

Clinical Aspects of Hand Osteoarthritis

- Non-pharmacological management, clinical assessment and disease impact

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November 2012

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*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1525*

ISBN 978-82-8264-508-9

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Cover: Inger Sandved Anfinssen.
Printed in Norway: AIT Oslo AS.

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Acknowledgements

For the last years I have been very fortunate to be a part of an internationally respected research group with a number of people engaging in and helping me with this thesis. I wish to express my gratitude to all of them.

First of all I would like to thank my excellent main supervisor Professor Till Uhlig. His engagement, support, knowledge and guidance were invaluable in conducting this thesis. I will forever be grateful to him. I am also deeply grateful to my co-supervisors Professor Kåre Birger Hagen and Dr Ingvild Kjekken. They contributed with insightful comments, interesting discussions and helped me ask the right questions. I admire their knowledge, efficiency and flexibility.

I also want to thank Professor Dr Tore Kristian Kvien who is the head of the department of Rheumatology at Diakonhjemmet Hospital. Without him this project would not have been possible. He has been involved in all aspects of this thesis, including planning the studies, reading all the manuscripts; and contributing generously with his knowledge.

I am grateful to my co-authors Espen Haavardsholm, Andrew Garratt, Barbara Slatkowsky-Christensen, Margreth Grotle, Emmanuel Maheu and Petter Mowinckel for being very helpful and generous with all their expertise and advice contributing to the manuscripts in this thesis.

I would like to thank Inge Christoffer Olsen for statistical tutoring, and Ida Haugen, Linda Fernandes, Nina Østerås, Anne Christie, my fellow physical therapists, and the PhD forum for interesting discussions and great companionship. I would also like to thank all the patients I have learned to know through the years who have inspired me in my work, and of course all of those who contributed to the studies.

Special thanks to my fantastic colleagues at the National Resource Center for Rehabilitation in Rheumatology (NKRR) and the staff at the Rheumatology Department at Diakonhjemmet Hospital, especially Therese Bjor Rønningen, Aase Frich, Anne Katrine Kongtorp, Sidsel

Arnkvern, Grete Helle, and the multidisciplinary OA team. Without their enthusiasm and flexibility regarding all the logistic challenges over the years, this project would not have been possible.

Furthermore I want to thank the patient representative, Wenche Irene Rambøl, and the medical librarian Hilde Flaatten for valuable assistance. Many thanks to Paul van Dooren at Diakonessenhuis in Utrecht for introducing me to rheumatic physical therapy and to Sørlandet Hospital Kristiansand for priming me in the field of rheumatology research.

Without the inspiration of my grandmother, the first physical therapist I knew, I would probably have chosen another path in life. Thank you for inspiring me. And a special thank to Dario Falcon Millan, my best friend and colleague who taught me never to give up. I miss both of them very much.

I want to express love and gratitude to my beloved family. A special thank to my husband Tom for support and understanding, and putting his needs behind mine through stressful periods. I am grateful to my parents and siblings for always being there for me. I feel very fortunate for having both a caring family and a job that I love. Finally, I want to express gratitude to my beloved sons, Iver and Isak for distracting me and bringing immense joy to my life. You inspire me and make me want to do better and learn from my mistakes.

Funding

Institutional support has been generously provided by the administration of Diakonhjemmet Hospital AS. Financial support was received with gratitude from EXTRA funds from the Norwegian Foundation for Health and Rehabilitation, the University of Oslo, the Norwegian Women's Public Health Association and Grethe Harbitz and Trygve Gythfeldt's legacy.

Abbreviations

ACR	American College of Rheumatology
AIMS-2	Arthritis Impact Measurement Scales-2
AMSTAR	Assessment of Multiple Systematic Reviews
AUSCAN	Australian/Canadian Osteoarthritis Hand Index
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
CMC-1	Carpometacarpal Joint
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
COX-2	Cyclogenase-2
DAS	Disease Activity Score (also DAS28, based on 28 joint counts)
DIP	Distal Interphalangeal
DMARD	Disease Modifying Anti-Rheumatic Drug
ES	Effect Size
ESR	Erythrocyte Sedimentation Ratio
et al.	And others
EULAR	European League Against Rheumatism
FIHOA	Functional Index for Hand Osteoarthritis
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAQ	Health Assessment Questionnaire
HRQOL	Health-related Quality Of Life
HOA	Hand Osteoarthritis
ICC	Intra-class Correlation Coefficient
ICF	International Classification of Functioning, Disability and Health
JSN	Joint Space Narrowing
MCID	Minimally Clinically Important Difference
MCP	Metacarpophalangeal Joint
MTP	Metatarsophalangeal Joint
NSAID	Non-Steroidal Anti-Inflammatory Drug

