 2005[45]	Familial OA (GOGO study), 700 (80), 69	KL	DIP, PIP, IP1, MCP, CMC1, STT	Present/absent of score ≥2 per joint group, summed total
Drape, 1996[32]	Secondary care (mucoid cyst), 23 (61), 63	Osteophytes, JSN (NVM)	DIP	Present/absent per joint group per feature
El-Sherif, 2008[46]	Secondary care, 40 (100), 57	KL	DIP, PIP, IP1, MCP, CMC1	Score per patient (most affected joint)
Grainger, 2007[54]	Secondary care, 15 (93), 59	Erosions (NVM)	DIP, PIP	Present/absent per joint
Hart, 1991[36]	Primary/secondary care (non-joint related problems), 541 (100), 54	KL	DIP, PIP, CMC1	Score per joint group (most affected joint)
Hart, 1994[37]	Primary care, 976 (100), age range 45-65	KL	DIP, PIP, CMC1	Score per joint group (most affected joint)
Haugen, 2012[21]	Secondary care (Oslo hand OA cohort), 106 (92), 69	KL OARSI Marginal erosions (NVM)	DIP, PIP, IP1, MCP, CMC1 DIP, PIP, IP1, MCP, CMC1 DIP, PIP, IP1, MCP, CMC1	Score per joint, summed total Score per joint per feature, summed total per feature Present/absent per joint
Haugen, 2013[24]	Secondary care (Oslo hand OA cohort), 190 (91), 62 (longitudinal analysis: 99 (92), 61)	KL OARSI	DIP, PIP, IP1, MCP, CMC1 DIP, PIP, IP1, MCP, CMC1	Score per joint, summed per joint group, summed total Score per joint per feature, summed total per feature

Table 2. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Scoring methods	Joints investigated	Analysis of radiographic scores
Huetink, 2012[59]	22 phantom joints, 22 human cadaver joints	Automatic JSN quantification	DIP, PIP, MCP	Millimeter per joint
Iagnocco, 2005[56]	Secondary care (inflam-matory OA), 110 (100), 67	Classical/ erosive OA (NVM)	DIP, PIP	Present/absent per patient
Jones, 2001[47]	Secondary care, 522 (67), 56	OARSI	DIP, CMC1	Score per joint per feature, summed per joint group
Jonsson, 2012[38]	General population (AGES-Reykjavik study), 381 (58), 76	KL	DIP, PIP, CMC1	Score per joint, present/absent of score ≥2 per joint group, summed total
Kallman, 1989[12]	General population (BLSA), 50 (0), 68	KL Kallman	DIP, PIP, IP1, CMC1 DIP, PIP, IP1, CMC1, STT	Score per joint, score per joint group, mean score total Score per joint per feature, score per joint group per feature, mean score total per feature
Keen, 2008[57]	Secondary care, 37 (84), 57	OARSI	DIP, PIP, MCP, CMC1	Present/absent per joint per feature
Kessler, 2000[11]	Advanced hip/knee OA patients (Ulm OA study) 50, range 51-79	Kessler Kallman Lane	DIP, PIP, CMC1 DIP, PIP, CMC1 DIP, PIP, CMC1	No. of affected joints per joint group Not specified Not specified
Kortekaas, 2011[48]	Secondary care, 55 (47), 61	OARSI	DIP, PIP, IP1, CMC1	Score per joint per feature, summed total per feature
Kwok, 2011[22]	Familial polyarticular OA (GARP), 235 (83), 65, and 471 controls	OARSI Anatomical phases Semi-automated measured JSW	DIP, PIP, MCP DIP, PIP DIP, PIP, MCP	Score per joint per feature, summed total per feature Present/absent per joint Score per joint, summed total
Lee, 2012[49]	General population (KLoSHA), 378 (48), 75	KL	DIP, PIP, IP1, MCP, CMC1	Summed per finger

Table 2. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Scoring methods	Joints investigated	Analysis of radiographic scores
Maheu, 2007[17]	Secondary care, 105 (93), 61	KL Kallman Global score Anatomical phases	DIP, PIP, MCP,CMC1 DIP, PIP, MCP,CM-C1,STT DIP, PIP, MCP,CM-C1,STT DIP, PIP, MCP	Summed total Summed total Summed total Summed total
Mancarella, 2010[23]	Secondary care, 35 (94), 66	KL Kallman	DIP, PIP, MCP DIP, PIP, MCP	Score per joint Score per joint
Marshall, 2009[39]	Primary care (hand pain), 592 (62), 64	KL	DIP, PIP, IP1, MCP, CMC1, STT	Present/absent of score ≥2 per joint group
Mathiessen, 2012[40]	Secondary care (Oslo hand OA cohort), 127 (91), 69	OARSI	DIP, PIP, IP1, MCP	Score per joint per feature
Olejárová, 2000[31]	Secondary care, erosive OA: 28 (93), 68; non-erosive OA: 24 (83), 65	Kallman	DIP, PIP, IP1, MCP, CMC1	Summed total
Ozkan, 2007[50]	Secondary care, 100 (87), 69	KL	DIP, PIP, MCP, CMC1	Score per patient (most affected joint)
Rees, 2012[41]	Secondary care (GOAL study participants with ≥1 node), 1939 (54), 68	KL OARSI	DIP, PIP, IP1, CMC1 DIP, PIP, IP1, CMC1	Score per joint Score per joint per feature
Saltzherr, 201361	Secondary care, 30 (70), median age 57	Eaton	CMC1, STT	Score per joint, score per joint per feature
Sonne-Holm, 2006[51]	General population (Copenhagen city hearth study), 3355 (61),age>20	Modified KL	CMC1	Score per joint, score per joint per feature
Stern, 2004[42]	Primary and secondary care (I-NODAL study), 71 (80), 67	KL	DIP, PIP, IP1, CMC1	Score per joint
Sunk, 2012[53]	Post mortem IP joints, 40 (44), median age 66	KL OARSI	DIP, PIP DIP, PIP	Score per joint Score per joint per feature
Verbruggen, 1996[14]	Unclear (radiographic OA), 46 (96), 57	Anatomical phases Anatomical lesions	DIP, PIP, MCP DIP, PIP, MCP	Summed total Summed total
Verbruggen, 2002[26]	Unclear (radiographic OA, 2 RCT's), 222 (92), 56	Anatomical phases Anatomical lesions	DIP, PIP, MCP DIP, PIP, MCP	Summed total Summed total

Table 2. *Continued*

First author, year of publication	Source population, no. of patients (% women), mean age (years)	Scoring methods	Joints investigated	Analysis of radiographic scores
Verbruggen, 2012[25]	Secondary care (RCT), 60 (85), 61	Anatomical phases GUSS	DIP, PIP DIP, PIP	No. of joints in each phase per patient Summed total
Van 't Klooster, 2008[60]	Familial polyarticular OA (GARP), 40 (33), 60	OARSI Automatic JSW quantification	DIP, PIP, MCP DIP, PIP, MCP	Score per joint Mean score per joint
Vlychou, 2009[58]	Secondary care (OA patients), 22 (91), 63	Osteophytes, erosion (NVM)	DIP, PIP, IP1, MCP, CMC1	Present/absent per joint per feature
Wittoek, 2011[55]	Secondary care, erosive OA: 9 (67), median 61; non-erosive OA: 5 (100), median 63	Osteophytes, erosions (NVM)	DIP, PIP	Present/absent per joint per feature
Zhang, 2002[52]	General population (Framingham hand OA study), 1032(64), age≥71	Modified KL	DIP, PIP, IP1, MCP, CMC1	Score per joint, present/absent of score ≥2 per patient

AGES, Age, Gene/Environment Susceptibility; BLSA, Baltimore Longitudinal Study of Aging; CMC1, first carpometacarpal joint; DIP, distal interphalangeal joint; GARP, Genenetics osteoArthritis and Progession; GOAL, Genetics of Osteoarthritis and Lifestyle; GOGO, Genetics of Generalized Osteoarthritis; I-NODAL, Investigation of Nodal Osteoarthritis to Detect an Association with Loci encoding IL-1; IP1, first interphalangeal joint; JSN, joint space narrowing; JSW, joint space width; KL, Kellgren-Lawrence; KLoSHA, Korean Longitudinal Study on Health and Aging; MCP, metacarpaphalangeal joint; no., number; NVM, non-validated method; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal joint; RCT, randomized controlled trial; STT, scaphotrapezotrapezoidal joint.

Discrimination

Reliability

Ten included articles provided data on the reliability of at least two radiographic scoring methods, shown in Table 3. The KL scoring method was assessed in seven of these studies.[12,16,17,20,21,23,24] Other assessed scoring methods were the Kallman (n = 4),[12,17,20,23] OARSI (n = 4),[16,21,22,24] anatomical phases (n = 4),[16,17,25,26] anatomical lesions (n = 1),26 GUSS (n = 1),[25] global score (n = 1),[17] and the semi-automated joint space width (JSW) measurement (n = 1).[22]

Eight studies provided cross-sectional data.[12,16,17,20-24] The ICCs as well as kappa values were shown to be reliable for all assessed total scores, and no differences between the scoring methods were observed. The ICCs and kappa values for the individual radiographic features depended on the scored feature; the lowest reliability was reported for the scoring of cysts and the highest for the scoring of erosions and osteophytes.[12,20,21]

In five of the studies readers performed the scoring independently of another reader, providing results on the interreader reliability.[12,16,17,21,24] The interreader ICCs and kappa values were somewhat lower than the intrareader values, especially for the Kallman method and for sclerosis as scored using the OARSI atlas.[12,17,24] Whether readers were from one or different centers did not seem to influence the reliability of the scoring methods.

Six studies provided data on the reliability of change of at least two radiographic scoring methods.[12,16,17,24-26] The reliability of change of KL, OARSI, Kallman, global, anatomical phases and GUSS scores was reported to be good for all methods.[12,16,17,24-26] Bijsterbosch et al. compared the SDC of three scoring methods on patient level, showing a small difference in favor of the KL score, followed by the anatomical phases and OARSI scores. Reported SDCs were a little higher over a six year interval than over a two year interval.[16] Haugen et al. assessed reliability of change in KL and OARSI scores, showing a good reliability for the KL score and most of the OARSI features. ICC and kappa values were somewhat lower for change scores than for baseline KL and OARSI scores. Except for change of sclerosis (OARSI), moderate to good reliability was reported for the scoring of change in KL and OARSI scores.[24] Kallman et al. evaluated agreement on progression in KL and Kallman scores on joint group level, showing that agreement was more often present in DIP joints than PIP joints and that agreement was lowest on the progression of cysts.[12]

Sensitivity to change

Table 4 shows the characteristics of the included studies describing data on sensitivity to change of radiographic scoring methods. Nine studies reported data on short-term follow-up (≤3 years), most of them on patient level.[16,17,25-31] Two studies evaluated change of summed KL, Kallman and anatomical phases scores, of which one study also evaluated the global score.[16,17] Maheu et al. reported SRMs over a 1 year interval of the global, KL, Kallman, anatomical phases and OARSI scores; all below 0.50, indicating that the responsiveness to change was small.[17] Bijsterbosch et al. detected somewhat more progression over a two year interval when scored following the KL or anatomical phases score as compared with the OARSI atlas.[16] The anatomical phases score was evaluated in two other studies,[25,26] one of these studies (a randomized controlled trial) also assessed change of GUSS. Progression over a one year interval was detected by both scoring methods, although no difference between treatment and placebo group was observed.[25]

Table 3. Studies providing data on reliability of scoring methods (n = 10)

First author	No. of readers, centers	Intrareader reliability*	Interreader reliability*
Cross-sectional studies			
Addimanda[20]	2 (consensus), 1	KL: ICC 0.994 Kallman: ICC 0.987, κ range per feature 0.42-0.81	N/A
Bijsterbosch[16]	3 (independent), 3	KL: ICC range per reader 0.90-0.96 OARSI: ICC range per reader 0.77-0.97 Anatomical phases: ICC range per reader 0.88-0.97	KL: ICC range per 2 readers 0.84-0.91 OARSI: ICC range per 2 readers 0.80-0.95 Anatomical phases: ICC range per 2 readers 0.81-0.95
Haugen[21]	2 (independent), 2	KL: ICC 0.97, κ 0.86 (one reader) OARSI (including marginal erosions): ICC range per feature 0.70-0.97, κ range per feature 0.75-0.88 (one reader)	KL: ICC 0.96, κ 0.79 OARSI (including marginal erosions): ICC range per feature 0.56-0.95, κ range per feature 0.62-0.81
Haugen[24]	2 (independent), 2	KL: ICC 0.97, κ 0.82 (one reader) OARSI: ICC range per feature 0.62-0.96, κ range per feature 0.64-0.81 (one reader)	KL: ICC 0.95, κ 0.70 OARSI: ICC range per feature -0.07-0.94, κ range per feature 0.00.-0.77
Kallman[12]	4 independent, 2	KL mean score: ICC 0.80, range per joint group 0.68-0.87 Kallman mean score: ICC per feature range 0.74-0.84, per feature per joint group range 0.62-0.93	KL mean score: ICC 0.74, range per joint group 0.74-0.81 Kallman mean score: ICC per feature range 0.29-0.71, per feature per joint group range 0.33-0.82
Kwok[22]	2 (consensus), 1	OARSI (JSN): ICC 0.92 Semi-automated JSW: ICC 0.99, mean difference 0.017 mm (SD 0.04), SDD 0.055 mm	N/A
Maheu[17]	2 (independent), 2	KL: ICC range per reader 0.988-0.991 Kallman: ICC range per reader 0.962-0.999 Global: ICC range per reader 0.922-0.961 Anatomical phases: ICC range per reader 0.999-0.999	KL: ICC 0.951 Kallman: ICC 0.706 Global: ICC 0.859 Anatomical phases: ICC 0.996
Mancarella[23]	2, not specified	KL: ICC score per joint 0.99 Kallman: ICC score per joint 0.99	

Table 3. *Continued*

First author	No. of readers, centers	Intrareader reliability*	Interreader reliability*
Longitudinal studies			
Bijsterbosch[16]	3 (independent), 3 Mean follow-up 2 years	KL: SDC range per reader 2.1-7.1 OARSI: SDC range per reader 1.2-10.2 Anatomical phases: SDC range per reader 1.4-7.8	KL: SDC 2.9 OARSI: SDC 4.1 Anatomical phases: SDC 2.7
	Mean follow-up 6 years	KL: SDC range per reader 3.7-8.1 OARSI: SDC range per reader 3.0-11.1 Anatomical phases: SDC range per reader 3.5-9.9	KL: SDC 3.8 OARSI: SDC 4.6 Anatomical phases: SDC 4.0
Haugen[24]	2(independent), 2 Mean follow-up 7 years	KL: ICC 0.93, κ 0.83 (one reader) OARSI: ICC range per feature -0.02-0.96, κ range per feature 0.00-0.90 (one reader)	KL: ICC 0.83, κ 0.53 OARSI: ICC range per feature -0.03-0.90, κ range per feature -0.03-0.71
Kallman[12]	4 (independent), 2 Mean follow-up 23 years	N/A	KL: scattered agreement Deformity/collaps: agreement Cysts: disagreement Osteophytes/JSN/sclerosis: scattered agreement.
Maheu[17]	2 (independent), 2 Mean follow-up 1 year	KL: ICC range per reader 0.990-0.998 Kallman: ICC range per reader 0.986-0.959 Global: ICC range per reader 0.939-0.956 Anatomical phases: ICC range per reader 0.941-0.988	KL: ICC 0.998 Kallman: ICC 0.995 Global: ICC 0.999 Anatomical phases: ICC 0.998
Verbruggen[26]	2 (independent), 1 Mean follow-up 3 year	Anatomical phases: agreement for 2 RCTs 84-93%, κ 0.6-0.8 Anatomical lesions: correlation for 2 RCTs r 0.7-0.9, R2 44-87%	Anatomical phases: agreement for 2 RCTs 81-85%, κ 0.6-0.7 Anatomical lesions: correlation for 2 RCTs r 0.7-0.8, R2 55-66%
Verbruggen[25]	2 (independent), 1 Mean follow-up 1 year	Anatomical phases: 96% agreement, κ 0.95 GUSS: ICC 0.97	Anatomical phases: 94% agreement, κ 0.92 GUSS: ICC 0.86, SDC 18

*Unless stated otherwise ICCs are for summed total scores on patient level, κ's on joint level.

GUSS, Ghent University Score System; ICC, intraclass correlation coefficient; κ, kappa; KL, Kellgren-Lawrence; OARSI, Osteoarthritis Research Society International; JSN, joint space narrowing; JSW, joint space width; N/A, not applicable; r, correlation coefficient; R2, explained variance; RCT, randomized controlled trial; SD, standard deviation; SDC, smallest detectable change; SDD, smallest detectable difference.

Five studies reported follow-up data of only one scoring method.[27-31] Botha-Scheepers et al. reported change of JSN and osteophytes as scored following the OARSI atlas over a two year interval.[27-29] Scoring of these features tended to be more sensitive to change when scoring radiographs in chronological order as compared with paired reading.27 Buckland-Wright et al. evaluated stereoscopic measurement of individual OA features during a 1.5 year interval, reporting change of most features.64 Olejárová et al. evaluated change of hand OA over a two year interval using the Kallman scoring method, reporting no significant difference in total score.[31]
In the three studies investigating long term follow-up data (>3 years), change in KL (n = 2), OARSI (n = 2), anatomical phases (n = 2) and anatomical lesions (n = 1) score was evaluated.[12,14,16,24] Studies with a longer follow-up duration detected higher occurrence of progression of OA features as well as higher mean radiographic change scores.[16]

Table 4. Studies providing data on sensitivity to change of radiographic scoring methods in hand osteoarthritis (n = 11)

First author	Mean follow-up (years)	Definition of progression	Sequence known/ unknown	Results relevant for evaluation of sensitivity to change
Short-term				
Bijsterbosch[16]	2	Change > SDC	Known	Percentage progression (range for 3 readers): - KL: 19-56% - OARSI: 7-38% - Anatomical phases: 13-52%
Botha-Scheepers[27]	2	≥1 score	Known/ unknown	Progression of JSN/osteophytes: - chronological reading: 1/15% (SRM 0.38/0.41) - paired reading: 5/15% (SRM 0.00/0.39)
Botha-Scheepers[28]	2	≥1 score	Unknown	JSN: 19% progression, mean change 0.3, SRM 0.34 Osteophytes: 22% progression, mean change 0.4, SRM 0.35
Botha-Scheepers[29]	2	≥1 score	Unknown	JSN: 24% progression (≥2/≥3/≥4 score: 10/4/3%) Osteophytes: 22% progression (≥2/≥3/≥4 score: 10/4/3%)
Buckland-Wright[30]	1.5	Change > variations in precision	Not specified	JSW: 62% narrowing (P < 0.02) Subchondral sclerosis: 60% increase, 34% decrease Osteophytes: increase in size and no. (P < 0.005) Juxta-articular radiolucencies: increase in size (P < 0.002), not in no.
Maheu[17]	1	Change in summed score	Unknown	SRM for 2 readers: - KL: 0.17/0.24 - Kallman: 0.26/0.29 - Global: 0.17/0.27 - Anatomical phases: 0.18/0.27

Table 4. *Continued*

First author	Mean follow-up (years)	Definition of progression	Sequence known/ unknown	Results relevant for evaluation of sensitivity to change
Olejárová[31]	2	Change in summed score	Unknown	Erosive OA: change 5.0, P > 0.05 Non-erosive OA: change 4.3, P > 0.05
Verbruggen[26]	3	Change in anatomical phases, Change in anatomical lesions	Known	Anatomical lesions showed different progression between trial arms, anatomical phases did not.
Verbruggen[25]	1	Change in ana-to-mical N/S/J phase to E phase, Change in summed score	Unknown	No. (%) joints with progression to E phase: - Total group: 24 (2.8%) of 848 N/S/J joints - Placebo treated: 15 (3.6%) of 429 N/S/J joints - Adalimumab treated: 9 (2.1%) of 419 N/S/J joints Mean difference GUSS (baseline palpable swelling yes/no): - Placebo: -5/3 - Adalimumab: 4/1
Long-term				
Bijsterbosch[16]	6	Change > SDC	Known	Percentage progression (range for 3 readers): - KL: 51-80% - OARSI: 33-74% - Anatomical phases: 27-66%
Haugen[24]	7.3	Change in score	Known	Progression (percentage of joints): - KL: 29% - OARSI: osteophytes 19%, JSN 13%, erosions 9%, malalignment 4%, cysts 2%, sclerosis 1%
Verbruggen[14]	4.6	Change in anatomical phases, Change in anatomical lesions	Known	Progression of anatomical lesions more frequent in PIP/DIP than MCP. Progression of anatomical phases in 43%. Progression according anatomical phases and anatomical lesions yielded comparable results.