NRS	Numeric Rating Scale (0-10)
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OR	Odds Ratio
PCA	Principal Component Analyses
PIP	Proximal Interphalangeal
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation
SDD	Smallest Detectable Difference
SF-36	Short-Form 36 Health Survey
SPSS	Statistical Package for the Social Sciences
SRM	Standardized Response Mean
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale (0-10)
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Osteoarthritis Index

Definitions

Aesthetic discomfort	An expression referring to how a person feels about their hand appearance. ‘Aesthetic’ comes from the Greek word <i>aisthetikos</i> meaning “sensitive, perceptive”, or from <i>aisthanesthai</i> “to perceive (by the senses or by the mind)”, or “to feel” (1).
Bio-psychosocial	“A view that health and illness involve the interplay of biological, psychological, and social factors in people’s lives” (2).
Disability	In this thesis used as an umbrella term for impairments, activity limitations or participation restriction (3).
Functioning	‘Function’ as used in this thesis is an umbrella term for Body Functions, Body Structures, Activities and Participation, based on the International Classification of Functioning, Disability and Handicap (3) definition.
Hand osteoarthritis	American College of Rheumatology criteria: If a) and three of the following four are present: a) hand pain, aching, or stiffness for most days of previous month, b) hard tissue enlargement of two or more joints*, c) swelling in less than three metacarpo-phalangeal joints, d) hard tissue enlargement of two or more distal inter-phalangeal joints, e) deformity of at least one hand joint*. *Ten selected joints are the second and third distal interphalangeal (DIP), the second and third proximal interphalangeal (PIP), and the first carpometacarpal (CMC-1) joints of both hands (4).
Participation	Involvement in a life situation (3).

List of papers

- I. Moe RH, Kjeken I, Uhlig T, Hagen KB. There is inadequate evidence to determine the effectiveness of non-pharmacological and non-surgical interventions for hand osteoarthritis: an overview of high-quality systematic reviews. *Phys Ther* 2009; 89(12): 1363-70.
- II. Moe RH, Garratt A, Slatkowsky-Christensen B, Maheu E, Mowinckel P, Kvien TK, Kjeken I, Hagen KB, Uhlig T. Concurrent evaluation of data quality, reliability and validity of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and the Functional Index for Hand Osteoarthritis (FIHOA). *Rheumatology (Oxford)* 2010; 49(12): 2327-36.
- III. Moe RH, Grotle M, Kjeken I, Hagen KB, Kvien TK, Uhlig T. Disease impact of hand osteoarthritis compared to hip, knee and generalized disease in specialist rheumatology health care. *Rheumatology (Oxford)*, published online August 25, 2012

Synopsis

Background

To be able to treat the patient with hand osteoarthritis (HOA) efficiently health professionals are dependent on information regarding patient experiences, clinical experience and research-based evidence. Overviews of existing scientific knowledge about non-pharmacological and non-surgical treatments for hip and knee OA are available, but not for HOA. There are outcome measures available for assessing functioning in hip and knee OA, but no outcome measures for HOA are available free of charge in Norwegian. Knowledge about disease impact in HOA compared to OA in other localizations is also limited.

Objectives

The overall objective of this thesis was to improve understanding about management, clinical assessment and disease impact in HOA. This included the following objectives I) To perform an overview of systematic reviews on the effect of non-pharmacological treatments in HOA, II) To validate patient reported outcomes (PROs) for functioning in HOA and III) To describe disease impact in patients with HOA compared to hip, knee and generalized OA.

Methods

Methods used were I) a systematic literature review, II) concurrent evaluation of two outcome measures for assessing hand function, and III) a cross-sectional study.

Results

I) There is insufficient high-quality evidence regarding non-pharmacological and non-surgical interventions for HOA. II) The Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and the Functional Index for Hand Osteoarthritis (FIHOA) are reliable and valid instruments suitable for measuring physical functioning in HOA. III) OA patients reported considerable levels of disease impact across localizations. Regardless of functional impairments related to the primary OA localization, patients generally reported high levels of impaired disease-specific functioning at other sites.

1. Introduction

As far as I can remember I have had a special fascination for the functioning of the human hand, probably influenced by my interest in the arts of music and painting.

During more than 15 years as a physical therapist within the field of rheumatology, patients have taught me about their challenges related to rheumatic diseases. I have been especially engaged in the care for patients with osteoarthritis, the most common joint disease, and having seen many patients with severe disease consequences I was surprised that it was so hard to find studies comparing the disease impact of the different localizations. In 2003 I was very lucky to be a part of setting up the multidisciplinary OA clinic at Diakonhjemmet Hospital after having been recruited by Professor Tore K. Kvien. The research-based evidence about living with osteoarthritis was to our knowledge to a great extent based on knowledge about knee OA. Seeing HOA patients referred to our clinic with various unmet needs that many primary clinicians clearly had avoided addressing, surprised me.

Important factors for evidence-based practice are detecting and generating useful evidence, and applying it in practice. When attempting to evaluate the effects of various treatments for osteoarthritis, we were surprised by the relative paucity of research-based evidence for the variety of treatments used in clinical care. When we wanted to evaluate hand functioning we found only a few outcome measures for hand OA used in clinical care and none of them seemed properly psychometrically tested. My curiosity was triggered, and I was eager to explore these issues further.

1.1 Clinical aspects in hand osteoarthritis

Osteoarthritis (OA) is one of the most common musculoskeletal diseases, traditionally regarded as a degenerative joint condition (5). According to the World Health Organization (WHO), osteoarthritis is one of the ten most disabling conditions among people above 30 years (6). It is also suggested that osteoarthritis will be the fourth leading cause of disability by 2020 (7). OA pathology affects the whole joint (8), and it can occur in any joint of the body, but it is most frequently observed in hands, hips and knees. Prevalence and diagnostics is dependent on the localization of OA and the diagnostic criteria used (9;10). The focus of research on the hip and knee joint has resulted in more knowledge about OA pathology and management, however in HOA there is still little research available (11). There may be challenges in diagnosing OA because symptoms can be different according to the joint localization affected (12), and the presence or absence of radiographic findings can be confusing (13).

A group of experts in the field of HOA recently wrote an opinion paper after reviewing research-based evidence about HOA, and concluded that more research is needed in the field (11). One of the most needed future research agendas mentioned was that of outcome measures in HOA, including the aspects of hand function. HOA has not been researched as much as hip and knee OA; therefore there is less knowledge available about pathogenesis and treatment for this type of OA (11).

1.1.1 Definition and criteria for classification of HOA

There are several existing systems for diagnosing osteoarthritis in practice, based on radiographic, pathological or clinical findings as well as the opinion of a physician or specialist (14). The international clinical criteria published by the American College of Rheumatology (ACR) are frequently used in studies (4). According to these criteria, a patient can be classified with HOA if hand pain, aching, or stiffness for most days of the previous month is present, combined with signs like hard tissue enlargement, swelling, and/or deformity (Table 1). It should be emphasised that these criteria are primarily developed for classification of patients to be included in clinical trials and observational

studies, and not as diagnostic criteria. The ACR criteria were based on a comparison between patients with inflammatory arthritis and patients with osteoarthritis in specialist care (15).

Table 1. The American College of Rheumatology criteria for the classification of hand osteoarthritis (4)

Criterion	Specification
Hand pain, aching, or stiffness	Most days of the prior month (Mandatory)
Hard tissue enlargement of two or more of 10 selected joints*	* Second and third distal interphalangeal (DIP), the second and third proximal interphalangeal (PIP), and the first carpometacarpal (CMC-1) joints of both hands.
Swelling in fewer than three metacarpo-phalangeal joints	
Hard tissue enlargement of two or more distal inter-phalangeal joints	
Deformity of at least one of 10 selected hand joints*	* Second and third distal interphalangeal (DIP), the second and third proximal interphalangeal (PIP), and the first carpometacarpal (CMC-1) joints of both hands.