DIP, distal interphalangeal joint; GUSS, Ghent University Score System; JSN, joint space narrowing; JSW, joint space width; KL, Kellgren-Lawrence; MCP, metacarpaphalangeal joint; no., number; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal joint; SDC, smallest detectable change; SRM, standardized response mean.

Feasibility

Four studies reported data regarding feasibility of radiographic scoring methods (Table 5).[11,16,17,22] The KL, anatomical phases and Kallman scoring methods were assessed in two studies.[16,17] The OARSI, Kessler and Lane scoring methods, as well as a non-validated global score and semi-automated JSW measurement, were all examined in only one study.[11,16,17,22]

The mean time to perform scoring ranged from 1.5 to 10-15 minutes per hand radiograph. The KL, anatomical phases and Kessler scoring methods seemed to be least time consuming while scoring according Kallman, Lane and the OARSI atlas needed more time to perform.[11,16,17] However, the time needed to perform the scoring differed per study.[11,16,17] Bijsterbosch et al. showed that the performance time increased in patients with higher levels of structural abnormalities; one minute increment in performance time was associated with 3.9 points in KL score (95% confidence interval (CI) 1.0 to 6.8), 8.0 (5.3 to 10.7) points in OARSI score, and 21.1 (12.9 to 29.2) points in the anatomical phases scoring method.[16]

Table 5. Studies providing data on feasibility of radiographic scoring methods in hand osteoarthritis (n = 4)

First author	No. of radiographs	Mean (SD) time to perform scoring
Bijsterbosch[16]	3	KL: 4.3 (2.5) min OARSI: 9.3 (6.0) min Anatomical phases: 2.8 (1.5) min
Kessler[11]	1	Kessler: 5 min per hand Kallman: 10-15 min per hand Lane: 10-15 min per hand
Kwok[22]	1	Semi-automated JSW measurement: 5.1 (2.8) min
Maheu[17]	1	KL: 1.9 (0.6) min Kallman: 3.5 (0.7) min Global score: 1.5 (0.5) min Anatomical phases: 1.6 (0.5) min

KL, Kellgren-Lawrence; OARSI, Osteoarthritis Research Society International; SD, standard deviation; min, minutes.

Validity

The 36 studies providing data regarding validity of radiographic scoring methods are listed in Table 6. Analyses on individual joint level were performed in 18 of these studies, and analyses on joint group or patient level were performed in 13 and 14 studies, respectively. Thirteen studies focused on structural findings at physical examination in comparison to radiographic OA findings.[20,22,33-42] Four studies presented correlation coefficients and kappa values, reporting that nodes at physical examination were weakly to moderately associated with radiographic hand OA.[34,35,37,38] The lowest agreement was reported in a study on clinical Heberden nodes and radiographic DIP osteophytes scored following the Burnett scoring method, performed on joint level (k = 0.36).[35] The highest correlation was reported in a study examining a clinical score consisting of nodes and deformity and the radiographic KL score, analyzed on joint group level (males r = 0.47, females r = 0.66).[38]

Two studies reported the association between two radiographic scoring methods and clinical nodes, both analyzed on a joint level.[20,41] Addimanda et al., examining KL and Kallman scores, reported the erosion and osteophyte features of the Kallman method to be

associated most strongly with nodes (OR 7.4 and 3.2 respectively).[20] Rees et al. examined the association between KL and OARSI scores and clinical nodes, reporting ORs only for the KL method (range per joint 2.3-21.2). Regarding the OARSI atlas, JSN was mentioned to be more strongly associated with clinical nodes than osteophytes.[41]

Seventeen studies assessed clinical symptoms and hand function in comparison to radiographic scoring methods (KL: n = 14, OARSI: n = 3, Kallman: n = 1, JWS/JSN: n = 1).[22,24,33,36,37,39,43-52,62] All studies reported significant associations between radiographic OA features and pain and disability, of which four showed a dose-dependent association between KL and OARSI scores and pain.[24,43,44,48] Of the nine studies assessing grip or pinch strength, only two did not find an association with radiographic OA (1x KL, 1x JSW/JSN, analyzed on patient level).[22,50]

Only one study assessed longitudinal data, showing incident or progressive KL or OARSI scores to be associated with incident pain on joint level and with change in Australian/Canadian Hand Osteoarthritis Index (AUSCAN) pain/function and grip strength.[24]

One study examined the association between the KL and OARSI scoring methods and histological findings on joint group level, showing a good correlation ($r \geq 0.7$) as well as a high sensitivity and specificity.[53]

Four studies assessed individual features of hand OA by both radiography and MRI.[21,32,54,55] The agreement between the two methods was lowest for the presence of cysts and highest for central erosions.[21] Three of the studies showed that MRI detected more osteophytes, cysts and erosions as compared to radiography.[32,54,55]

One study assessed individual features of CMC1 and STT OA by both radiography and CT, reporting the latter to detect more JSN, osteophytes, subchondral sclerosis, cysts, erosions and subluxation.[61]

even studies used both US and radiography to assess hand OA signs.[23,40,48,55-58] Six of the studies examined individual radiographic features and reported US to detect more osteophytes and erosions than radiography. A study on KL and Kallman scores reported a negative correlation between radiographic JSN and US-detected cartilage thickness on joint level.[23]

Three studies examined hand OA using digital photography and radiography.[38,42,47] Two studies, performed on joint group level, reported a good correlation between OARSI scores and Heberden nodes on digital photography ($r = 0.74$), and a weak to moderate correlation between summed KL scores and summed digital photograph score (comprising enlargement and deformity) on digital photography (males $r = 0.35$, females $r = 0.53$).[38,47]

Finally, two studies examined quantitative measures of JSW, both on individual joint level.[59,60] Van 't Klooster et al. showed that automatic JSW quantification was associated with JSN scored according to the OARSI atlas.[60] Huetink et al. reported that automatic JSW quantification has a high accuracy in measuring the true JSW (assessed by micrometer).[59]

Table 6. Studies providing data on validity of scoring methods (n = 37)

First author	Validation method	Results relevant for evaluation of validity
Clinical: structural findings at physical examination		
Addimanda[20]	Heberden/Bouchard nodes (yes/no)	OR (95%CI) for nodes on joint level, adjusted for disease duration, BMI: - KL: 2.20 (2.09, 2.31) - Kallman: 1.17 (1.62, 1.72) - Kallman JSN: 2.57 (2.40, 2.75) - Kallman osteophytes: 3.19 (2.97, 3.42) - Kallman central erosions: 7.4 (6.0, 10.1)
Bagge[33]	Nodes/periarticular enlarge-ment, instability, squaring (yes/no ≥1 fea-ture per joint)	Correlated with KL score in all joint groups (correlation coefficient not provided), test for linear trend: P < 0.01. Clinical features also present in KL 0 joint groups.
Caspi[34]	Nodes, malalignment DIP/ PIP (summed)	Correlation with OARSI: - summed total: r 0.4 (P 0.001) - DIP/PIP: range per joint r 0.18-0.52 (P 0.004-0.0001)
Cicuttini[35]	Heberden nodes (yes/no)	κ with DIP osteophytes (Burnett): 0.36 (95%CI 0.33, 0.39)
Hart[36]	Nodes (yes/no)	Sensitivity for KL ≥2: range per joint group 19-49% Specificity for KL ≥2: range per joint group 87-98%
Hart[37]	Nodes IP (graded 0-4), squaring CMC1 (grade 0-1)	Prevalence node ≥2: KL0: 3%, KL1: 19%, KL2: 48%, KL3: 74%, KL4: 82% Prevalence squaring: KL0: 5%, KL1: 11%, KL2: 25%, KL3: 41%, KL4: 70% (correlation coefficient not specified)
Jonsson[38]	Nodes, deformity (graded 0-3, summed)	Correlation summed score with summed total KL: males r 0.47, females r 0.66 Prevalence KL ≥2 (DIP 67%, PIP 32%, CMC1 20%) higher as com-pared to clinical grade ≥2 (DIP 54%, PIP 19%, CMC1 10%)
Kwok[22]	Nodes (yes/no)	β (95%CI) for nodes on joint level, adjusted for age, sex, BMI, family effect, mean phalanx width: - JSW: -0.37 (-0.40, -0.34) - JSN: 0.48 (0.42, 0.55)
Marshall[39]	Nodes, deformity, enlarge-ment (yes/no)	OR (95%CI) of presence of ≥1 feature for: - KL ≥2 in CMC1: 2.2 (1.5, 3.3) - KL ≥2 in any thumb joint: 3.1 (2.1, 4.5)
Mathies-sen[40]	Nodes (yes/no)	Osteophytes (OARSI) in 30% of joints, nodes in 37% of joints
Rees[41]	Nodes (yes/no)	KL ≥2 associated with any node on patient level: OR range per joint 2.26-21.23 (adjusted for age, sex, BMI, hand dominance, trauma, occupation, sports). JSN/osteophytes (OARSI) also associated with nodes (P < 0.001); ORs of JSN greater than ORs of osteophytes in all joints except for IP1/CMC1.
Stern[42]	Nodes (yes/no)	Sensitivity for KL ≥2: range per joint group 42-100% Specificity for KL ≥2: range per joint group 17-94%
Clinical: symptoms, function		
Bagge[33]	Pain/stiffness (interview, yes/no)	Correlated with KL score in all joint groups (correlation coefficient not provided), test for linear trend: P < 0.01.

Table 6. *Continued*

First author	Validation method	Results relevant for evaluation of validity
Ceceli[62]	Pain (VAS), disability (DASH questionnaire), dexterity (Purdue pegboard test), grip/pinch strength	Correlation with summed Kallman score right/left hand: - Pain: r 0.17 / 0.18 (P > 0.05) - Disability: r 0.29 / 0.30 (P < 0.05) - Dexterity: r -0.26 / -0.30 (P < 0.05) - Grip strength: r -0.37 / -0.40 (P < 0.05) - Pinch strength: r range per test -0.31 to -0.25 / -0.35 to -0.27 (P < 0.05)
Dahaghin[43]	Pain (interview, yes/no)/ disability (HAQ)	OR (95%CI) for KL ≥2/≥3/4 on patient level, adjusted for age, sex: - pain: 1.9 (1.5, 2.4) / 1.8 (1.3, 2.5) / 3.6 (2.2, 5.8) - disability: 1.5 (1.1, 2.1) / 1.6 (1.1, 2.5) / 1.6 (0.9, 2.9) Pain associated with KL ≥2 in PIP/CMC1/STT, disability with KL ≥2 in MCP. Adjusted OR (95%CI) for KL ≥2 in all joint groups: pain 2.7 (1.4, 5.2), disability 2.7 (1.3, 6.0).
Ding[44]	Pain (questionnaire, yes/no per joint, summed)	Correlation with summed total KL: r 0.26 (P 0.0005) Correlation with no. KL≥2 joints: r 0.28 (P 0.0005) PR (95%CI) for pain on joint level, adjusted for age, occupation: - KL 2: 1.70 (1.44, 2.01) - KL ≥3: 5.17 (4.34, 6.16) Adjusted PR (95%CI) for mild / moderate pain on joint level: - KL 2: 1.93 (1.54, 2.41) / 2.21 (1.58, 3.10) - KL ≥3: 4.92 (3.77, 6.43) / 11.73 (8.95, 15.38)
Dominick[45]	Grip/pinch strength	β (P-value) for grip / pinch strength, adjusted for age, sex, pain, chondro-calcinosis, hand hypermobility: - Summed total KL: -0.67 (<0.001) / -0.16 (<0.001) - KL ≥2 PIP: -6.67 (0.003) / -1.17 (0.070) - KL ≥2 MCP: -3.32 (0.114) / -1.78 (0.003) - KL ≥2 CMC: -9.06 (<0.001) / -1.03 (0.049) - KL ≥2 per finger: range -1.81 to -11.08 (p<0.05)
El-Sherif[46]	AUSCAN, morning stiffness (minutes), grip strength, Ritchie index	AUSCAN pain/function higher in KL4 than KL2 (P < 0.05) Correlation with KL score: - AUSCAN pain: r 0.459 (p 0.003), function: r 0.394 (P 0.012) - Grip strength right hand: r -0.322 (P 0.043) Other measures not significantly correlated with KL.
Hart[36]	Tenderness, pain on movement (physical examination, yes/no)	Comparison tenderness / pain on movement with KL ≥2: - sensitivity: range per joint group 7-26% / 1-22% - specificity: range per joint group 92-99% / 96-99%
Hart[37]	Pain, stiffness (interview, yes/no)	Prevalence symptoms in patients with KL <2: 15%, KL2: 49%, KL3-4: 81%; test for linear trend: P < 0.01

Table 6. *Continued*

First author	Validation method	Results relevant for evaluation of validity
Haugen[24]	Tenderness on palpation (yes/no), grip strength, AUSCAN	Cross-sectional OR (95%CI) for tenderness on joint level, adjusted for age, sex: - KL score 1/2/3/4: 1.4 (1.2, 1.7) / 3.0 (2.4, 3.7) / 6.8 (4.5, 10) / 5.3 (3.3, 8.6) - OARSI osteophytes score 1/2/3: 2.8 (2.3, 3.4) / 4.3 (3.0, 6.3) / 4.5 (2.9, 7.0) - OARSI JSN score 1/2/3: 0.9 (0.7, 1.2) / 1.9 (1.4, 2.5) / 2.5 (1.7, 3.7) - OARSI erosions: 3.3 (2.3, 4.9), malalignment: 2.8 (2.0, 3.9), cysts: 2.2 (1.4,3.3), sclerosis: 2.6 (1.1, 6.0) AUSCAN pain associated with summed KL and OARSI osteophytes/ JSN. AUSCAN function associated with summed KL and OARSI osteophytes, JSN, erosions, cysts. Grip strength associated with summed KL and all OARSI features except for sclerosis. Summed KL per joint group only associated with grip strength (CMC1 strongest). Adjusted OR (95%CI) of progressive/incident scores for incident tenderness: - KL score 1/2/3/4: 1.2 (0.7, 2.0) / 1.5 (0.9, 2.4) / 5.7 (3.0, 11) / 11 (4.0, 33) - OARSI osteophytes: 3.0 (2.0, 4.4), JSN: 2.8 (1.7, 4.7), erosions: 8.4 (4.7, 15), malalignment: 3.8 (1.9, 7.4), cysts: 2.2 (0.9, 5.0), sclerosis: 2.4 (0.8, 8.0) Increasing summed KL and OARSI JSN/malalignment associated with increased AUSCAN function. More malalignment associated with less grip strength. Change summed KL per joint group not associated with AUSCAN/ grip strength.
Jones[47]	AUSCAN, grip strength	Association with summed OARSI per joint group, adjusted for age/ sex/other joints/Heberden nodes: - AUSCAN pain: PIP β 0.17, CMC1 β 0.14 ($P < 0.05$) - AUSCAN function: PIP β 0.15, CMC1 β 0.19 ($P < 0.05$) - grip strength: PIP β -0.12, CMC1 β -0.09 ($P < 0.05$)
Korteka-as48	AUSCAN, pain (VAS), Doyle index of hands	OR (95%CI) for pain on palpation on joint level, adjusted for age, sex, BMI: - osteophytes score 1/2/3: 2.2 (1.7, 2.9) / 3.9 (2.6, 5.9) / 4.8 (2.7, 8.4) - JSN score 1/2/3: 2.0 (1.4, 2.8) / 5.3 (3.1, 9.1) / 6.4 (2.7, 14.8) Summed osteophytes/JSN not associated with AUSCAN pain, VAS, Doyle.
Kwok[22]	AUSCAN, pain on palpation (yes/no), grip strength, mobility	β (95%CI) for JSW / JSN on joint level, adjusted for age, sex, BMI, family effect, mean phalanx width: - self-reported pain: -0.21 (-0.27, -0.16) / 0.39 (0.30, 0.48) - pain on palpation: -0.25 (-0.29, -0.21) / 0.37 (0.29, 0.44) No. joints with self-reported pain/pain on palpation, AUSCAN pain/function and mobility associated with summed JSW/JSN. Grip strength not associated.
Lee[49]	Grip/pinch strength, disa-bility (DASH questionnaire)	Associations with summed KL, adjusted for age/sex ($P < 0.05$): - grip strength: thumb β -1.05, 3rd finger β -2.17 - pinch strength: thumb β -0.28, 2nd finger β -0.26 - disability: thumb β 1.53, 2nd finger β 0.63, 3rd finger β 3.97