Radiographic definition

HOA is a clinical diagnosis, however the radiographic definition of OA is based on pathophysiologic signs visible on radiographs (16). Conventional X-ray visualizes bony tissue in two-dimensional pictures and is the most commonly used imaging modality for confirming the clinical diagnosis (17). However, the use of other imaging methods like Magnetic Resonance Imaging (MRI) and ultrasound (US) have also increased over the last years, especially in research. The most commonly used radiographic criteria for HOA were formulated by Kellgren and Lawrence (18). This is a global OA score from 0-4, on which grade 2 or more indicates definite OA. When radiographs are normal, OA is graded 0; with minute osteophytes, grade 2; grade 3 includes definite osteophytes; grade 3 joint space narrowing, and grade 4 joint space narrowing and sclerosis of the subchondral bone. They also published an atlas with example images which facilitate the reading. The random population sample studied to develop these radiographic criteria was 54-64 years (19). When presenting the radiographic criteria for HOA in 1963, Kellgren underlined that the structural radiographic findings were only indirectly related to the disease osteoarthritis and did not tell anything about symptoms or disability. Joint space narrowing in MCP joints was

not included in the criteria for HOA because that feature is closely related to RA (20). It is also suggested that MCP involvement in HOA is rare (21). The relationship between radiographic and symptomatic OA is not strong. Radiographic OA is related to pain but the degree of joint destruction is not strongly associated with the degree of symptoms (22). The use of imaging in clinical care may also have adverse effects if used frequently without symptomatology; however the radiation dosages in hand joints are small. Positive findings on imaging may convince the individual that he or she has a disease even when features on imaging are not relevant for their clinical condition (22). Some argue that radiography should be used only when clinical diagnoses are uncertain (23).

Symptomatic definition

The definition symptomatic osteoarthritis is often used when both joint related symptoms and radiographic signs are available (24). Knee OA is classified including radiography, while HOA is classified without radiography according to the ACR criteria because radiographs in HOA are less sensitive and specific than clinical examinations (4). It is shown that individuals without OA symptoms can have severe joint destruction on radiographs and that patients with OA symptoms can have normal radiographs (25). Radiographic HOA has been more studied than symptomatic HOA (11), but individuals with symptomatic HOA are those in need of treatment and thus seen in clinical care (16).

The prevalence numbers of symptomatic and radiographic HOA are different, for example data from the Framingham study show that 40% of men and 58% of women have radiographic HOA while of these only 8% men and 17% women have symptomatic HOA (26). There is an association between radiographic signs and pain in HOA shown in a systematic review, and the more severe the radiographic signs, the higher the chance of reporting pain, but the magnitude of these associations vary (16). A clinical challenge is that symptomatic HOA is dependent on the symptoms at the time point when the patient is assessed, and it is well known that the symptoms in OA are characterized by fluctuations (27;28).

Differential diagnosis of HOA

It has been suggested that diagnosing OA in clinical care generally should be based on anamnesis and physical examination, and that radiography can be used to rule out differential diagnoses or to confirm clinical findings. Differential diagnoses of OA are

focused on excluding other diseases or sources of symptoms like referred pain, other soft tissue conditions and somatisation (22).

The clinical signs of psoriatic arthritis (PsA) in the hand are very similar to HOA. Enthesopathies are common in both diseases and the joints are painful and tender and restricted in motion. A major local difference between the two is that finger joints in PsA have more marked inflammation and oedema than osteoarthritic finger joints (29). The CASPAR criteria are developed to diagnose PsA and include assessment of radiographic differences to differentiate between the various arthropathies (30). Rheumatoid Arthritis (RA) is a systemic inflammatory disease which is characterized by inflammation and destruction of synovial joints, including the hand. The classification system for RA is focused on ruling out other joint diseases (31). Haemochromatosis is a multisystem disorder with increased iron storage. In the hand it commonly affects the MCP 2 and 3 (32) and is, when the clinical signs are classical thus not often confused with erosive HOA (33).

Clinical criteria for hip, knee and generalized OA

There are various existing criteria for the classification of hip and knee OA. Well known criteria for symptomatic hip and knee OA are the ACR criteria. Knee OA can be confirmed if knee pain is present, age is above 38 years, and if there is morning stiffness and crepitus located to the knee (34). Classifying hip OA can be based on hip pain combined with either 1) painful and restricted internal rotation ≥ 15 degrees, morning stiffness ≤ 60 minutes, and age above 50 years, or 2) internal rotation ≤ 15 degrees and erythrocyte sedimentation rate (ESR) ≤ 45 mm/hour; and if no ESR alternatively: hip flexion ≤ 115 degrees (35).

There is no international agreement on criteria for generalized osteoarthritis. It has been argued that OA in several joints can be more disabling than when fewer joints are involved (36;37). The definitions used in studies include HOA only or HOA combined with knee, spine or metatarso phalangeal (MTP) OA. Some of the different definitions of generalized OA used in studies are presented in Table 2.

Table 2. Different definitions for generalized OA used in the literature

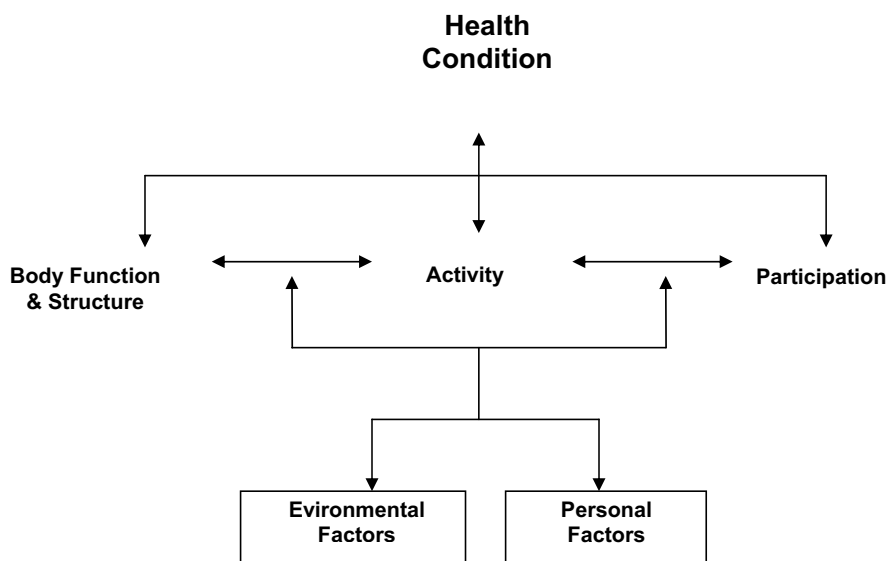
Author, year	Definition
Kellgren and Moore, 1952 (38)	Heberden's nodes or CMC-1 OA, or both
Loughlin, 1994 (39)	Presence of Heberden's nodes
Dougados, 1996 (40)	Bilateral fingers or spinal OA and bilateral knee joint affection
Cooper, 1996 (41)	2 or more joint groups affected below the age of 47 years, or the involvement of 5 joint groups above 60 years
Gunther, 1998 (42)	Radiographic OA in two or more joint groups
Kessler, 2000 (43)	>2 PIP or DIP and at least one CMC-1
Min, 2005 (44)	Radiographic OA in >2 joint sites
Carroll, 2006 (45)	Heberden's or Bochar'd's nodes with PIP, DIP, knee and MTP joint involvement
Zhang, 2008 (46)	HOA and OA at other localizations

1.1.2 Functional consequences of osteoarthritis

The main topics in this thesis are clinical assessment, impact and management of functional consequences of hand OA. The bio-psychosocial understanding of function as systematized and described in the International Classification of Functioning, Disability and Health (ICF) is therefore used as a theoretical framework for this thesis. The ICF was developed as complementary to the International Classification of Diseases (ICD-10) and contains more than 1450 categories of different health domains, providing a unified and standard language for description of health and health-related conditions (3) to be used by all health professions. It includes specified categories on different health domains, for example the sensation of pain, structure of the hand, and work-related participation. The main health domains are sorted according to Body Function and Structure, Activity and Participation, Environmental and Personal factors (Figure 1). The Personal factors are not yet described in detail by the framework.