Table 6. *Continued*

First author	Validation method	Results relevant for evaluation of validity
Marshall[39]	AUSCAN, pain during activity/pain in past month (questionnaire, yes/ no), grip/ pinch strength, grind test, Finkelstein's test	OR (95%CI) for KL ≥2 in CMC1 / any thumb joint: - Pain during activity: 2.1 (1.5, 2.9) / 2.2 (1.6, 3.2) - Pain in past month: 1.5 (1.0, 2.1) / 1.4 (1.0, 2.0) - Grind test: 1.8 (1.1, 2.9) / 1.7 (1.0, 2.9), Finkelstein's test not associated.
Ozkan[50]	Grip/pinch strength, Dreiser's functional index, disability (HAQ)	Disability KL score <2/2/3-4: 2.40 / 2.10 / 6.45 (KL3-4 vs KL<2/2 P < 0.05) Dreiser's index KL score <2/2/3-4: 2.73 / 2.10 / 9.25 (KL3-4 vs KL<2/2 P <0.05) Grip/pinch strength not different between KL scores.
Sonne-Holm[51]	Pain CMC1 (interview, yes/ no)	OR (95%CI) for pain, adjusted for age, sex, BMI: - KL: 1.48 (1.33, 1.65) - Sclerosis / cyst: 1.48 (1.23, 1.77) / 1.23 (1.03, 1.47) JSW and osteophytes not associated.
Zhang[52]	Functional limitations (questionnaire), grip strength	Patients with KL ≥2 and joint pain/aching/stiffness had more functional limitations and lower grip strength; age adjusted difference (95%CI) men 3.1 kg (1.8, 4.4), women 1.9 kg (1.4, 2.4)
Histological		
Sunk[53,69]	Modified Mankin score (range 0-14; >5 = OA)	Correlation with KL score (DIP/PIP): r 0.87/0.79 (P < 0.0001) Correlation with OARSI JSN: r 0.77/0.76, osteophytes: r 0.89/0.69 (P < 0.0001) Sensitivity KL ≥2 for Mankin >5 (DIP/PIP): 84.6/54.2%, specificity: 100/100%
Drape[32]	Pedicled cysts DIP (yes/no)	19 pedicled cysts: 16 associated with osteophytes/JSN on CR, 3 no osteophytes/JSN on CR
Grainger[54]	Erosions (central/marginal, yes/no)	37 MRI erosions: 24% also on CR (44% of central, 5% of marginal erosions) All CR erosions also on MRI
Haugen[21]	Oslo hand OA score (graded per feature)	Agreement with osteophytes κ 0.41, JSN κ 0.50, central erosions κ 0.75, central/marginal erosions κ 0.43, cysts κ 0.11, malalignment κ 0.50
MRI		
Wittoek[55]	Erosions, osteophytes (yes/ no)	Prevalence erosions: MRI PIP 29%, DIP 68%, CR PIP 11%, DIP 38%. PIP osteophytes (erosive/non-erosive) hand OA MRI 25/50%, CR 42/40%. DIP osteophytes: MRI and CR >80%.
CT		
Saltzherr61	JSN, osteophytes, subchondral sclerosis, cyst, erosion, subluxation (OA defined on no. of features)	Prevalence of individual features and OA higher according to CT than CR
US		
Iagnocco[56]	Erosions (yes/no)	US erosions in 16 (72.7%) of 22 CR erosive hand OA patients. No US erosions in CR classical hand OA patients (n = 88).
Keen[57]	JSN, osteophytes (yes/no)	Osteophytes: κ 0.54 (77.8% agreement) JSN: κ 0.436 (74.6% agreement)
Kortekaas[48]	Osteophytes (yes/no)	US osteophytes 69%, OARSI osteophytes 46%
Mancarella[23]	Cartilage thickness (mm)	Negatively correlated with KL and Kallman score (P < 0.0001)

Table 6. *Continued*

First author	Validation method	Results relevant for evaluation of validity
Mathiessen[40]	Osteophytes (yes/no)	OARSI osteophytes in 30% of joints, US osteophytes in 53% of joints. CR and US: 57.3% exact agreement, 88.3% close agreement.
Vlychou[58]	Central erosions, osteophytes (yes/no)	CR detected less erosions/osteophytes (17/47%) than US (35/55%), P < 0.05. Difference most apparent in DIP and PIP.
Wittoek[55]	Erosions, osteophytes (yes/no)	CR detected less erosions (PIP 11%, DIP 38%) than US (21, 52%) in erosive and non-erosive hand OA. CR detected less PIP osteophytes (41%) than US (54%). CR and US both detected >80% DIP osteophytes.
Digital photography		
Jones[47]	Heberden nodes (yes/no)	Correlation with OARSI score ≥1 in DIP joints: r 0.74 (P < 0.001)
Jonsson[38]	Tissue enlargement/ deformity (graded 0-3 per joint, summed)	Prevalence OA higher according to KL ≥2 (DIP 67%, PIP 32%, CMC1 20%) as compared to digital photograph ≥2 (DIP 33%, PIP 20%, CMC1 3%). Correlation summed score with summed total KL: males r 0.35, females r 0.53
Stern[42]	Hard tissue enlargement (yes/no)	Sensitivity for KL ≥2: range per joint 17-74% Specificity for KL ≥2: range per joint 67-92%
Other measures of JSW		
Huetink[59]	True JSW by micrometer	Compared to automatic JSN quantification: Mean difference (SD): phantom joints: 0.052 (0.014) mm, cadaver joints: 0.210 (0.115) mm SDD: phantom joints 0.028 mm, cadaver joints: 0.226 mm
Van 't Klooster[60]	Automatic JSW quantification (mm)	Association with OARSI JSN: R2 0.54, P < 0.01

AUSCAN, Australian/Canadian Hand Osteoarthritis Index; β, beta coefficient; BMI, body mass index; CI, confidence interval; CMC1, first carpometacarpal joint; CR, conventional radiography; CT, computed tomography; DASH, Disabilities of the Arm Shoulder and Hand; DIP, distal interphalangeal joint; HAQ, Health Assessment Questionnaire; IP1, first interphalangeal joint; JSN, joint space narrowing; JSW, joint space width; κ, kappa; KL, Kellgren-Lawrence; kg, kilogram; MCP, metacarpaphalangeal joint; mm, millimeter; MRI, magnetic resonance imaging; no., number; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International;, OR, odds ratio; PIP, proximal interphalangeal joint; PR, prevalence ratio; r, correlation coefficient; R2, explained variance; STT, scaphotrapezotrapezoidal joint; US, ultrasound; VAS, visual analogue scale.

DISCUSSION

This review aimed at evaluating the radiographic scoring methods used in hand OA research and to assess their metric properties. We noticed that a wide variety of scoring methods has been used in studies evaluating radiographic hand OA. Furthermore, the joints that were examined and the analysis of the obtained scores differed extensively across studies. Evaluation of metric properties of the evaluated scoring methods regarding reliability, sensitivity to change, feasibility and validity did not reveal major differences.

Both intra- and interreader reliability of all evaluated radiographic scoring methods were good for summed scores and global scores, for both cross-sectional and longitudinal radiographic scoring. When grading individual radiographic features, the highest reliability was reported for the scoring of erosions and osteophytes and the lowest for the scoring of cysts.

When evaluating sensitivity to change, only one study evaluated this in different groups of patients (trial arms) using different scoring methods. Although such comparative studies may provide the best insights in sensitivity to change, the included observational follow-up studies showed the ability to detect change in structural damage over time with conventional radiography. Change over time was observed even in short term follow-up studies (<3 years). Reported SRMs were similar for all evaluated scoring methods.

The feasibility of scoring methods has been described in a limited number of studies. The performance time of the scoring differed not only across the evaluated scoring method but also across studies, and was shown to increase with the amount of structural damage.

A large number of studies investigated the validity of radiographic OA findings in comparison with clinical findings at physical examination (such as nodes and deformities) and symptoms and function; there was large variation between these studies. This could be due to the various analyses of radiographic and clinical findings, e.g., joint level versus patient level, and individual features versus summed scores. Furthermore, studies were difficult to compare because of the use of different effect measures, such as odds ratios, correlation coefficients, sensitivity and specificity. In general we can say that there was moderate agreement between radiographic features and structural findings at physical examination. The association of radiographic findings with hand function and symptoms was reported to be stronger than the association with findings at physical examination. All evaluated radiographic scores were associated with grip strength and pain, the relation with pain was observed on joint level as well as on patient level, and was shown to be dependent on the radiographic severity. No differences between the evaluated radiographic scoring methods were observed. Only few studies assessed longitudinal associations between radiography and pain or function, requiring further validation.

In comparison with other imaging methods, radiography appeared to detect fewer structural damage than MRI, CT and US, and more structural damage than digital photography. However, the findings on MRI, CT and digital photography require further confirmation because of limited evidence. Agreement between radiography and other imaging methods was assessed most often on joint level and differed per feature.

Although no major differences regarding the metric properties of the evaluated radiographic scoring methods were observed in this review, the examined joints and analysis of the obtained scores were shown to differ extensively across studies. All kinds

of presentation of radiographic outcome measures were used, such as scores per joint, summed scores, presence/absence of radiographic OA features, or the highest scored joint. Summed scores were used most frequently for evaluation of the reliability of radiographic scoring methods and change of structural damage over time, analyzed on patient level. When evaluating the validity of scoring methods, analyses on individual joint level or on joint group level were performed most often.

The various examined joints within hand OA research has been described before in a review by Marshall et al. In addition, they evaluated the use of definitions of hand OA, reporting some agreement in the definition of individual joint OA but a wide variation in defining overall hand OA.[65] Kerkhof et al. showed that the use of varying definitions of radiographic OA within the same study leads to different results.[66] Therefore, as stated before by Haugen et al., standardization of the evaluation and definition of radiographic hand OA with respect to scoring methods, examined joints and required number of affected joints could reduce the variation across studies.[67]

Based on this review, it is not possible to decide on what radiographic scoring method should be recommended in hand OA research. Although no major differences regarding metric properties of the scoring methods were observed, the amount of supporting evidence differed for the evaluated methods, which may provide an argument for recommendation of specific scoring methods. Most evidence across all evaluated domains is available for the KL and OARSI scoring methods. Although global scoring methods may be more reliable than the scoring of individual radiographic features, individual features may be more suitable for evaluation of specific study objectives. Therefore, the OARSI scoring method may be recommended for evaluation of individual radiographic features in addition to use of the KL scoring method for global radiographic assessment. The OARSI Task Force recommendations for the design and conduct of clinical trials in hand OA already stated that the use of either aggregate radiographic scores or grading of individual features depends on the aim of study.[9] However, consensus should be reached on a more specific definition; when should a global or individual feature score be used and what specific scoring method should be recommended. Furthermore, consensus on the evaluated joints, presentation of the radiographic outcome measures and the definition of hand OA will help to enhance the comparability of studies in hand OA.

A limitation of this study is that the methodological quality of the included studies was not assessed, due to the heterogeneity across studies regarding their purpose. The heterogeneity regarding examined joints and analyses of obtained radiographic scores did not enable performance of a meta-analysis. Furthermore, publication bias was not addressed.

Although we aimed to provide a comprehensive overview of available literature, the formulated inclusion and exclusion criteria resulted in a specific selection of studies.

Consequently, some radiographic scoring methods were not included in this review, being the Eaton-Littler classification system and the recently developed interphalangeal OA radiographic simplified (iOARS) score. These methods have not been evaluated for reliability together with another method.[68,69]

Since sensitivity to change was evaluated in follow-up studies assessing hand OA by at least two radiographic scoring methods in case of long-term follow-up studies (>3 year), a number of studies or abstracts evaluating change in KL and OARSI scores could not be included.[3,70-72]

In the evaluation of the feasibility of the available radiographic scoring methods in hand OA, we did not focus on the importance of radiographic techniques. Dela Rosa et al. evaluated the reliability of scoring OA of the CMC1s according to the Eaton method when using different X-ray views, showing that a combination of the posterior-anterior, lateral and Bett's view showed a higher reliability than using only one or two views.[73] Standardization of radiographic techniques might further enhance comparability of studies in hand OA.

In conclusion, this systematic review provides an overview of the radiographic scoring methods used in the assessment of structural damage in hand OA. We showed that several scoring methods are available, evaluation of their metric properties regarding reliability, sensitivity to change, feasibility and validity did not reveal major differences. The examined joints and analysis of the obtained radiographic scores differed extensively across all studies. To enhance comparability across studies in hand OA, consensus has to be reached on a preferred scoring method, as well as on the examined joints and the used outcome measure.

REFERENCES

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
2. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
3. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis 2011;70:1581-6.
4. Mahendira D and Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. Osteoarthritis Cartilage 2009;17:1263-8.
5. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:377-88.
6. Towheed TE. Systematic review of therapies for osteoarthritis of the hand. Osteoarthritis Cartilage 2005;13:455-62.
7. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.
8. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage 1996;4:217-43.
9. Maheu E, Altman RD, Bloch DA, Doherty M, Hochberg M, Mannoni A et al. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International. Osteoarthritis Cartilage 2006;14:303-22.
10. Kellgren JH and Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
11. Kessler S, Dieppe P, Fuchs J, Sturmer T, Gunther KP. Assessing the prevalence of hand osteoarthritis in epidemiological studies. The reliability of a radiological hand scale. Ann Rheum Dis 2000;59:289-92.
12. Kallman DA, Wigley FM, Scott WW, Jr., Hochberg MC, Tobin JD. New radiographic grading scales for osteoarthritis of the hand. Reliability for determining prevalence and progression. Arthritis Rheum 1989;32:1584-91.
13. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3(Suppl A):3-70.
14. Verbruggen G and Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum 1996;39:308-20.
15. Verbruggen G, Wittoek R, Vander CB, Elewaut D. Morbid anatomy of 'erosive osteoarthritis' of the interphalangeal finger joints: an optimised scoring

system to monitor disease progression in affected joints. Ann Rheum Dis 2010;69:862-7.
16. Bijsterbosch J, Haugen IK, Malines C, Maheu E, Rosendaal FR, Watt I et al. Reliability, sensitivity to change and feasibility of three radiographic scoring methods for hand osteoarthritis. Ann Rheum Dis 2011;70:1465-7.
17. Maheu E, Cadet C, Gueneugues S, Ravaud P, Dougados M. Reproducibility and sensitivity to change of four scoring methods for the radiological assessment of osteoarthritis of the hand. Ann Rheum Dis 2007;66:464-9.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
19. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
20. Addimanda O, Mancarella L, Dolzani P, Punzi L, Fioravanti A, Pignotti E et al. Clinical and radiographic distribution of structural damage in erosive and nonerosive hand osteoarthritis. Arthritis Care Res (Hoboken) 2012;64:1046-53.
21. Haugen IK, Boyesen P, Slatkowsky-Christensen B, Sesseng S, Bijsterbosch J, van der Heijde D et al. Comparison of features by MRI and radiographs of the interphalangeal finger joints in patients with hand osteoarthritis. Ann Rheum Dis 2012;71:345-50.
22. Kwok WY, Bijsterbosch J, Malm SH, Biermasz NR, Huetink K, Nelissen RG et al. Validity of joint space width measurements in hand osteoarthritis. Osteoarthritis Cartilage 2011;19:1349-55.
23. Mancarella L, Magnani M, Addimanda O, Pignotti E, Galletti S, Meliconi R. Ultrasound-detected synovitis with power Doppler signal is associated with severe radiographic damage and reduced cartilage thickness in hand osteoarthritis. Osteoarthritis Cartilage 2010;18:1263-8.
24. Haugen IK, Slatkowsky-Christensen B, Boyesen P, van der Heijde D, Kvien TK. Cross-sectional and longitudinal associations between radiographic features and measures of pain and physical function in hand osteoarthritis. Osteoarthritis Cartilage 2013;21:1191-8.
25. Verbruggen G, Wittoek R, Vander CB, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. Ann Rheum Dis 2012;71:891-8.
26. Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. Clin Rheumatol 2002;21:231-43.
27. Botha-Scheepers S, Watt I, Breedveld FC, Kloppenburg M. Reading radiographs in pairs or in chronological order influences radiological progression in osteoarthritis. Rheumatology (Oxford) 2005;44:1452-5.
28. Botha-Scheepers S, Riyazi N, Watt I, Rosendaal FR, Slagboom E, Bellamy N et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. Ann Rheum Dis 2009;68:1260-4.
29. Botha-Scheepers SA, Watt I, Slagboom E, Meulenbelt I, Rosendaal FR, Breedveld FC et al. Influence of familial factors on radiologic disease progression over two years in siblings with osteoarthritis at multiple sites: a prospective longitudinal cohort study. Arthritis Rheum 2007;57:626-32.

30. Buckland-Wright JC, Macfarlane DG, Lynch JA, Clark B. Quantitative microfocal radiographic assessment of progression in osteoarthritis of the hand. Arthritis Rheum 1990;33:57-65.
31. Olejarova M, Kupka K, Pavelka K, Gatterova J, Stolfa J. Comparison of clinical, laboratory, radiographic, and scintigraphic findings in erosive and nonerosive hand osteoarthritis. Results of a two-year study. Joint Bone Spine 2000;67:107-12.
32. Drape JL, Idy-Peretti I, Goettmann S, Salon A, Abimelec P, Guerin-Surville H et al. MR imaging of digital mucoid cysts. Radiology 1996;200:531-6.
33. Bagge E, Bjelle A, Eden S, Svanborg A. Osteoarthritis in the elderly: clinical and radiological findings in 79 and 85 year olds. Ann Rheum Dis 1991;50:535-9.
34. Caspi D, Flusser G, Farber I, Ribak J, Leibovitz A, Habot B et al. Clinical, radiologic, demographic, and occupational aspects of hand osteoarthritis in the elderly. Semin Arthritis Rheum 2001;30:321-31.
35. Cicuttini FM, Baker J, Hart DJ, Spector TD. Relation between Heberden's nodes and distal interphalangeal joint osteophytes and their role as markers of generalised disease. Ann Rheum Dis 1998;57:246-8.
36. Hart DJ, Spector TD, Brown P, Wilson P, Doyle DV, Silman AJ. Clinical signs of early osteoarthritis: reproducibility and relation to x ray changes in 541 women in the general population. Ann Rheum Dis 1991;50:467-70.
37. Hart D, Spector T, Egger P, Coggon D, Cooper C. Defining osteoarthritis of the hand for epidemiological studies: the Chingford Study. Ann Rheum Dis 1994;53:220-3.
38. Jonsson H, Helgadottir GP, Aspelund T, Sverrisdottir JE, Eiriksdottir G, Sigurdsson S et al. The use of digital photographs for the diagnosis of hand osteoarthritis: the AGES-Reykjavik study. BMC Musculoskelet Disord 2012;13:20.
39. Marshall M, van der Windt D, Nicholls E, Myers H, Dziedzic K. Radiographic thumb osteoarthritis: frequency, patterns and associations with pain and clinical assessment findings in a community-dwelling population. Rheumatology (Oxford) 2011;50:735-9.
40. Mathiessen A, Haugen IK, Slatkowsky-Christensen B, Boyesen P, Kvien TK, Hammer HB. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis 2013;72:51-6.
41. Rees F, Doherty S, Hui M, Maciewicz R, Muir K, Zhang W et al. Distribution of finger nodes and their association with underlying radiographic features of osteoarthritis. Arthritis Care Res (Hoboken) 2012;64:533-8.
42. Stern AG, Moxley G, Sudha Rao TP, Disler D, McDowell C, Park M et al. Utility of digital photographs of the hand for assessing the presence of hand osteoarthritis. Osteoarthritis Cartilage 2004;12:360-5.
43. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Ann Rheum Dis 2005;64:682-7.
44. Ding H, Solovieva S, Vehmas T, Riihimaki H, Leino-Arjas P. Finger joint pain in relation to radiographic osteoarthritis and joint location--a study of middle-aged female dentists and teachers. Rheumatology (Oxford) 2007;46:1502-5.
45. Dominick KL, Jordan JM, Renner JB, Kraus VB. Relationship of radiograph-