According to ICF, the concept 'function' is an umbrella term for Body Functions, Body Structures, Activities and Participation (47). This description includes disease impact composed of factors such as physical functioning, stiffness, pain, fatigue, disease activity, and psychosocial factors. When normal functioning of a body part is impaired, it can result in disability, an altered capacity to meet personal, societal or occupational demands (48).

Figure 1, International Classification of Functioning, Disability and Health (3)



The different localizations of OA vary according to anatomy, function, risk factors and symptoms and thus impact function and clinical management (12). Several of the consequences of HOA are location-specific like grip strength, fine finger movements and aesthetic damage (12). Joint-related symptoms associated with osteoarthritis are pain, stiffness, functional impairments (49), swelling, deformity and reduced health-related quality of life (50). It has been shown in a longitudinal setting that OA symptoms captured by patient reported outcome measures (PROs) on pain functioning can deteriorate or improve at comparable rates (51) indicating that there is a relationship between the degree of OA and symptoms.

Body structure

The hand consists of twenty-nine bones connected to each other by synovial joints, ligaments and muscles and constitutes the functional unit of a hand. Hand movement consists of complex series of muscular involvement including several joints. The main

blood supply in the hand is originated in the brachial artery and the nerves involved are nervus medianus, nervus radialis and nervus ulnaris (48). The biomechanical characteristics of the saddle-shaped CMC-1 joint involve movements in multiple planes and little bony stability. Hand gripping and pinching can transmit forces up to 13 times those affecting the tip of the thumb (52), which may be a reason for the frequent involvement of this joint in HOA.

The pathologic OA process is often referred to as a disturbed homeostasis of anabolic and catabolic processes of the joint tissues (53). OA involves failure of the whole joint as an organ (14). Research and new imaging strategies have shown that practically all local joint structures of the OA joint are affected, even in early HOA (54). This has also been studied in knee (55;56) and hip OA (57).

Changes in knee synovitis observed on MRI have been associated with changes in pain severity, and extra-articular structures as ligaments and bursae are more common in individuals with knee OA and knee pain than among individuals without pain (58).

The varying degree of radiographic findings in OA can be confusing (13), and the definition or classification of OA affects prevalence numbers. The proposed radiographic classification system for osteoarthritis based on joint space narrowing and osteophytes by Kellgren and Lawrence 1957 (18) is still one of the most frequently used structural grading systems in hand osteoarthritis (59). The ACR criteria are based more on clinical observation.

In HOA enthesitis is also an early seen feature (60) as inflammation at the origin and insertion of the collateral ligaments (61). A feature of early HOA is tender collateral ligaments. MRI examinations in early HOA of the DIP and PIP joints have shown the involvement of enthesopathies which possibly are involved in the location of bone disease and nodules (29). Disruptions of the collateral ligaments have been associated with HOA, however such disruptions are also more frequent in older persons (54).

Cartilage loss has traditionally been a well known sign of osteoarthritis (22). Cartilage is a-neural and pain and cartilage loss is not strongly correlated with knee OA (27). Bone is

more flexible and adapts better to stress than cartilage (22). Also, bone marrow lesions seem to be related to pain in knee OA (62).

An inverse relationship has been reported between osteoarthritis and osteoporosis in the lower limbs. This may be due to a higher peak bone-mass close to affected joints (63). This finding may not be extrapolated to people with HOA, due to findings from a Finnish study where both DIP and CMC-1 were associated with osteoporosis (64). A study on elderly adults did not detect increased bone mineral density in HOA, but there were indications that women with HOA had lower bone mineral density of the hip (65).

HOA is often associated with Heberden and Bouchard nodes (4). The presence of nodes has been hypothesized as a sign of generalized OA (20). Nodules are visible and palpable lumps usually located laterally related to dorso-lateral joint margins or central midline nodes. They can be painful or asymptomatic, grow fast or slow, and theories suggests that they may develop from osteophytes where there is little connective tissue to restrict their growth. The DIP and PIP joints have little connective tissue except from thin capsules keeping the synovium in its place, and thus less obstruction to nodular growth. Others believe that the nodules are synovial cysts caused by capsular rupture, that the reason for location is caused by low resistance from the capsule and extra-articular structures, and that the familial incidence may be related to the inherited degree of strength of the connective tissue (66).