ic and clinical variables to pinch and grip strength among individuals with osteoarthritis. Arthritis Rheum 2005;52:1424-30.
46. El-Sherif HE, Kamal R, Moawyah O. Hand osteoarthritis and bone mineral density in postmenopausal women; clinical relevance to hand function, pain and disability. Osteoarthritis Cartilage 2008;16:12-7.
47. Jones G, Cooley HM, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. Osteoarthritis Cartilage 2001;9:606-11.
48. Kortekaas MC, Kwok WY, Reijnierse M, Huizinga TW, Kloppenburg M. Osteophytes and joint space narrowing are independently associated with pain in finger joints in hand osteoarthritis. Ann Rheum Dis 2011;70:1835-7.
49. Lee HJ, Paik NJ, Lim JY, Kim KW, Gong HS. The impact of digit-related radiographic osteoarthritis of the hand on grip-strength and upper extremity disability. Clin Orthop Relat Res 2012;470:2202-8.
50. Ozkan B, Keskin D, Bodur H, Barca N. The effect of radiological hand osteoarthritis on hand function. Clin Rheumatol 2007;26:1621-5.
51. Sonne-Holm S and Jacobsen S. Osteoarthritis of the first carpometacarpal joint: a study of radiology and clinical epidemiology. Results from the Copenhagen Osteoarthritis Study. Osteoarthritis Cartilage 2006;14:496-500.
52. Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002;156:1021-7.
53. Sunk IG, Amoyo-Minar L, Niederreiter B, Soleiman A, Kainberger F, Smolen JS et al. Histopathological correlation supports the use of x-rays in the diagnosis of hand osteoarthritis. Ann Rheum Dis 2013;72:572-7.
54. Grainger AJ, Farrant JM, O'Connor PJ, Tan AL, Tanner S, Emery P et al. MR imaging of erosions in interphalangeal joint osteoarthritis: is all osteoarthritis erosive? Skeletal Radiol 2007;36:737-45.
55. Wittoek R, Jans L, Lambrecht V, Carron P, Verstraete K, Verbruggen G. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. Ann Rheum Dis 2011;70:278-83.
56. Iagnocco A, Filippucci E, Ossandon A, Ciapetti A, Salaffi F, Basili S et al. High resolution ultrasonography in detection of bone erosions in patients with hand osteoarthritis. J Rheumatol 2005;32:2381-3.
57. Keen HI, Wakefield RJ, Grainger AJ, Hensor EM, Emery P, Conaghan PG. Can ultrasonography improve on radiographic assessment in osteoarthritis of the hands? A comparison between radiographic and ultrasonographic detected pathology. Ann Rheum Dis 2008;67:1116-20.
58. Vlychou M, Koutroumpas A, Malizos K, Sakkas LI. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. Osteoarthritis Cartilage 2009;17:1283-7.
59. Huetink K, van 't Klooster R, Kaptein BL, Watt I, Kloppenburg M, Nelissen RG et al. Automatic radiographic quantification of hand osteoarthritis; accuracy and sensitivity to change in joint space width in a phantom and cadaver study. Skeletal Radiol 2012;41:41-9.

60. van 't Klooster R, Hendriks EA, Watt I, Kloppenburg M, Reiber JH, Stoel BC. Automatic quantification of osteoarthritis in hand radiographs: validation of a new method to measure joint space width. Osteoarthritis Cartilage 2008;16:18-25.
61. Saltzherr MS, van Neck JW, Muradin GS, Ouwendijk R, Luime JJ, Coert JH et al. Computed tomography for the detection of thumb base osteoarthritis: comparison with digital radiography. Skeletal Radiol 2013;42:715-21.
62. Ceceli E, Gul S, Borman P, Uysal SR, Okumus M. Hand function in female patients with hand osteoarthritis: relation with radiological progression. Hand (N Y) 2012;7:335-40.
63. Marshall M, van der Windt D, Nicholls E, Myers H, Hay E, Dziedzic K. Radiographic hand osteoarthritis: patterns and associations with hand pain and function in a community-dwelling sample. Osteoarthritis Cartilage 2009;17:1440-7.
64. Buckland-Wright JC, Macfarlane DG, Lynch JA. Sensitivity of radiographic features and specificity of scintigraphic imaging in hand osteoarthritis. Rev Rhum Engl Ed 1995;62:14S-26S.
65. Marshall M, Dziedzic KS, van der Windt DA, Hay EM. A systematic search and narrative review of radiographic definitions of hand osteoarthritis in population-based studies. Osteoarthritis Cartilage 2008;16:219-26.
66. Kerkhof HJ, Meulenbelt I, Akune T, Arden NK, Aromaa A, Bierma-Zeinstra SM et al. Recommendations for standardization and phenotype definitions in genetic studies of osteoarthritis: the TREAT-OA consortium. Osteoarthritis Cartilage 2011;19:254-64.
67. Haugen IK and Boyesen P. Imaging modalities in hand osteoarthritis--and perspectives of conventional radiography, magnetic resonance imaging, and ultrasonography. Arthritis Res Ther 2011;13:248.
68. Spaans AJ, van Laarhoven CM, Schuurman AH, van Minnen LP. Interobserver agreement of the Eaton-Littler classification system and treatment strategy of thumb carpometacarpal joint osteoarthritis. J Hand Surg Am 2011;36:1467-70.
69. Sunk IG, Amoyo-Minar L, Stamm T, Haider S, Niederreiter B, Supp G et al. Interphalangeal Osteoarthritis Radiographic Simplified (iOARS) score: a radiographic method to detect osteoarthritis of the interphalangeal finger joints based on its histopathological alterations. Ann Rheum Dis 2014;73:1983-9.
70. Altman RD, Fries JF, Bloch DA, Carstens J, Cooke TD, Genant H et al. Radiographic assessment of progression in osteoarthritis. Arthritis Rheum 1987;30:1214-25.
71. Paradowski PT, Lohmander LS, Englund M. Natural history of radiographic features of hand osteoarthritis over 10 years. Osteoarthritis Cartilage 2010;18:917-22.
72. Maheu E, Cadet C, Carrat F, Barthe Y, Berenbaum F. Radiologic progression of hand osteoarthritis over 2.6 years according to various methods of calculation - data from the SEKOIA trial. 2013;
73. Dela Rosa TL, Vance MC, Stern PJ. Radiographic optimization of the Eaton classification. J Hand Surg Br 2004;29:173-7.
74. Burnett S, Hart DJ, Cooper C, Spector T.D. A radiographic atlas of osteoarthritis. 1994;
75. Eaton RG and Glickel SZ. Trapeziometacarpal osteoarthritis. Staging as a rationale for treatment. Hand Clin 1987;3:455-71.

76. Lane NE, Nevitt MC, Genant HK, Hochberg MC. Reliability of new indices of radiographic osteoarthritis of the hand and hip and lumbar disc degeneration. J Rheumatol 1993;20:1911-8.

Overview of literature search per database

Total d.d. 21-11-2013: 1873 references, extracted from the following databases:

- PubMed: 963
- Embase: 1234, of which 506 unique
- Web of Science: 830, of which 274 unique
- CINAHL: 205, of which 108 unique
- COCHRANE: 60, of which 22 unique

PubMed

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CHAPTER 9

Summary and discussion

Osteoarthritis (OA) is a highly prevalent disease and a major cause of disability.[1] The pathogenesis of OA is largely unknown; however, several risk factors are known to contribute to disease development. Although the clinical burden of OA is high, treatment modalities are currently limited to alleviation of symptoms.[2,3] The lack of disease-modifying treatment is not only due to the incomplete understanding of the pathogenesis of OA but also to the lack of high-quality studies on OA treatment. In order to develop better treatment modalities, increase of the understanding of the underlying mechanisms leading to OA development may provide targets for disease modification. Furthermore, knowledge regarding appropriate outcome measures that can be applied in OA research has to be increased for adequate assessment of potential treatment effects.
Therefore, **part I** of this thesis describes studies aiming to increase the understanding of the mechanisms underlying the association between known risk factors such as obesity and OA. In addition, **part II** of this thesis focuses on appropriate outcome measures that can be applied in hand OA research.

Part I. Mechanisms underlying the association between risk factors and OA

Part I of this thesis focuses on the mechanisms underlying the association between known risk factors and OA, especially on obesity in association to OA of both weight-bearing and non-weight-bearing joints. Since obesity acts as a risk factor for OA in both weight-bearing and non-weight-bearing joints, obesity-associated systemic factors could play an important role in OA, in addition to mechanical overload.[4,5] Data of the Netherlands Epidemiology of Obesity (NEO) study has been used for this part of the thesis.[6]

Mechanical stress and systemic processes in different types of OA
In **chapter 2** we investigated the relative contribution of surrogates for mechanical stress and systemic processes in OA of weight-bearing and non-weight-bearing joints. Surrogates for mechanical stress were weight and fat free mass whereas the metabolic syndrome was a surrogate for systemic processes. Fat mass could act as surrogate for both mechanical stress and systemic processes by adjusting for either the metabolic syndrome or weight. Analyses on the association of these measures with clinical OA of the weight-bearing knee joints alone, non-weight-bearing hand joints alone or with OA of both knees and hands suggested that in knee OA, whether or not in co-occurrence with hand OA, surrogates for mechanical stress are the most important risk factors. In hand OA alone on the contrary, surrogates for systemic processes seem the most important risk factors.
The association of surrogates for mechanical stress with knee OA is in accordance with the current literature and supports the hypotheses of damaged joint tissue due to excessive mechanical stress on the joint surface of obese individuals.[7-11] The contribution of mechanical and systemic processes to presence of both knee and hand OA has not been assessed before. Although our hypothesis was that this type of polyarticular OA might be driven by systemic processes, presence of both knee and hand OA was associated with surrogates for mechanical stress, even after adjustment for metabolic factors, just as the presence of knee OA alone was associated to these factors. This suggests that co-occur-

rence of knee and hand OA may represent presence of two different types of OA instead of being driven by a common underlying pathogenic mechanism. The relatively strong association between mechanical stress and knee OA may dominate the association between the metabolic syndrome and hand OA when assessing their associations with OA co-occurring in knees and hands. The association between the metabolic syndrome and presence of hand OA alone might be explained by systemic inflammation. As further investigated and discussed in **chapter 3**, adipose tissue is known as a source of pro- and anti-inflammatory cytokines which have been related to the metabolic syndrome[12] and have been suggested to affect joint tissues.[13-15]

Adiposity and OA in non-weight-bearing joints

In **chapter 3**, the association between adiposity and OA was investigated by analyzing the association of adipose tissue and its abdominal distribution with presence of OA in the non-weight-bearing hand joints. Fat percentage and fat mass were estimated using bioelectrical impedance analysis and the waist-to-hip ratio was calculated. Visceral adipose tissue and subcutaneous adipose tissue were assessed using abdominal magnetic resonance (MR) imaging. Associations between these measures of adiposity and clinical hand OA were analyzed in men and women separately because of the anthropomorphic differences between the sexes. Fat percentage, fat mass and the waist-to-hip ratio were associated with hand OA in both men and women. In addition, in contrast with the amount of subcutaneous adipose tissue, the amount of visceral adipose tissue was associated with hand OA in men.

This suggests that both the adipose tissue mass and its distribution are of importance in the pathogenesis of hand OA. Especially visceral fat seems involved. Although this is the first study showing this association, visceral fat has previously been associated with other obesity-related comorbidities as diabetes mellitus, atherosclerosis and metabolic risk factors.[16-20]

As described above, adipose tissue secretes cytokines which seem to act locally in joint tissues. Especially visceral fat has been suggested to secrete these bioactive cytokines,[21] acting as a pathogenic fat depot involved in the pathogenesis of hand OA.

The association between visceral adipose tissue and hand OA was not significant in women, this may be explained by the greater overall mass of fat and reduced susceptibility to accumulate visceral fat in women as compared with men. Other explanations could be a role of unmeasured or unknown factors such as hormonal status or genetic effects in hand OA in women, overshadowing a possible effect of visceral fat.

Obesity and OA in weight-bearing joints

In **chapter 4**, the association of fat mass and skeletal muscle mass with OA of the knees was assessed in order to enhance the understanding of the role of obesity in knee OA. The amounts of fat mass and skeletal muscle mass were assessed both as absolute mass in kilograms and as percentage of the total body mass. Again, associations were investigated separately in men and women. Fat mass, fat percentage and skeletal muscle mass were all positively associated with knee OA, while the percentage of skeletal muscle was negatively associated with knee OA. Especially a high fat mass relative to a low skeletal muscle mass ratio was unfavourable.

The positive association between skeletal muscle mass and OA could be explained by

differences in physical activity or joint loading. In obese individuals, the amount of skeletal muscle increases due to increased loading. However, this increase in skeletal muscle mass is not sufficient in relation to the total weight gain since fat mass increases more with increasing weight, resulting in a lower skeletal muscle percentage in obese individuals. This explains the opposite associations of the skeletal muscle as absolute amount and as percentage of the total body mass with OA. The metabolic syndrome, frequently occurring in obese individuals, may provide an alternative explanation for the negative association between skeletal muscle percentage and knee OA. In individuals with the metabolic syndrome, insulin resistance and systemic inflammation can result in changes in striated muscle, causing loss of muscle mass and muscle weakness.[22]
The sex-stratified analyses suggested that in men skeletal muscle mass was most important in knee OA whereas in women fat mass was most important. This suggests that the pathogenesis of knee OA in men might be mainly biomechanical whereas the aetiology in women is mainly systemic. Since a low fat mass relative to high skeletal muscle mass was beneficial in both men and women, interventions aiming at improvement of skeletal muscle in addition to weight reduction might be useful in the prevention and treatment of knee OA in both sexes.
The different measures of skeletal muscle mass and fat mass were associated both with clinical and structural knee OA, showing that all parameters associated with clinical OA were associated even stronger with structural OA, especially in women. The use of both clinical and structural classified OA revealed a large discrepancy between these two definitions; about one third of the individuals with clinical or structural OA met both definitions. This discrepancy underscores the difference between the definitions; whereas in clinical OA objective symptoms as pain are of great importance, structural OA diagnosis was based only on structural abnormalities assessed by MR imaging.

Structural abnormalities identifying symptomatic OA
Although OA is characterized by degenerative changes of joint structures, not all structural abnormalities are specific for OA since they can also be present in individuals without OA.[23-26] In **chapter 5**, we investigated which specific structural abnormalities on specific locations within the knee joint could best discriminate presence of symptomatic OA in the same knee to increase the understanding of the disease processes leading to symptomatic OA. Structural abnormalities on different locations within the joint (osteophytes, cartilage loss, bone marrow lesions, cysts, meniscal abnormalities, effusion, Baker's cyst) were assessed by MR imaging. The association between all structural abnormalities on different locations within the joint and symptomatic knee OA was assessed taking co-occurrence of all structural abnormalities into account. In the entire study population, comprising individuals with and without symptomatic knee OA, structural abnormalities were highly frequent in both the tibiofemoral and patellofemoral compartments of the knee. When assessing what structural abnormalities could best distinguish between individuals with and without symptomatic knee OA, Baker's cysts showed the strongest regression coefficient for presence of symptomatic knee OA, followed by effusion and structural abnormalities as osteophytes and bone marrow lesions, most prominent in the medial side of the tibiofemoral compartment of the knee.
Although this is not the first study assessing structural abnormalities in relation to presence of symptomatic knee OA or knee pain, it is innovative because of the analyses taking

co-occurrence of all assessed structural abnormalities in all locations within the knee into account. This may explain the differences observed in this study as compared with available literature as well as the conflicting results within available literature. A systematic review on structural abnormalities in relation to knee pain in OA reports supporting evidence for the role of effusion and bone marrow lesions in symptomatic knee OA; however the role of osteophytes and cartilage defects was not clear because of conflicting results.[27] Our study showed a clear association of osteophytes, especially in the medial side of the tibiofemoral joint, with symptomatic knee OA. Although we observed a high prevalence of cartilage defects, they were found to be of less importance in symptomatic knee OA than osteophytes. This may be explained by the frequent co-occurrence of cartilage defects and osteophytes that was observed within the study population. When taking this co-occurrence into account, only one of these abnormalities will be associated with presence of symptomatic OA.
Baker's cysts co-occurred with other structural abnormalities in the knee joint less frequently than cartilage defects and osteophytes and were found to be a good marker to distinguish individuals with symptomatic knee OA from those without. Development of Baker's cysts has been suggested to be caused by inflammation since synovial inflammation in the knee has been associated with Baker's cysts.[28] Perhaps treatment of knee OA has to focus on prevention of development of Baker's cysts by treatment of inflammation.

OA and risk factors in relation to health-related quality of life

OA is the second largest contributor to disability of all musculoskeletal disorders and has negative impact on health-related quality of life (HRQOL).[1,29-31] Some of the known risk factors for OA have not only been associated with development of OA but also with a decreased HRQOL. It could be that presence of OA together with such a risk factor that also has impact on HRQOL results in strengthening of both adverse associations with HRQOL. To gain insight into possible targets for improvement or prevention of decline in HRQOL in knee OA patients, in **chapter 6** we evaluated the impact of knee OA and its modifiable or preventable risk factors obesity, fat free mass (as proxy for muscle mass) and comorbidities. In addition, the interaction between knee OA and these risk factors in relation to HRQOL was examined. HRQOL was assessed using the Short Form 36 Physical Component Summary score. Knee OA was associated with a clinically relevant reduced HRQOL, as were its risk factors, obesity, comorbidities, and low fat free mass. In men, fat free mass interacted with knee OA, leading to an additional decrease of HRQOL in the case of co-occurrence of low fat free mass and knee OA. No such interactions with obesity or comorbidities were observed.
In accordance with the previous discussed chapters also this study showed different results for men and women. While in men a low percentage of fat free mass was associated with impaired HRQOL, the most impaired HRQOL for women was observed in individuals with knee OA in the highest tertile of fat free mass. It may well be that the amount and intensity of physical activity, probably related to both the amount of muscle mass and to HRQOL, is higher in men than in women. Although the exact underlying mechanism for the observed difference is not clear, our findings supports the hypothesis of differences in the pathogenesis of knee OA between men and women, as well as in the effects on HRQOL.

Although disease-modifying treatment is not yet available for knee OA, this study suggests that especially improvement of fat free mass may improve HRQOL in knee OA patients. This is supported by a study that reported weight reduction and performance of exercises to improve HRQOL in knee OA patients.[32] Although to a lesser extent interventions aiming at obesity and prevention or strict control and treatment of comorbidities may also maintain or improve HRQOL in knee OA patients. This has not yet been evaluated in a longitudinal study.

Discussion and future perspectives

This thesis increases the understanding of the mechanisms underlying the association between known risk factors and OA in different joints, focusing especially on obesity. In the association between obesity and OA both mechanical and systemic mechanisms are involved, where mechanical processes have the most important role in OA of weight-bearing joint and systemic processes in OA of non-weight-bearing joints.

As discussed by Cicuttini et al. in a response to the study on the relative contribution of mechanical stress and systemic processes in OA of different joints described in **chapter 2**, the different risk factors may overlap in their effect on the joints although the mechanisms by which such risk factors specifically affect joints may differ (see appendix 1). **Chapter 2** suggests a major effect of systemic processes in OA of non-weight-bearing joints and a major effect of mechanical processes on OA of weight-bearing joints. In their response to this study, Cicuttini et al. mentioned previously shown associations between markers for metabolic processes (increased fat mass, glucose levels, inflammatory cytokines) and cartilage loss (described as early preclinical stage of OA) of the weight-bearing knee joint. In addition, they describe low grade synovitis and the adipokine adiponectin to be associated with cartilage loss in knee OA.[33] Although these associations suggest a systemic or local effect of metabolic processes in the early development of knee OA, biomechanical factors were not taken into account in these analyses. As described in **chapter 2**, it could be that systemic processes have a minor effect on knee OA but are overshadowed by the major effect of mechanical factors.

However, all associations between different measures of obesity and OA described in this thesis were the result of cross-sectional analyses. Longitudinal data could confirm and further elucidate the role of both biomechanical and systemic mechanisms in the pathogenesis of OA. Follow-up data of the NEO study are currently obtained and will be of help. To further unravel the role of systemic processes in OA development, measures of the underlying mechanisms should be assessed over time.

Also additional cross-sectional studies in other assumed underlying mediating processes, such as adipokines, hyperglycemia or diabetes mellitus and atherosclerosis are of interest. Measurement of adipokines, such as leptin, adiponectin, resistin and visfatin, will provide more insight in the systemic role of adipose tissue in OA development. These are especially of interest in hand OA development, since in an earlier study we showed a negative association between adiponectin and radiographic progression of hand OA.[34] The role of atherosclerosis in OA development may be further investigated by relating measures of atherosclerosis such as cholesterol levels and the intima media thickness to OA development. Involvement of the glucose metabolism in OA development, suggested to act via insulin-like growth factor I resistance of chondrocytes, striated muscle changes due to insulin resistance, or via formation of advanced glycation end (AGE) products,

can be assessed by measuring glucose and insulin concentrations, insulin resistance and products of the glycation process. Within the NEO study we already assessed cross-sectional associations of serum glucose and insulin concentrations and HbA1c (an early stage glycation product) with hand OA, showing only an association of fasting glucose concentrations and HbA1c with hand OA in men. No association was found with OA of the knees or with OA of both knees and hands. Insulin concentrations and insulin resistance were not associated with any type of OA.[35] These cross-sectional data of the NEO study suggest that the glucose metabolism does not seem to play a major role in OA. The association of glucose and HbA1c as measure of the glycation process with hand OA was only observed in men and should be confirmed by other studies. However, it is interestingly that this association only to be observed in men is in line with **chapter 3**, where we reported an association between the systemically active amount of visceral adipose tissue and hand OA also in men. More research should be performed, using sex-stratified analyses, to further elucidate the role of glucose metabolism and other systemic processes especially in men.

This thesis suggests some potential targets for treatment of OA and for treatment or prevention of decreased HRQOL due to OA. Longitudinal research is warranted to further investigate these potential targets. Reducing inflammatory processes may be beneficial, either locally by preventing the development of Baker's cysts and associated symptomatic OA or systemically by inhibiting the systemic processes leading to OA development. Furthermore, interventions aimed at increasing or maintaining HRQOL in OA patients should be further explored since OA is not only a major cause of disability but also results in impaired HRQOL. Longitudinal studies should also explore the effect of increasing fat free mass and prevention or treatment of obesity and comorbidities on HRQOL in OA patients.

Part II. Identification of appropriate outcome measurements for hand OA research

Although the need for trials on disease-modifying treatment modalities for OA is high, performance of high-quality studies is difficult because of the use of many different and poor outcome measures, especially in hand OA. This hampers adequate assessment of the disease process and possible treatment effects. **Part II** of this thesis therefore focuses on the identification of appropriate outcome measures that can be applied in hand OA research. In the framework of the Outcome Measures in Rheumatology (OMERACT) Hand OA working group, which aims to develop a core set of outcome measures for research on hand OA,[36] we performed two systematic reviews to assess available instruments for measurement of the domains pain, physical function, patient global assessment and imaging in hand OA in order to enable recommendations for use in clinical trials.

Assessment of pain, physical function or patient global assessment in hand OA

In **chapter 7**, we evaluated the use of instruments measuring pain, physical function or patient global assessment in studies on hand OA, as well as the metric properties of these instruments. Metric properties were assessed with the OMERACT filter, including discrimination (reliability, sensitivity to change), feasibility and validity. In 66 included studies,

various questionnaires and performance-/assessor-based instruments were applied for evaluation of pain, physical function or patient global assessment. No major differences regarding metric properties were observed between the instruments although the amount of supporting evidence varied. The most frequently evaluated questionnaires were the Australian/Canadian Hand OA Index (AUSCAN) pain subscale and visual analogue scale (VAS) pain for pain assessment and the AUSCAN function subscale and Functional Index for Hand OA (FIHOA) for assessment of physical function. Excellent reliability was shown for the AUSCAN and FIHOA and good sensitivity to change for all mentioned instruments; additionally the FIHOA had good feasibility. Good construct validity was suggested for all mentioned questionnaires. The most commonly applied performance-/assessor-based instrument were grip and pinch strength for assessment of physical function, in addition to assessment of pain by palpation. For these measures good sensitivity to change and construct validity were established. The AUSCAN, FIHOA, VAS pain, grip and pinch strength and pain on palpation were most frequently tested and provided most supporting evidence for good metric properties.

Radiographic assessment of hand OA

In **chapter 8** we focused on imaging, evaluating the use of conventional radiography in studies on hand OA and assessing the metric properties of the different available radiographic scoring methods, again using the OMERACT filter. In the 48 included studies, 13 different scoring methods had been used for evaluation of radiographic hand OA. The number of examined joints differed extensively and the obtained scores were analyzed in various ways. The reliability of the assessed radiographic scoring methods was good for all evaluated scoring methods, for both cross-sectional and longitudinal radiographic scoring. The responsiveness to change was similar for all evaluated scoring methods. There were no major differences in feasibility between the evaluated scoring methods, although the evidence was limited. There was limited knowledge about the validity of radiographic OA findings compared with clinical nodules and deformities, whereas there was better evidence for an association of radiographic findings with symptoms and hand function.

Although no major differences regarding metric properties of the scoring methods were observed, the amount of supporting evidence differed for the evaluated methods. Most evidence across all evaluated domains was available for the Kellgren-Lawrence (KL) and Osteoarthritis Research Society International (OARSI) scoring methods. For the Verbruggen-Veys anatomical phase score, supporting evidence was observed across all evaluated domains except for validity. For the Kallman scoring method, supporting evidence was observed across all domains except for sensitivity to change. Although global scoring methods may be more reliable than the scoring of individual radiographic features, individual features may be more suitable for evaluation of specific study objectives. To enhance the comparability of studies in hand OA, consensus has to be reached on the preferred scoring methods, the examined joints, the presentation of radiographic outcome measures and the definition of hand OA, in relation to the study aim.

OMERACT12 meeting

The results of both literature reviews were presented and discussed during the OMERACT12 meeting (see appendix 2).[37] In the discussion on instruments measuring pain, there was agreement to use the VAS or numeric rating scale as a preliminary instrument for self-reported pain. It was noted that further information is needed on a number of items: whether overall hand pain or single joint pain should be assessed, which joints should be assessed, how the questions should be asked and which anchors should be used. In the discussion on instruments assessing physical function, there was concern about the use of the FIHOA due to some too sex role-specific items, cultural differences and items with low secular relevance. The alternative, i.e., the AUSCAN, had the disadvantage of limited access due to mandatory payment for use. Therefore, it was voted to use the FIHOA for assessment of the physical function domain until more research has been performed for a more contemporary instrument. It was agreed to use grip and pinch strength as preliminary instruments for hand strength and the count of tender joints upon palpation as a preliminary instrument for assessment of joint activity.

In the discussion on radiographic scoring methods consensus was reached on applying the most widely used and currently best validated measures, since there are only limited data for some of the other available scoring methods. It was agreed to use either the KL, OARSI, Verbruggen-Veys anatomical phases or the Kallman scoring method as preliminary instruments for assessment of structural damage.

Discussion and future perspectives

The systematic reviews in **part II** of this thesis increase the knowledge of available instruments for measurement of the domains pain, physical function, patient global assessment and imaging in hand OA. Since we aimed at providing a thorough overview of the current literature we included all studies providing information on available instruments and any of their metric properties reliability, sensitivity to change, feasibility and validity, independent of the study aim. Because of the large heterogeneity across studies regarding their purpose (primarily aiming at evaluation of instruments or applying instruments for other primary aims) and study design, the methodological quality of the included studies was not assessed. For further assessment of the instruments measuring the mentioned domains in hand OA the quality of the studies evaluating the instruments should be taken into account.

In addition, the OMERACT Hand OA working group made a research agenda describing items for further research. Regarding measurement of the domain pain, VAS or numeric rating scale questions should be developed and validated. Furthermore, a new measure for intermittent and constant hand OA pain should be developed and the subdomain tender joints should be investigated. In addition, the value of patient-performed joint count versus physician-performed joint count should be investigated. Regarding measurement of physical function, instruments that are commonly used by hand therapists such as the Disability of the Arm, Shoulder and Hand and Michigan Hand Outcomes Questionnaire should be more thoroughly evaluated for use in hand OA. For measurement of patient global assessment, quality interviews should be performed. For further assessment of the domain imaging, the metric properties of ultrasound and MR imaging should be investigated, as well as the value of computed tomography scans in hand OA. After further assessment of the different available instruments, consensus can be reached

on which instruments should be used for measurement of the different core domains in different settings (clinical trials with specific aims or clinical practice). Consensus on standardized instruments for measurement of OA will enhance performance of high-quality trials and development of disease-modifying treatments for OA.

Although further assessment of instruments measuring the domains pain, physical function, patient global assessment and imaging in hand OA is necessary, the results of the two systematic reviews included in this thesis already contributed to an update of the recommendations for the conduct and design of clinical trials in hand OA, described by a Task Force set-up by the OARSI.[38] The purpose of this Task Force is to provide evidence-based guidance on the design, execution and analysis of clinical trials in hand OA where published evidence is available, supplemented by expert opinion where evidence is lacking. This guidance will enhance the quality and comparability of future studies in OA.

In addition to the identification of appropriate instruments for standardized measurement of outcomes, improvement of the classification criteria for hand OA will also enhance the performance of high-quality studies. Within the current widely used ACR classification criteria for hand OA all hand phenotypes are lumped together, which could result in heterogeneous study populations since different subtypes of hand OA are not distinguished by these criteria. Development of classification criteria addressing different subtypes of hand OA such as interphalangeal or thumb base OA will be of help in identifying these different entities and enhance high-quality research in hand OA.

The combination of enhancement of high-quality research in OA and further elucidation of the mechanisms underlying the disease process could ultimately lead to development of disease-modifying treatment modalities for OA instead of the current limitation to only symptom-modifying treatments.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163-96.
2. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012;64:465-74.
3. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. Nat Rev Rheumatol 2014;10:242-51.
4. Anderson JJ and Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
5. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van OG et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761-5.
6. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol 2013;28:513-23.
7. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis 2007;66:1244-8.
8. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. Osteoarthritis Cartilage 2008;16:367-72.
9. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. Obesity (Silver Spring) 2006;14:1274-81.
10. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008;16:232-40.
11. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1995;22:488-93.
12. Mattu HS and Randeva HS. Role of adipokines in cardiovascular disease. J Endocrinol 2013;216:T17-T36.
13. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;48:3118-29.
14. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-5.
15. Tilg H and Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-83.
16. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY et al.

Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39-48.
17. Indulekha K, Anjana RM, Surendar J, Mohan V. Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). Clin Biochem 2011;44:281-7.
18. Hanley AJ, Wagenknecht LE, Norris JM, Bryer-Ash M, Chen YI, Anderson AM et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. Diabetologia 2009;52:2079-86.
19. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke 2007;38:2422-9.
20. Ditomasso D, Carnethon MR, Wright CM, Allison MA. The associations between visceral fat and calcified atherosclerosis are stronger in women than men. Atherosclerosis 2010;208:531-6.
21. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev 2006;2:367-73.
22. Rojas-Rodriguez J, Escobar-Linares LE, Garcia-Carrasco M, Escarcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860-8.
23. Beattie KA, Boulos P, Pui M, O'Neill J, Inglis D, Webber CE et al. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. Osteoarthritis Cartilage 2005;13:181-6.
24. Baranyay FJ, Wang Y, Wluka AE, English DR, Giles GG, Sullivan RO et al. Association of bone marrow lesions with knee structures and risk factors for bone marrow lesions in the knees of clinically healthy, community-based adults. Semin Arthritis Rheum 2007;37:112-8.
25. Guymer E, Baranyay F, Wluka AE, Hanna F, Bell RJ, Davis SR et al. A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women. Osteoarthritis Cartilage 2007;15:1437-42.
26. Hayashi D, Felson DT, Niu J, Hunter DJ, Roemer FW, Aliabadi P et al. Pre-radiographic osteoarthritic changes are highly prevalent in the medial patella and medial posterior femur in older persons: Framingham OA study. Osteoarthritis Cartilage 2014;22:76-83.
27. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70:60-7.
28. Chatzopoulos D, Moralidis E, Markou P, Makris V, Arsos G. Baker's cysts in knees with chronic osteoarthritic pain: a clinical, ultrasonographic, radiographic and scintigraphic evaluation. Rheumatol Int 2008;29:141-6.
29. Alkan BM, Fidan F, Tosun A, Ardicoglu O. Quality of life and self-reported disability in patients with knee osteoarthritis. Mod Rheumatol 2014;24:166-71.
30. Woo J, Lau E, Lee P, Kwok T, Lau WC, Chan C et al. Impact of osteoarthritis on quality of life in a Hong Kong Chinese population. J Rheumatol 2004;31:2433-8.

31. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res 2005;17:255-63.
32. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263-73.
33. Cicuttini FM and Wluka AE. Osteoarthritis: Is OA a mechanical or systemic disease? Nat Rev Rheumatol 2014;10:515-6.
34. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 2011;70:1282-4.
35. Garessus EDG, Mutsert Rd, Visser AW, Rosendaal FR, Kloppenburg M. No association between impaired glucose metabolism and osteoarthritis. Submitted for publication.
36. Kloppenburg M, Boyesen P, Smeets W, Haugen IK, Liu R, Visser W et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014;41:810-8.
37. Kloppenburg M, Boyesen P, Visser W, Haugen IK, Smeets W, Greibrokk E et al. Report from the hand osteoarthritis workshop: Set of core domains and preliminary set of instruments for use in clinical trials and observational studies. 2015;42:2190-7.
38. Kloppenburg M, Maheu E, Kraus VB, Cicuttini F, Doherty M, Dreiser RL et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis. Osteoarthritis Cartilage 2015;23:772-86.

CHAPTER 10

Nederlandse samenvatting

Artrose is de meest voorkomende musculoskeletale aandoening en een belangrijke oorzaak van pijn, stijfheid en functiebeperking van de gewrichten. Het is een multicausale aandoening waarbij alle gewrichtsweefsels worden aangedaan; behalve degeneratieve veranderingen van kraakbeen en subchondraal bot treedt ook inflammatie van het synoviale weefsel op. De pathogenese van artrose is grotendeels onbekend, wel zijn verschillende risicofactoren bekend die bijdragen aan de ontwikkeling van artrose. Zowel systemische als lokale biomechanische factoren lijken hierbij een rol te spelen. Bekende risicofactoren zijn bijvoorbeeld leeftijd, vrouwelijk geslacht en overgewicht.
Hoewel het klinisch effect van artrose groot is, zijn behandelmogelijkheden beperkt tot verlichting van symptomen. Het tekort aan behandelingen die aangrijpen op het ziekteproces zelf komt niet alleen door gebrek aan kennis over de pathogenese van artrose maar ook door de afwezigheid van goede studies naar de behandeling van artrose. Om betere behandelmogelijkheden te ontwikkelen is meer begrip nodig van de mechanismen die leiden tot artrose, en bovendien is meer kennis nodig van uitkomstmaten die toegepast kunnen worden in onderzoek naar artrose om de effecten van behandeling adequaat te kunnen meten.
Dit proefschrift bestaat derhalve uit twee delen. Het eerste deel beschrijft studies die gericht waren op het begrijpen van de mechanismen onderliggend aan de relatie tussen artrose en bekende risicofactoren zoals overgewicht. Het tweede deel van dit proefschrift richt zich op het identificeren van geschikte uitkomstmaten voor toepassing in onderzoek naar artrose.

Deel I. Mechanismen onderliggend aan de relatie tussen risicofactoren en artrose

Deel I van dit proefschrift richt zich op de mechanismen die ten grondslag liggen aan de relatie tussen artrose en bekende risicofactoren; hierbij wordt in het bijzonder ingegaan op de associatie tussen overgewicht en artrose. Omdat overgewicht een risicofactor is voor artrose in zowel gewichtsdragende als niet-gewichtsdragende gewrichten lijken in deze relatie zowel mechanische overbelasting als overgewicht-geassocieerde systemische factoren een rol te spelen. Voor dit deel van het proefschrift werd gebruik gemaakt van gegevens uit de Nederlandse Epidemiologie van Obesitas (NEO) studie. De NEO studie is een onderzoek in de algemene bevolking dat werd opgezet om de mechanismen van obesitas-gerelateerde aandoeningen zoals artrose te ontrafelen. De studiepopulatie bestaat uit 6,673 individuen uit de Leidse regio tussen de 45 en 65 jaar oud van wie een meerderheid overgewicht of vetzucht had. Alle deelnemers vulden uitgebreide vragenlijsten in en ondergingen een lichamelijk onderzoek, inclusief gewrichtsonderzoek van de hand- en kniegewrichten. Bij 1,285 deelnemers werd daarnaast nog een ‘magnetic resonance imaging’ (MRI) scan van de knie verricht om structuurafwijkingen in het kniegewricht te onderzoeken.

Obesitas en artrose in gewichtsdragende en niet-gewichtsdragende gewrichten

In **hoofdstuk 2** hebben we de relatieve bijdrage van mechanische belasting en systemische processen in artrose in gewichtsdragende (knie) en niet-gewichtsdragende (hand) gewrichten onderzocht. Hierbij hebben we gebruik gemaakt van gegevens uit de NEO studie en cross-sectionele analyses verricht. Als surrogaat voor mechanische belasting werden gewicht en vetvrije massa gebruikt, en voor systemische processen het metabool syndroom. Vetmassa was hierbij zowel een maat voor mechanische belasting als voor systemische processen door te corrigeren voor respectievelijk het metabool syndroom of voor gewicht. In knieartrose bleken de surrogaatmaten voor mechanische belasting de belangrijkste risicofactoren terwijl surrogaatmaten voor systemische processen de belangrijkste risicofactoren bleken in handartrose. Ook hebben we de relatie tussen risicofactoren en artrose in zowel de hand als knie bestudeerd. Hoewel de hypothese voorafgaand aan ons onderzoek was dat bij artrose in meer dan één gewricht systemische processen het belangrijkst zouden zijn, bleek de aanwezigheid van artrose in zowel de knie als hand juist geassocieerd te zijn met surrogaatmaten voor mechanische belasting, net als bij de aanwezigheid van artrose in alleen de knie. Dit suggereert dat het tegelijk voorkomen van artrose in de knie en hand twee verschillende typen artrose representeert in plaatst van veroorzaakt te worden door een gedeeld onderliggend systemisch mechanisme. De associatie tussen mechanische belasting en knieartrose lijkt de associatie tussen het metabool syndroom en handartrose te maskeren bij het gelijktijdig voorkomen van hand- en knieartrose.

De associatie tussen het metabool syndroom en handartrose kan worden verklaard door een effect van systemische inflammatie. Vetweefsel is een bron van pro- en anti-inflammatoire cytokines. Deze cytokines kunnen gerelateerd zijn aan het metabool syndroom en lijken ook effect te hebben op gewrichtsweefsels. In **hoofdstuk 3** werd de relatie tussen adipositas en artrose onderzocht door de associatie tussen vetweefsel en de abdominale verdeling hiervan met artrose in de niet-gewichtsdragende handen te analyseren. In verband met de antropomorfe verschillen tussen mannen en vrouwen werden deze apart van elkaar geanalyseerd. Vetpercentage, vetmassa en de middel-heup-ratio waren geassocieerd met handartrose in zowel mannen als vrouwen. Daarnaast was in mannen de hoeveelheid visceraal vetweefsel geassocieerd met handartrose, in tegenstelling tot de hoeveelheid subcutaan vetweefsel. Dit suggereert dat zowel de hoeveelheid vet als de verdeling hiervan van belang zijn in de pathogenese van handartrose. Vooral visceraal vet lijkt een rol te spelen, wat verklaard kan worden doordat de uitscheiding van cytokines die gewrichtsweefsels kunnen beïnvloeden met name lijkt te gebeuren door visceraal vet.

Om het inzicht in de rol van overgewicht in het ontstaan van knieartrose te vergroten, onderzochten we in **hoofdstuk 4** de associatie van vetmassa en skeletspiermassa met knieartrose. Vetmassa, vetpercentage en spierskeletmassa waren positief geassocieerd met de aanwezigheid van knieartrose, terwijl spierskelet als percentage van het totale lichaamsgewicht negatief geassocieerd was met knieartrose. Vooral een hoge vetmassa gecombineerd met een lage spierskeletmassa bleek ongunstig. In obese individuen neemt de hoeveelheid spierskelet toe door de verhoogde belasting van het gewicht. Deze toename in spierskeletmassa is echter minder dan de totale gewichtstoename (voornamelijk vetmassa), resulterend in een verlaagd spierskeletpercentage in individuen met overgewicht. Dit verklaart de omgekeerde associaties met artrose tussen spierskelet als absolute massa en als percentage van het totale gewicht. De analyses werden ook in dit hoofdstuk apart in

mannen en vrouwen verricht, en hierbij bleek de spierskeletmassa het sterkst gerelateerd te zijn aan knieartrose in mannen terwijl vetmassa het belangrijkst bleek in knieartrose in vrouwen. Dit suggereert een vooral biomechanische etiologie van artrose in mannen terwijl artrose in vrouwen bovenal door systemische processen gedreven lijkt te worden. Echter een hoge spierskeletmassa relatief aan een lage vetmassa was in beide seksen gunstig, interventies die zich richten op verbetering van de spierskeletmassa in combinatie met gewichtsreductie kunnen daarom geschikt zijn als preventie en behandeling van knieartrose in zowel mannen als vrouwen.

Structurele afwijkingen en symptomatische artrose

Artrose kan op verschillende manieren gedefinieerd worden, zowel op basis van symptomen en afwijkingen bij lichamelijk onderzoek (klinische artrose) als op basis van structuurafwijkingen zichtbaar op MRI (structurele artrose). De in **hoofdstuk 4** beschreven associaties van vetmassa en spierskeletmassa met knieartrose werden zowel met klinische artrose als met structurele artrose gevonden. Wel viel een grote discrepantie op tussen deze twee definities van knieartrose; slechts een derde van de individuen met klinische of structurele artrose had beide. Hoewel artrose gekenmerkt wordt door degeneratieve veranderingen in het gewricht zijn niet al deze structurele afwijkingen specifiek voor artrose, want ook in individuen zonder artrose worden degeneratieve veranderingen in het gewricht gezien. Om de processen die tot symptomatische artrose leiden beter te begrijpen, hebben we in **hoofdstuk 5** onderzocht welke structurele afwijkingen op specifieke locaties in het kniegewricht het best kunnen onderscheiden tussen het wel en niet hebben van symptomatische artrose in dezelfde knie, rekening houdend met het tegelijk voorkomen van meer dan één structurele afwijking. Zowel in individuen met als zonder symptomatische knieartrose waren vaak structurele afwijkingen zichtbaar op MRI, zowel in het tibiofemorale als in het patellofemorale compartiment van het kniegewricht. Van al deze structurele afwijkingen bleek de aanwezigheid van een Bakerse cyste het best te onderscheiden tussen het wel of niet aanwezig zijn van symptomatische artrose in dezelfde knie. Verder bleken effusie en structurele afwijkingen als osteofyten en beenmerglaesies de aanwezigheid van symptomatische artrose ook goed te kunnen onderscheiden, met name structurele afwijkingen aan de mediale zijde van het tibiofemorale compartiment. Gezien eerder onderzoek gesuggereerd heeft dat Bakerse cysten veroorzaakt worden door ontsteking zal behandeling van knieartrose zich misschien moeten richten op preventie van ontwikkeling van Bakerse cysten door het behandelen van ontsteking.

Artrose en risicofactoren in relatie tot gezondheidsgerelateerde kwaliteit van leven

Artrose levert de op een na grootste bijdrage aan functionele beperking van alle musculoskeletale aandoeningen en heeft een negatieve invloed op de gezondheidsgerelateerde kwaliteit van leven. Een aantal van de bekende risicofactoren voor artrose zijn niet alleen geassocieerd met de ontwikkeling van artrose maar ook met een verminderde gezondheidsgerelateerde kwaliteit van leven. De aanwezigheid van artrose tegelijk met een van deze risicofactoren resulteert mogelijk in versterking van beide negatieve associaties met de gezondheidsgerelateerde kwaliteit van leven. Om inzicht te krijgen in mogelijke aangrijppunten voor verbetering of preventie van vermindering van de gezondheidsgerelateerde kwaliteit van leven in patiënten met knieartrose hebben we in **hoofdstuk 6** het effect van knieartrose en van de te beïnvloeden of te voorkomen risicofactoren overgewicht,

lage vetvrije massa (als surrogaat voor spiermassa) en comorbiditeiten geëvalueerd. Daarnaast werd de interactie tussen knieartrose en deze risicofactoren in relatie tot de gezondheidsgerelateerde kwaliteit van leven onderzocht. Zowel knieartrose als de risicofactoren overgewicht, lage vetvrije massa en comorbiditeiten waren geassocieerd met een klinisch relevante vermindering van de gezondheidsgerelateerde kwaliteit van leven. Daarbij gaf gelijktijdige aanwezigheid van knieartrose en lage vetvrije massa in mannen een additionele vermindering van de gezondheidsgerelateerde kwaliteit van leven. Dit suggereert dat toename van de vetvrije massa (verbetering van spiermassa) de gezondheidsgerelateerde kwaliteit van leven in patiënten met knieartrose kan verbeteren. Daarnaast kunnen interventies die zich richten op overgewicht en preventie of behandeling van comorbiditeiten ook van belang zijn om de gezondheidsgerelateerde kwaliteit van leven in patiënten met knieartrose te behouden of verbeteren.

Deel II. Identificatie van geschikte uitkomstmaten voor onderzoek naar handartrose

Hoewel de behoefte aan onderzoek naar behandelmogelijkheden die aangrijpen op het ziekteproces van artrose groot is, is het uitvoeren van studies van goede kwaliteit hiernaar moeilijk door de vele verschillende en soms matig geëvalueerde uitkomstmaten die beschikbaar zijn, met name in handartrose. Dit belemmert de adequate evaluatie van het ziekteproces en effecten van potentiële behandelingen. **Deel II** van dit proefschrift richt zich daarom op het identificeren van geschikte uitkomstmaten voor toepassing in onderzoek naar handartrose. In het kader van de 'Outcome Measures in Rheumatology' (OMERACT) handartrose werkgroep, die als doel heeft om een kernset van uitkomstmaten voor onderzoek naar handartrose te ontwikkelen, hebben we twee systematische reviews verricht. Deze systematische reviews evalueren de beschikbare instrumenten voor het meten van de domeinen pijn, fysieke functie, patient global assessment (algeheel welbevinden), en beeldvorming in handartrose om aanbevelingen te kunnen doen voor het gebruik van deze instrumenten in klinisch onderzoek.

Pijn, fysiek functioneren en patient global assessment in handartrose

In **hoofdstuk 7** hebben we het gebruik van instrumenten voor het meten van pijn, fysiek functioneren en patient global assessment in onderzoek naar handartrose geëvalueerd, alsmede de metrische eigenschappen van deze instrumenten. De metrische eigenschappen werden geëvalueerd volgens het OMERACT filter, namelijk discriminatie (betrouwbaarheid en gevoeligheid voor verandering), uitvoerbaarheid en validiteit. Met behulp van een systematische zoekstrategie identificeerden we 66 publicaties over onderzoek waarin verschillende vragenlijsten en testen werden toegepast om pijn, fysiek functioneren en patient global assessment te meten. Er werden geen grote verschillen in metrische eigenschappen tussen de instrumenten geobserveerd, echter de hoeveelheid ondersteunend bewijs verschilde wel sterk tussen de instrumenten. De meest frequent geëvalueerde vragenlijsten waren de 'Australian/Canadian Hand Osteoarthritis Index' (AUSCAN) pijn subschaal en de visueel analoge schaal (VAS) pijn voor het meten van pijn, en de AUSCAN functie subschaal en 'Functional Index for Hand Osteoarthritis' (FIHOA) voor het meten van fysiek functioneren. Uitstekende betrouwbaarheid werd aangetoond voor zowel de

AUSCAN als de FIHOA. De uitvoerbaarheid van de FIHOA was goed. Goede gevoeligheid voor verandering en validiteit werden gesuggereerd voor alle beschreven instrumenten. De meest toegepaste testen waren de grijp- en knijpkracht voor het meten van fysiek functioneren en het meten van pijn door middel van palpatie. Voor deze beide testen werden goede gevoeligheid voor verandering en validiteit aangetoond.

Radiografische evaluatie van handartrose

Hoofdstuk 8 richt zich op beeldvorming, hierin hebben we het gebruik van conventionele röntgenfoto's in studies naar handartrose en de metrische eigenschappen van de beschikbare scoremethoden voor evaluatie van deze röntgenfoto's geëvalueerd, opnieuw gebruikmakend van het OMERACT filter. We identificeerden door een systematische zoekstrategie 48 publicaties waarin 13 verschillende scoremethoden waren gebruikt voor de radiografische evaluatie van handartrose. Het aantal onderzochte gewrichten verschilde opvallend tussen de studies en de verkregen scores werden op verschillende manieren geanalyseerd. Hoewel er geen grote verschillen waren met betrekking tot de metrische eigenschappen van de scoremethoden, verschilde de hoeveelheid ondersteunend bewijs voor de gebruikte scoremethoden. Het meeste bewijs voor alle geëvalueerde domeinen was beschikbaar voor de 'Kellgren-Lawrence' en 'Osteoarthritis Research Society International' scoremethoden. Voor de 'Verbruggen-Veys anatomical phase score' werd ondersteunend bewijs gevonden voor alle geëvalueerde domeinen behalve voor validiteit. Voor de 'Kallman' scoremethode werd ondersteunend bewijs gevonden voor alle domeinen behalve voor de gevoeligheid voor verandering. Om de vergelijkbaarheid van studies naar handartrose te verbeteren moet consensus worden bereikt over de te gebruiken scoremethoden, de te evalueren gewrichten, de analysemethode van de scores en de definitie van handartrose. In de keus zal rekening moeten worden gehouden met het doel van de studies.

Toekomstperspectieven

Overgewicht wordt als een van de belangrijkste risicofactoren voor het ontstaan van artrose gezien, maar door welke mechanismen is nog grotendeels onbekend. De bevindingen beschreven in **deel I** van dit proefschrift vergroten ons begrip van deze mechanismen. Verder wordt beschreven welke structurele afwijkingen in het kniegewricht de aanwezigheid van symptomatische artrose het best karakteriseren. Tot slot hebben we de bijdrage van een aantal modificeerbare risicofactoren vastgesteld in de gezondheidsgerelateerde kwaliteit van leven in patiënten met knieartrose. Al deze bevindingen geven aangrijppunten voor het verbeteren van de behandeling van artrose, zowel gericht op de symptomen als op het ziekteproces zelf. Een kanttekening hierbij is dat de associaties beschreven in dit proefschrift allemaal cross-sectioneel zijn. Longitudinaal onderzoek door de tijd kan deze associaties bevestigen en de precieze pathogenese van artrose verder ophelderen. Follow-up gegevens van de NEO studie worden op dit moment verzameld en kunnen hierbij van nut zijn.

Deel II van dit proefschrift vergroot de kennis van beschikbare instrumenten voor het meten van de domeinen pijn, fysiek functioneren, patient global assessment en beeldvorming in handartrose. De resultaten van de beide overzichtsartikelen in dit deel werden gepresenteerd en bediscussieerd tijdens de OMERACT12 meeting. Daarbij werd consensus bereikt over het toepassen van de instrumenten waarvoor op dit moment het meeste onder-

steunende bewijs beschikbaar is. Voor de hiaten in de kennis van een aantal instrumenten werd een onderzoeksagenda opgesteld waarin items voor nader onderzoek beschreven werden. Na verdere evaluatie van de beschikbare instrumenten kan consensus worden bereikt over de toepassing van specifieke instrumenten voor het meten van de verschillende domeinen, dit zal de uitvoering van studies van hoge kwaliteit bevorderen.
De combinatie van bevordering van onderzoek van hoge kwaliteit en het verder ophelderen van de pathogenese van artrose kunnen uiteindelijk leiden tot het ontwikkelen van behandelmogelijkheden die aangrijpen op het ziekteproces in plaats van de huidige beperking tot verlichting van symptomen van artrose.

APPENDICES

APPENDIX 1

Comment in Nature Reviews Rheumatology on 'The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study (Annals of the Rheumatic Diseases 2015;74(10):1842-7)'

Is osteoarthritis a mechanical or systemic disease?

F.M. Cicuttini and A.E. Wluka

Nature Reviews Rheumatology 2014;10:515-516.

Osteoarthritis (OA) is a heterogeneous group of diseases with different pathogenesis in different joints. What effect do metabolic factors, inflammation and obesity have on OA in non-loadbearing structures? A new study reports that, in the absence of knee OA, systemic processes are important in the pathogenesis of hand OA.

A new paper by Visser et al.[1] examines the question of whether osteoarthritis (OA) is predominantly a biomechanical or systemic disease, and whether these mechanisms differ in hand and knee OA. They concluded that, although mechanical factors are probably more important in knee OA whether or not it coexists with hand OA, systemic processes, such as inflammation, aberrant metabolic regulation and obesity, control the pathogenesis of hand OA. How should these results be interpreted in the context of other evidence in the field?

The first thing to consider is that an increasing body of evidence shows that OA is joint failure – an outcome with myriad causes. It is now apparent that, in order to explore risk factors for OA, a joint-specific approach, such as that used by Visser et al.,[1] is needed. Although different risk factors, such as obesity and physical activity, overlap in their effect on joints, the mechanisms by which such risk factors specifically affect joints might differ. What do we know about the role of different biomechanical and systemic factors in knee OA? With the advent of sensitive, noninvasive imaging modalities such as MRI, it is now possible to visualize knee OA on a spectrum from a normal joint through to one with clinically and radiographically evident OA (Figure 1). By the time the first knee joint changes are detected by radiography, more than 10% of cartilage is already lost.[2] In addition, to better understand the role of a risk factor, its effect on structural change needs to be examined at different stages of the disease because the susceptibility of the joint to the risk factor in question might vary according to the severity of the pathological changes.

A large body of evidence based on highly sensitive MRI now shows that reduced knee cartilage volume is associated with metabolic factors, including increased fat mass and serum glucose levels. These MRI data correlate with radiographic evidence of OA and can predict increased knee pain and the risk of joint replacement.[3] Knee cartilage volume is also negatively associated with the concentration of circulating inflammatory cytokines, such as IL-6 and TNF,[4] as well as C-reactive protein (CRP), a systemic marker of inflammation.[5] Consistent with these findings, low-grade synovitis is common in patients with OA and is associated with cartilage loss.[6] Evidence also indicates that the adipokine leptin is an important mediator of the effect obesity has on knee cartilage.[7] Taken together, these data suggest that metabolism-related inflammatory factors substantially affect early stages of the pathogenesis of knee OA.

By contrast, Visser et al.[1] concluded that mechanical stress rather than systemic factors are important in knee OA. This conclusion was based on a cross-sectional examination of 6,673 participants aged 45 to 65 years, including 5,002 participants who were selected for BMI ≥27 kg/m^2, thereby providing a study group enriched for overweight individuals, and 1,671 participants selected as a reference from the general population. The definition of OA was based on the ACR clinical criteria, so no imaging was performed. Surrogates for mechanical stress (weight, fat-free mass, fat mass [adjusted for metabolic factors]) and systemic processes (metabolic syndrome, fat mass [adjusted for weight]) were used to examine the effect of mechanical stress and systemic processes, respectively, on OA. Knee OA was associated with weight and fat-free mass, adjusted for metabolic factors, with an OR of 1.49 (95% CI 1.32 to 1.68) and 2.05 (95% CI 1.60 to 2.62), respectively, but

was not associated with fat mass. As this study was cross-sectional, it has the potential problem of 'reverse causation': patients with knee pain might have gained weight or their body composition might have changed as a consequence of clinical knee OA. Studies examining asymptomatic individuals have correlated fat mass and markers of metabolism related-inflammation with structural changes to joints.[7] Nevertheless, these findings, in patients with clinical OA, are consistent with other data showing that biomechanical factors predominate in established OA; for example, minor degrees of knee malalignment have a more substantial pathogenic role in later rather than earlier stages of the disease.[8] With cartilage loss already present by the time OA is identified by clinical and radiographic analysis, it is not surprising to find that the local biomechanical environment in the knee has also changed and is the main factor contributing to disease progression. In contrast to the mechanical pathogenesis of knee OA, the data from Visser et al.[1] support a prominent role for metabolic factors in the aetiology of hand OA; hand OA was associated with the metabolic syndrome, adjusted for weight, with an OR of 1.46 (95% CI 1.06 to 2.02). For decades, obesity has been recognized as a risk factor for hand OA.[9] Given that we do not walk on our hands, this risk factor is circumstantial evidence against a mechanical pathogenesis for OA. The study by Visser et al.[1] further supports this concept; however, the 3rd National Health and Nutrition Examination Survey found no relationship between serum concentrations of leptin and the presence of clinical hand OA,[10] suggesting an alternative systemic pathway of OA pathogenesis. That is not to say that the results from Visser et al.[1] are definitive that systemic factors drive hand OA, or that they exclude the role of biomechanics; only muscle mass was examined as a surrogate for a mechanical effect of hand OA. One could argue that total-body muscle mass might not be a good surrogate measure of mechanical factors relevant to hand OA. Thus, further work in this area is needed.

What can we conclude? OA is not a single disease, but a heterogeneous condition, resulting from a variety of different exposures. These new data from Visser et al.[1] and others suggest that the pathogenesis of OA needs to be examined on a joint-by-joint basis. To not do so is likely to impede our understanding of the pathogenesis of OA and the identification of novel drug targets for prevention and treatment. The emerging data suggest that, although mechanical factors might have a larger role in established or late OA, systemic factors have a substantial effect on the knee joint structure in preclinical OA (Figure 1). Although mechanical factors are also involved in hand OA, the case for a systemic mechanism in the pathogenesis of this condition seems clearer. Thus, in regards to the question of whether OA is a mechanical or systemic disease, perhaps the correct answer is ... it depends.

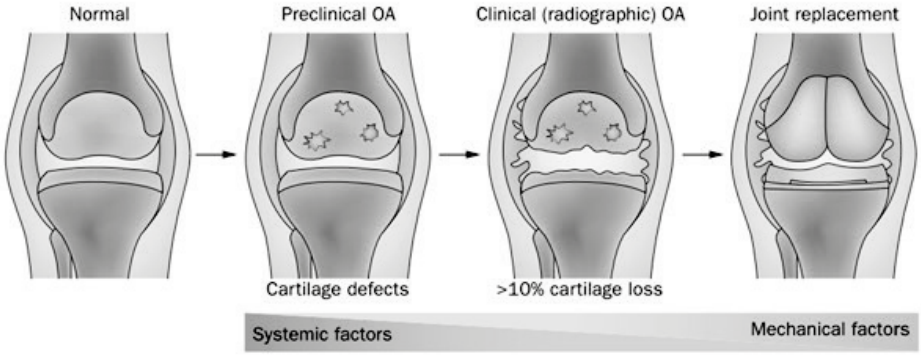

Figure 1. The spectrum of knee OA. OA can be considered as being on a spectrum from a healthy joint to preclinical disease and the beginning of cartilage damage (which is now detectable by MRI), through to radiographically evident OA and end-stage joint replacement. Systemic metabolic and inflammatory factors predominate in the early stages of knee OA, whereas mechanical factors seem to be more important in the later stages.
OA, osteoarthritis.

REFERENCES

1. Visser AW, de Mutsert R, le Cessie C, den Heijer M, Rosendaal FR, Kloppenburg M. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2014 [Epub ahead of print].
2. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthritis Cartilage 2004;12:169–174.
3. Cicuttini FM, Jones G, Forbes A, Wluka AE. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. Ann Rheum Dis2004;63:1124–7.
4. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, Ding C. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage 2010;18:1441–7.
5. Jin X, Beguerie JR, Zhang W, Blizzard L, Otahal P, Jones G, Ding C. Circulating C reactive protein in osteoarthritis: a systematic review and metaanalysis. Ann Rheum Dis 2015;74(4):703-10.
6. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, Lynch JA, Lewis CE, Torner J, Zhang Y. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804–9.
7. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, Jones G.Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis 2008;67:1256–61.
8. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis Rheum 2009;61:459–67.
9. Carman WJ, Sowers M, Hawthorne VM, Weissfel LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol 1994;139:119–29.
10. Massengale M, Reichmann WM, Losina E, Solomon DH, Katz JN. The relationship between hand osteoarthritis and serum leptin concentration in participants of the Third National Health and Nutrition Examination Survey. Arthritis Res Ther 2012;14(3):R132.

APPENDIX 2

Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies

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ABSTRACT

Objective
During OMERACT 12, a workshop was held with the aim to endorse a core set of domains for 3 settings: clinical trials of symptom and structure modification and observational studies. Additional goals were to endorse a core set of contextual factors for these settings, and to define preliminary instruments for each core domain. Finally, an agenda for future research in hand osteoarthritis (OA) was to be proposed.

Methods
Literature reviews of preliminary instruments for each core domain of the proposed core set for hand OA in the settings described above. Literature review of radiographic scoring methods and modern imaging in hand OA were also performed. Proposed contextual factors for a core set were identified through 2 Delphi exercises with participation of hand OA experts, patient partners, and OMERACT participants.

Results
Results from Delphi exercises and systematic literature reviews were presented and discussed. It was agreed that a preliminary core domain set for the setting clinical trials of symptom modification should contain at least "pain, physical function, patient global assessment, joint activity and hand strength." The settings clinical trial of structure modification and observational studies would in addition include structural damage. Preliminary instruments for the proposed domains were agreed on. A list of prioritized contextual factors was defined and endorsed for further research. A research agenda was proposed for domain instrument validation according to the OMERACT Filter 2.0.

Conclusion
Preliminary core sets for clinical trials of symptom and structure modification and observational studies in hand osteoarthritis, including preliminary instruments and contextual factors, were agreed upon during OMERACT 12.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder involving all components of the joint.[1] All joints may be involved, but the hand is a predilection site. The phenotype hand OA warrants special attention, because hand OA is in itself polyarticular, making it complex to study. Moreover, hand OA is frequently accompanied by OA in other joint sites, such as the knees or hips.[2] Hand OA is not one phenotype, but comprises several subsets, such as nodal hand OA, thumb base OA, and erosive hand OA,[3,4] which are associated with different risk factors, requiring different treatment strategies. Currently, insight in underlying pathophysiologic mechanisms of hand OA is limited and insufficient treatment options exist.[5] Therefore, high-quality observational cohorts and clinical trials are warranted, requiring optimal sets of outcome measures for adequate assessment of hand OA.

In 2010 the Outcome Measures in Rheumatology (OMERACT) hand OA working group was assembled, comprising health professionals, researchers, and patient research partners (PRP), with interest and experience in hand OA, aiming at defining a set of core domains using the OMERACT framework.[6] Previously, four core domains (pain, function, patient global assessment, and imaging) for knee, hip, and hand OA trials of ≥1 year duration were defined for phase III clinical trials following the OMERACT III consensus conference.[7] An Osteoarthritis Research Society International taskforce added the following domains: mobility, deformity, inflammation, performance, stiffness, and esthetic damage.[8] However, the above-mentioned set of core domains has several shortcomings: only the clinical trial setting was addressed, patients were not involved in the process, and the core sets lacked incorporation of hand OA–specific aspects.[9,10]

First, the OMERACT hand OA group performed a Delphi exercise among hand OA group members and OMERACT participants to identify a set of core domains.[6] Potential domains were identified from a qualitative study with 10 focus groups among 56 patients with hand OA from five European countries.[11] This was done separately for four settings: clinical trials of symptom modification and structure modification, observational studies, and clinical record keeping. Results of the Delphi exercises were discussed in a special interest group (SIG) during OMERACT 11 and resulted in a proposed set of core domains.[6] Further, it was agreed during the SIG to apply the new OMERACT Filter 2.0 in the development process.[12] Further discussions were held at annual meetings of the American College of Rheumatology (ACR) in 2012 and 2013.

As a next step we proposed a workshop during OMERACT 12 with the following objectives: (1) to endorse a core domain set for three settings, clinical trials of symptom modification, of structural modification, and of observational studies, (2) to endorse a core set of contextual factors for the same settings, (3) to define a preliminary set of instruments for each core domain, and (4) to propose a research agenda for domain instrument validation according to the OMERACT Filter 2.0.

MATERIALS AND METHODS

Delphi Exercise

Prior to the OMERACT 12 meeting, we performed a Delphi exercise to reach consensus about the contextual factors that should be considered as mandatory in hand OA studies. In Delphi round 1 an initial list of 36 potential contextual factors was circulated to experts in hand OA, PRP, and OMERACT participants. The list was derived from hand OA experts, hand OA patient focus groups, OMERACT participants, and an International Classification of Functioning review.[13] Potential contextual factors, i.e., variables that are not outcomes of the study but need to be recognized (and measured) to understand the study results,[12] included demographics, OA-specific factors, physical health, mental health, physical fitness, and others. Participants were asked to divide 100 points among the contextual factors they considered important; participants were explicitly encouraged to include additional factors. Domains with high agreement (average >6 points) were kept, whereas domains with low agreement (average <1 point) were excluded. Factors with moderate agreement and suggested factors were voted on in Delphi round 2.

Literature Reviews of Instruments to Assess Hand OA Outcomes

A systematic search of the medical literature up to January 2014 was performed to identify instruments measuring pain, physical function, patient global assessment, joint activity, and hand strength and to summarize their metric properties, i.e., discrimination (reliability, sensitivity to change), feasibility, and validity. Inclusion criteria required for studies to evaluate these aspects differed per item (Visser et al, manuscript submitted).[14] Another systematic review of the medical literature up to November 2013 was performed to evaluate the use of radiography in hand OA and to assess the reliability, sensitivity to change, validity, and feasibility of the different available radiographic scoring methods.[15]

OMERACT 12 Hand OA Workshop

A plenary session was held during which presentations were given: (1) On results of the Delphi exercises concerning core domains and later discussions (MK); (2) on the Delphi exercises concerning contextual factors (PB); (3) on systematic literature searches concerning instruments to assess pain, function, patient global, hand strength, and tender joints (AWV); (4) on searches to assess structural damage by radiography (AWV); and (5) on searches to assess joint activity or disease activity at joint level and structural damage using modern imaging techniques (IKH).

Subsequently, 4 breakout sessions took place to discuss (1) core domains in outcome measures, (2) contextual factors, (3) instruments to assess patient reported outcomes and performance measures, and (4) imaging instruments. Summaries of the breakout sessions were reported back during a plenary session. During this final plenary session, votes were taken; voters could “agree,” “not agree,” or “not know.”

RESULTS

Endorsement of Domains for a Core Domain Set for 3 Settings

Based on results of the Delphi exercise and discussions during OMERACT 11, the proposed core domains included pain, physical function, patient global assessment, joint activity, health-related quality of life (HRQOL), reduced strength, pain medication, structural damage, and reduced mobility.[6] The proposed core domain set was widely discussed during a breakout session attended by 11 physicians, 2 PRP, 1 representative from industry, 2 researchers, and 2 research fellows.

Discussions touched upon similarities and differences between "reduced strength" and "physical function," and the term "hand strength" was proposed instead of "reduced strength." HRQOL was included as a core domain. However, HRQOL contains different domains, and instruments are not available. Therefore, HRQOL was included as a non-mandatory domain until disease-specific instruments are available. After discussion, the proposed domain "pain medication" was incorporated as a potential contextual factor. After the breakout session, it was proposed that in the setting of clinical trials of symptom modification, a preliminary set of core domains should at least contain pain, physical function, patient global assessment, HRQOL (although not mandatory as long as no disease-specific instruments are available), joint activity, and hand strength. In the final plenary, 47 (89%) of the voting participants agreed; 11% did not agree; and none responded "don't know."

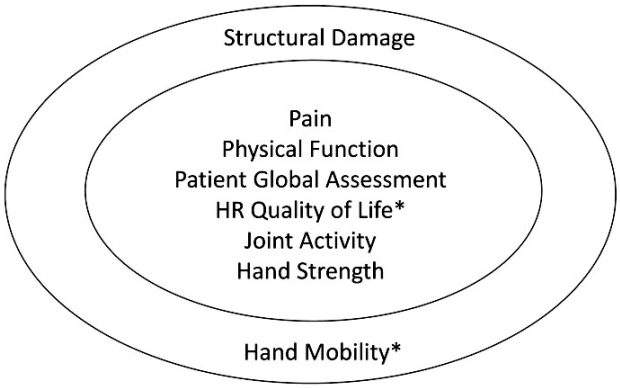

Figure 1. Preliminary set of endorsed core domains for hand osteoarthritis studies. Inner circle: Domains for all settings, i.e., clinical trials of symptom modification, clinical trials of structure modification, and observational studies. Outer circle: Domains for some settings, i.e., clinical trials of structure modification and observational studies.

*Domains not mandatory as long as no disease-specific instruments are available.

HR, health-related.

For the setting of clinical trials of structure modification, the breakout group proposed to define subdomains as radiographic damage, esthetic damage, bony damage, and deformity. Further, "reduced mobility" was discussed: whether it is distinct from or similar to physical function, as well as the current lack of an appropriate instrument; "hand mobility" was suggested as a more appropriate term. Finally, it was agreed by 41 voting participants (76%) that a preliminary set of core domains for clinical trials of structure modification contain at least the domains endorsed for clinical trials of symptom modification and structural damage and mobility; 13% did not agree and 11% did not know. Thirty-eight (72%) agreed that the preliminary set of endorsed core domains for the assessment of hand OA in observational studies is similar to that for structure modification; 11% did not agree and 17% did not know (Figure 1).

Definition of a Preliminary Set of Instruments for Each Core Domain

Patient-reported outcomes and performance tests

In the systematic literature review, 66 studies concerning hand OA were included, in which various questionnaires, perform - ance-based instruments, and assessor-based instruments were applied. No major differences regarding metric properties were observed between the instruments, although the amount of supporting evidence varied.

The most frequently evaluated questionnaires were the Australian Canadian Hand OA Index (AUSCAN) pain subscale[16] and visual analog scale (VAS) or numerical rating scale (NRS) for pain assessment, and the AUSCAN function subscale and Functional Index of Hand OA (FIHOA)[17] for physical function assessment. Excellent reliability was shown for the AUSCAN and FIHOA and good sensitivity to change for all mentioned instruments; additionally, the FIHOA had good feasibility. No validation by comparing to a gold standard has been performed; however, good construct validity was suggested for all instruments. Grip and pinch strength to assess hand strength and palpation of tender joints to assess joint activity[18] were commonly applied. For these measures, good sensitivity to change and construct validity were established. Supporting evidence (Table 1) was presented and discussed in a breakout session, attended by 2 PRP, 1 representative from the pharmaceutical industry, 2 occupational therapists, 1 statistician, 1 epidemiologist, and several rheumatologists.

There was general agreement to use the VAS or NRS to assess pain. A single question was generally preferred over multiple pain questions. Further information is needed whether overall hand pain or joint pain specifically should be assessed, which joints should be assessed, how questions should be asked, and which anchors should be used. During voting, 49 participants (88%) agreed on either the VAS or NRS as a preliminary instrument for the self-reported pain domain; 4% did not agree; and 9% did not know. There was concern about the use of the FIHOA to assess physical function because of sex role-specific items (men use screwdrivers and women sew), cultural issues (e.g., handshake), and some items with low secular relevance, e.g., writing for a long period of time versus typing on computer. The alternative AUSCAN instrument had the disadvantage of limited access due to a mandatory fee. Therefore, it was voted by 31 participants (61%; 18% did not agree; 22% did not know) to use the FIHOA for the physical function domain for the time being. Research is warranted for a more contemporary instrument. To measure the hand strength domain, 43 participants (81%) agreed on use of grip/pinch strength as a preliminary instrument; 13% did not agree; and 6% did not know. Although it was agreed

that more studies are needed, 43 participants (75%) agreed on use of the tender joint count on palpation as a preliminary instrument to assess joint activity; 11% did not agree, and 14% did not know.

Table 1. Supporting evidence from at least 3 studies for the most frequently applied instruments for evaluation of pain, physical function or patient global assessment. From Visser et al. J Rheumatol (manuscript submitted).14

	Reliability	Sensitivity to change	Feasibility	Validity
Questionnaires				
AUSCAN	+	+	- #	+
FIHOA	+	+	+**	+
VAS pain		+		+
Performance-/assessor-based instruments				
Grip strength	+*	+		+
Pinch strength	+*	+		+
Tenderness/pain on palpation	+*	+		+*

+ established evidence

* supporting evidence in only 2 studies

** supporting evidence in only 1 study

not available in public domain

AUSCAN, Australian/Canadian Hand Osteoarthritis Index; FIHOA, Functional Index for Hand Ostearthritis; VAS, visual analogue scale.

Radiographic scoring methods

The domain structural damage includes the subdomain radiographic damage. The systematic literature review revealed 13 different scoring methods that evaluated radiographic hand OA; some scores were more extensively studied than others.[15] Data on reliability, validity, sensitivity to change, and feasibility were available. There were major differences between studies in the number of examined joints and the way scores were analyzed. The reliability of the assessed radiographic scoring methods was good for all evaluated scoring methods, although longitudinal performance was tested only for some methods. The validity of radiographic OA findings compared to that of clinical findings such as nodules and deformities was limited, but the association of radiographic findings with symptoms and hand function was better. The sensitivity to change was comparable for all evaluated scoring methods, as well as the smallest detectable change. Few studies explored the feasibility of the radiographic scoring methods. Apart from time required for scoring (longer for individual features than for composite scores), no major differences between the evaluated scoring methods was shown. The metric properties are summarized in Table 2 for the most extensive studied scores.

The systematic review served as starting point in the breakout session (attended by 2 radiologists and 13 rheumatologists) discussing imaging instruments. The group supported that radiographs provide information on structural damage measures. There was consensus on including the most widely used and currently best-validated measures in a core set for structural damage. During voting it was agreed by 46 participants (87%) to use the Kellgren-Lawrence method, the OARSI atlas, the Verbruggen-Veys method, or the Kallman method as preliminary instruments for the structural damage domain; 6% did not agree; and 8% did not know.

Table 2. Supporting evidence for most frequently applied radiographic scoring methods. Modified from Visser et al. Osteoarthritis Cartilage 2014;22:1710-2315; with permission.

	Reliability	Sensitivity to change	Feasibility	Validity
Composite score				
KL[17]	+	+	+	+
Individual features				
Anatomical phases18	+	+	+	
OARSI19	+	+	+	+
Kallman20	+		+	+

+ established evidence

KL, Kellgren-Lawrence; OARSI, Osteoarthritis Research Society International.

Modern imaging methods

Updated literature overviews[19] of ultrasonography (US) and magnetic resonance imaging (MRI) scoring systems and metric properties were presented; the data were limited. US enables a dynamic image of joints and allows visualization of osteophytes, but also marginal erosions and synovitis. US studies of patients with hand OA have reported high prevalence of greyscale synovitis, while power Doppler activity is less frequent. One preliminary US scoring system has been developed for hand OA including assessment of synovitis (greyscale hypertrophy/effusion and power Doppler) and osteophytes on semiquantitative scales.[20] An US atlas for assessment of osteophytes was developed with excellent intra- and inter-reader reliability.[21] Preliminary studies have shown that validity and sensitivity in comparison with radiography of US seems good; however, more data are needed.[22]

MRI provides a multiplanar image of all joint components; it is the only imaging modality enabling the visualization of bone marrow lesions (BML). Synovitis, based on gadolinium enhancement, is frequent in patients with hand OA; the frequency of BML varies. A preliminary MRI scoring system, which includes assessment of osteophytes, joint space narrowing, erosions, cysts, malalignment, synovitis, flexor tenosynovitis, BML, collateral ligament pathology and BML at insertion sites, has shown good reliability.[23] Lately, this scoring system was revised by OMERACT.[24] Knowledge about validity is limited.

In the breakout group, modern imaging techniques were discussed. The group noted that US and MRI provide information about inflammation and structural damage, with the benefit of multiplanar visualization and highlighting of the complex multitissue pathology in OA. It was felt that experience from rheumatoid arthritis could be transferred, although caution should be taken, especially, when evaluating very small joints. The group noted that knowledge is needed concerning metric properties of these modern imaging modalities. This notion was supported during voting: 98% of voting participants agreed to have US and MRI on the research agenda.

Endorsement of a preliminary core set of contextual factors for 3 settings.
The Delphi round 1 and 2 had 54 and 21 respondents, respectively. Age and sex as contextual factors reached high agreement across all settings in round 1, whereas hand OA subsets reached high agreement solely for the setting of symptom modification trials. Ethnicity, alcohol consumption, previous surgery for OA in locations other than hands, energy functions, control of voluntary movements, and effects of weather were excluded from further voting owing to low agreement. In round 2, body mass index (BMI), hand OA symptom duration, and hand OA subsets reached high agreement for all settings. Treatment for OA, comorbidities, OA in other specified joint sites, and fulfillment of the ACR Hand OA criteria reached high agreement for some settings and moderate agreement for others (Table 3).

Table 3. Candidate contextual factors for hand OA studies that resulted from Delphi exercises.

	Symptom Modiciation Trials	**Structure Modification Trials**	**Observational Studies**
Age	9.3*	9.3*	9.4*
Sex	8.3*	8.2*	8.3*
Body mass index	7.7	9.2	8.4
Handedness	5.6	5.6	5.5
Postmenopausal state	4.2	3.8	3.4
Socioeconomic status	3.1	2.4	3.8
Smoking	3.3	2.5	2.7
Current occupation	4.7	5.0	4.2
Work absenteeism/pension due to OA	2.0	1.8	1.8
Hand OA subsets	6.1*	16.5	8.3
Symptom duration	8.9	8.6	7.9
Disease duration	5.1	5.0	4.1
Secondary OA	0.7	2.0	1.9
Previous trauma of the hands	1.6	2.3	1.9
OA in other specified joint sites	6.5	5.2	6.7
Treatment for OA	8.3	6.5	5.8
Previous specified surgery for hand OA	3.1	3.5	2.7
Use of orthotics for hand OA	3.3	2.4	2.1
Previous surgery for OA other location	0.3	1.5	1.1
Family history of hand OA	2.2	2.8	3.8
Hand exercise	2.0	2.8	1.8
Comorbidities	6.8	4.9	5.2
Impairment of body functions due to comorbidities	2.5	NA	NA
Treatment for comorbidities	1.2	NA	NA
Sleep functions	1.2	0.2	0.7
Emotional functions	2.0	0.2	0.5
Coping and illness perceptions	3.2	0.7	2.8

Table 3. *Continued*

	Symptom Modiciation Trials	Structure Modification Trials	Observational Studies
Activities/hobbies requiring intensive use of the hands	2.7	3.5	1.7
Lower extremity exercise	0.2	0.3	0.2
Mental status	0.9	NA	0.6
Fulfilling ACR hand OA criteria	6.2	NA	4.1
Nutritional habits	NA	0.8	0.3
Degree of catastrophizing	1.7	NA	NA
Frustration	NA	0.2	NA
Use of stress management techniques	NA	NA	0.5
Activity limitation	NA	NA	1.6

* Candidate contextual factors with high agreement from Delphi round. Dark grey shading: high agreement (average score >6); light grey shading: moderate agreement (average score between 1 and 6); no shading: low agreement (average score <1).

ACR, American College of Rheumatology; NA, not applicable; OA, osteoarthritis.

Results of the Delphi exercise were discussed in a breakout session, among 6 rheumatologists, 1 occupational therapist, and 1 PRP. The group discussed generic issues regarding contextual factors and hand OA–specific issues. On a general level, there is a methodological need for validation of contextual factors. It was felt that a "core" contextual factor requires rigorous evidence that this factor influences the result of disease/drug on core outcome. However, there is no current consensus on the level of evidence required. Overall, the group held the opinion that the Delphi exercise was complex, with a large list of candidate contextual factors. The 100-point approach of the Delphi exercise and the choice of cutoff were debated. Although the results from the Delphi exercise were thought to be more informative than decisive, the breakout group agreed that the factors with high agreement from the Delphi exercise represent candidate contextual factors; i.e., age, sex, BMI, hand OA subsets, hand OA symptom duration, treatment for OA, OA in other specified joint sites, fulfillment of the ACR hand OA criteria, and comorbidities. The vast majority of voting participants [50 (93%)] agreed to continue research on the prioritized candidate contextual factors. Breakout group discussions and later voting supported the suggestion of 1 common set of contextual factors in hand OA across different settings [41 voting participants (75%) agreed; 9 (16%) did not agree; 5 (9%) did not know].

DISCUSSION

Discussions and voting during the consensus meeting at OMERACT 12 resulted in a preliminary set of core domains and subdomains, from which the majority was similar for 3 settings. The (sub)domains were distributed over the core area life impact and pathophysiological manifestations, according to the OMERACT filter 2.0, as depicted in Table 4. Preliminary instruments were identified for some (sub)domains. But for several others, research is needed to define disease-specific instruments. The results are summarized in Table 5. Candidate contextual factors have been identified, but need further investigation. Several items were introduced for further research (Table 6).

Table 4. Preliminary core outcomes measurement set according to the OMERACT Filter 2.0.

Death	**Life impact**	**Pathophysiological Manifestations**
Adverse event	• Pain	• Pain
	• Physical function	• Physical function
	• Patiënt global assessment	• Patiënt global assessment
	• Hand strength	• Joint activity (tender joints, soft swollen joints*)
	• HRQOL*	• Hand strength
		• Structural damage (radiographic damage, aesthetic damage*, body damage*, deformity*)
		• Hand mobility*
Candidate contextual factors		
• Age		
• Sex		
• BMI		
• Fulfillment ACR hand OA criteria		
• Hand OA subsets		
• Symptom duration		
• OA at other joint sites		
• Concomitant treatment for OA		
• Comorbidities		

* Domains not mandatory as long as no disease-specific instruments are available.

ACR, American College of Rheumatology; BMI, body mass index; HRQOL, health-related quality of life; OA, osteoarthritis.

Table 5. Preliminary set of core (sub) domains with preliminary instruments.

Domains	Subdomains	Instruments Settings	
		Clinical Trials of Symptom Modification	Clinical Trials of Structure Modification and Observational Studies
Pain		Pain VAS/NRS	Pain VAS/NRS
Physical function		FIHOA	FIHOA
Patient global assessment		Research	Research
Joint activity	Tender joints	Tender joint count	Tender joint count
	Soft swollen joints	Research	Research
Hand strength		Grip/pinch strength	Grip/pinch strength
HRQOL*		Research	Research
Structural damage	Radiographic damage		Kellgren Lawrence or Verbruggen-Veys or Kallman or OARSI
		Aesthetic damage*	Research
		Body damage*	Research
		Deformity*	Research
Hand mobility*			Research

* Domains not mandatory as long as no disease-specific instruments are available.
VAS/NRS: visual analog scale/numerical rating scale; FIHOA: Functional Index for Hand Osteoarthritis; OARSI: Osteoarthritis Research Society International.

Table 6. Future research for domain instrument validation according to the OMERACT Filter 2.0.

- A definition for each contextual factor in hand OA should be formulated
- Performance of a literature review to assess the level of evidence for the different candidate contextual factors
- Identification or development of potential instruments to assess contextual factors, where applicable
- Disease-specific instruments have to be developed for the (sub)domains HRQOL, aesthetic damage, bony damage, deformity, and hand mobility
- Development and testing of VAS/NRS questions to measure the domain pain
- Development of a new measure for hand pain in analogy to knee and hip pain (Intermittent and Constant OA Pain for the hand)
- Evaluation of instruments that are commonly used by hand therapists, such as the DASH, PRWHE, and Michigan Hand Outcome Questionnaire, for use in hand OA.
- Investigation what hand OA contributes to grip strength or pinch strength relative to other conditions that affect hand strength or function
- Performance of qualitative interviews: how to measure patient global assessment
- Investigation of the subdomain tender joints
- Further evaluation of the instrument to assess tender joints (Doyle index), with respect to validation in OA — e.g., what is the added value of joint count to other domains, like pain. How many joints and which ones should be incorporated in the tender joint count? How should the tender joint count be performed? Is there a floor effect?
- To develop instruments to assess soft swollen joints and bony damage
- Investigation of the value of patient-performed joint count (e.g., self-complete homunculus) versus physician-performed joint count
- Investigation of the metric properties of US and MRI
- Investigation of the value of CT

CT, computerized tomography; DASH, Disabilities of the Arm Shoulder and Hand; HRQOL, health-related quality of life; MRI, magnetic resonance imaging; OA, osteoarthritis; PRWHE, Patient-rated Wrist Hand Evaluation; US, ultrasound; VAS/NRS, visual analog scale/numerical rating scale.

REFERENCES

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115-26.
2. Kellgren JH, Moore R. Generalized osteoarthritis and Heberden's nodes. Br Med J 1952;1:181-7.
3. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis 2009;68:8-17.
4. Kloppenburg M, Kwok WY. Hand osteoarthritis—a heterogeneous disorder. Nat Rev Rheumatol 2012;8:22-31.
5. Kloppenburg M. Hand osteoarthritis-nonpharmacological and pharmacological treatments. Nat Rev Rheumatol 2014;10:242-51.
6. Kloppenburg M, Boyesen P, Smeets W, Haugen I, Liu R, Visser W, et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014;41:810-8.
7. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.
8. Maheu E, Altman RD, Bloch DA, Doherty M, Hochberg M, Mannoni A, et al. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International. Osteoarthritis Cartilage 2006;14:303-22.
9. Egger P, Cooper C, Hart DJ, Doyle DV, Coggon D, Spector TD. Patterns of joint involvement in osteoarthritis of the hand: the Chingford Study. J Rheumatol 1995;22:1509-13.
10. Poole J, Sayer AA, Hardy R, Wadsworth M, Kuh D, Cooper C. Patterns of interphalangeal hand joint involvement of osteoarthritis among men and women: a British cohort study. Arthritis Rheum 2003;48:3371-6.
11. Stamm T, van der Giesen F, Thorstensson C, Steen E, Birrell F, Bauernfeind B, et al. Patient perspective of hand osteoarthritis in relation to concepts covered by instruments measuring functioning: a qualitative European multicentre study. Ann Rheum Dis 2009;68:1453-60.
12. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, D'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT Filter 2.0. J Clin Epidemiol 2014;67:745-53.
13. Rudolf KD, Kus S, Chung KC, Johnston M, LeBlanc M, Cieza A. Development of the International Classification of Functioning, Disability and Health core sets for hand conditions—results of the World Health Organization International Consensus process. Disabil Rehabil 2012;34:681-93.
14. Visser AW, Bøyesen P, Haugen IK, Schoones Jan, van der Heijde DM, Rosendaal F, et al. Instruments measuring pain, physical function or patient global assessment in hand osteoarthritis – a systematic literature search. J Rheumatol (submitted).
15. Visser AW, Boyesen P, Haugen IK, Schoones JW, van der Heijde DM, Rosendaal FR, et al. Radiographic scoring methods in hand osteoarthritis - a systematic literature search and descriptive review. Osteoarthritis Cartilage 2014;22:1710-23.

16. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002;10:863-9.
17. Dreiser RL, Maheu E, Guillou GB, Caspard H, Grouin JM. Validation of an algofunctional index for osteoarthritis of the hand. Rev Rhum Engl Ed 1995;62 Suppl 1:43S-53S.
18. Bijsterbosch J, Wassenaar MJ, le Cessie S, Slagboom PE, Rosendaal FR, Huizinga TW, et al. Doyle Index is a valuable additional pain measure in osteoarthritis. Osteoarthritis Cartilage 2010;18:1046-50.
19. Haugen IK, Hammer HB. Role of modern imaging techniques in hand osteoarthritis research and clinical practice. Curr Rheumatol Rep 2014;16:399.
20. Keen HI, Lavie F, Wakefield RJ, D'Agostino MA, Hammer HB, Hensor E, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. Ann Rheum Dis 2008;67:651-5.
21. Mathiessen A, Haugen IK, Slatkowsky-Christensen B, Boyesen P, Kvien TK, Hammer HB. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis 2013;72:51-6.
22. Wittoek R, Jans L, Lambrecht V, Carron P, Verstraete K, Verbruggen G. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. Ann Rheum Dis 2011;70:278-83.
23. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, Haavardsholm EA, Sesseng S, Kvien TK, et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. Ann Rheum Dis 2011;70:1033-8.
24. Haugen IK, Ostergaard M, Eshed I, McQueen FM, Bird P, Gandjbakhch F, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. J Rheumatol 2014;41:386-91.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
26. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum 1996;39:308-20.
27. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A: A1-56.
28. Kallman DA, Wigley FM, Scott WW Jr., Hochberg MC, Tobin JD. New radiographic grading scales for osteoarthritis of the hand. Reliability for determining prevalence and progression. Arthritis Rheum 1989;32:1584-91.

LIST OF PUBLICATIONS

Visser AW, Bøyesen P, Haugen IK, Schoones JW, van der Heijde DM, Rosendaal FR, Kloppenburg M. Instruments measuring pain, physical function or patient global assessment in hand osteoarthritis – a systematic literature search. J Rheumatol 2015;42(11):2118-34.

Kloppenburg M, Bøyesen P, **Visser AW**, Haugen IK, Boers M, Boonen A, Conaghan PG, Hawker GA, Kvien TK, Landewé R, Uhlig T, Smeets W, Greibrokk E, van der Heijde DM. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies. J Rheumatol 2015;42(11):2190-7.

Visser AW, de Mutsert R, Bloem JL, Reijnierse M, Kazato H, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M; Netherlands Epidemiology of Obesity Study Group. Do knee osteoarthritis and fat-free mass interact in their impact on health-related quality of life in men? Results from a population-based cohort. Arthritis Care Res (Hoboken) 2015;67(7):981-8.

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

Visser AW, Bøyesen P, Haugen IK, Schoones JW, van der Heijde DM, Rosendaal FR, Kloppenburg M. Radiographic scoring methods in hand osteoarthritis--a systematic literature search and descriptive review. Osteoarthritis Cartilage 2014;22(10):1710-23.

Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR,Kloppenburg M; NEO Study Group. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015;74(10):1842-7.

Visser AW, Ioan-Facsinay A, de Mutsert R, Widya RL, Loef M, de Roos A, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M; NEO Study Group. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Res Ther 2014;16(1):R19.

Kloppenburg M, Bøyesen P, Smeets W, Haugen IK, Liu R, **Visser AW**, van der Heijde DM. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014;41(4):810-8.

de Lange-Brokaar BJ, Ioan-Facsinay A, Yusuf E, **Visser AW**, Kroon HM, Andersen SN, Herb-van Toorn L, van Osch GJ, Zuurmond AM, Stojanovic-Susulic V, Bloem JL, Nelissen RG, Huizinga TW, Kloppenburg M. Degree of synovitis on MRI by comprehensive whole knee semi-quantitative scoring method correlates with histologic and macroscopic features of synovial tissue inflammation in knee osteoarthritis. Osteoarthritis Cartilage 2014;22(10):1606-13.

Visser AW, de Mutsert R, Loef M, le Cessie S, den Heijer M, Bloem JL, Reijnierse M, Rosendaal FR, Kloppenburg M; NEO Study Group. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. Osteoarthritis Cartilage 2014;22(2):197-202.

Bijsterbosch J, **Visser AW**, Kroon HM, Stamm T, Meulenbelt I, Huizinga TW,Kloppenburg M. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. Ann Rheum Dis 2010;69(3):585-7. Erratum in: Ann Rheum Dis 2012;71(6):1106.

Bijsterbosch J, Scharloo M, **Visser AW**, Watt I, Meulenbelt I, Huizinga TW, Kaptein AA, Kloppenburg M. Illness perceptions in patients with osteoarthritis: change over time and association with disability. Arthritis Rheum 2009;61(8):1054-61.

CURRICULUM VITAE

Willemien Visser werd op 19 maart 1986 geboren in Alkmaar. Na het behalen van haar VWO diploma in 2004 aan het Trinitas College te Heerhugowaard is zij gestart met de studie Geneeskunde aan de Universiteit Leiden. Vanaf het derde jaar van haar studie deed zij onderzoek bij de afdeling reumatologie in het Leids Universitair Medisch Centrum (LUMC), gericht op pijn en functionele beperkingen in hand artrose.
In 2008 werd dit voortgezet als wetenschapsstage naar ziekte perceptie in hand artrose. Na het doorlopen van de co-schappen deed zij in 2010 een tweede wetenschapsstage naar de genetische predispositie van gewrichtsschade in reumatoïde artritis, dit onderzoek werd vanuit de afdeling reumatologie in het LUMC verricht in het Landspitali University Hospital in Reykjavik, IJsland. In 2011 behaalde zij het arts-examen aan de Universiteit Leiden.
Vanaf februari 2011 was zij als arts-onderzoeker verbonden aan de afdeling reumatologie van het LUMC. Onder leiding van prof.dr. M. Kloppenburg en prof.dr. F.R. Rosendaal werkte zij aan het onderzoek beschreven in dit proefschrift. Tevens heeft zij tijdens deze periode een start gemaakt met de opleiding tot epidemioloog B via de afdeling klinische epidemiologie (opleider: prof.dr. F.R. Rosendaal).
In mei 2014 is zij begonnen aan de opleiding tot reumatoloog in het LUMC (opleider: prof. dr. T.W.J. Huizinga). Momenteel volgt zij de vooropleiding interne geneeskunde in het Medisch Centrum Haaglanden te Den Haag (opleider: dr. A.H. Bootsma). Naar verwachting zal zij haar opleiding tot reumatoloog in 2020 afronden.

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