Several attempts have been made to divide OA into different phenotypes but few of these have been convincingly confirmed genetically or in different populations (22). One subtype often referred to in the literature is erosive disease. Erosions are common in OA and it has been held possible that all subtypes of HOA are erosive (67). Individuals may have erosive HOA if they fulfil the ACR criteria for HOA including radiographic erosions (68), and are characterized by subchondral bone erosions and the infrequency of involvement of the thumb base and the MCP II and III (69). Erosive HOA can be suspected when clinically observing multiple erosions or ankylosis, especially in the DIP and PIP joints (69). There is no agreement whether erosive OA is a separate disease, an aggressive form of generalized OA or just a normal pattern of HOA (68;70). Erosive OA has been linked to inflammation, and the ability to detect erosions has improved with the new imaging possibilities over the last years. It is shown that MRI can detect up to four times more HOA erosions than conventional roentgen (67).

Body Function

The pain mechanisms in OA are not fully understood; many factors are involved in the pain processes and perceived by the individual, all factors being captured in the bio-psychosocial theory (22). Patients with hip and knee OA explain that they experience both a constant dull type of pain and a more acute and unexpected type of pain that often is intermittent at early stages of OA and more constant at later stages (27). Patients with hip and generalized OA reported having higher mean pain scores than knee and HOA (n=25.589) in a study from Italian general practice (71).

Muscular weakness and instability of the joint affected is often described as associated with pain and disability (72). Patients with hip and knee OA have weaker muscular strength around the affected joints (73;74), and strengthening exercises are one of the core non-pharmacological treatments recommended for low limb OA (12;75); however data from the Framingham study showed that a high maximum grip strength in patients with hand OA was associated with an increased risk of OA in PIP, MCP and CMC-1 joints in men, and MCP in women (76).

Grip and pinch strength seem to decrease with increasing degree of radiographic HOA (77). Data from the Framingham study on elderly adults show that people with symptomatic HOA had 10% reduced grip strength, and more physical impairments when writing and handling small objects (Odds Ratio 3.49) than people without symptomatic HOA (78). This may also impact HRQOL (50;79).

Movement restriction in osteoarthritis may be due to pain, thickening of the capsule or new bone formation (21). Stiffness or tightening of the joints is typically observed in the morning or after inactivity periods. The duration of stiffness after inactivity seldom lasts longer than 30 minutes. Stiffness in OA has been linked to the presence of inflammation (80), and reducing inflammation has been suggested to reduce stiffness (80). Swelling can be a sign of synovitis or bony enlargement typical for the joint affected. Inflammation in HOA has been found both in early and late stages of OA (81). In HOA swelling, deformity and nodules are often described in a context of aesthetic damage (82).

Another important symptom in OA related to Body Function is instability and ‘giving way’ (83;84). Instability in hip and knee OA is associated with registered falls (85), possibly explained by muscular weakness. Muscle strength is more often affected around symptomatic joints compared to non-symptomatic joints (86). In a 30 months prospective study of women without radiographic OA at baseline, results showed that those who had developed radiographic knee OA had on average borderline significantly ($p=0.053$) lower knee extensor strength at baseline (87). An Icelandic study associated joint hyper-mobility as measured by the Beighton criteria (88) to CMC-1 OA (89), indicating that hyperlaxity is a risk factor for CMC-1 OA. Hyperlaxity has in another study been identified as a protector against PIP OA (90).

People with radiographic HOA are at increased risk for knee and hip OA, and there are indications that overweight persons with HOA have an even higher risk of knee OA (91). Overweight is also a risk factor for HOA, indicating that the influence of overweight is not purely biomechanical (92), but also may include for example fat metabolic disturbances. Biomechanical factors are important in weight bearing joints, but also in the hand when approximation or movement occur as a result of contracting muscles when performing various tasks (93). Radiographic HOA has been associated with higher BMI in a Finnish population study (94;95).

Activity and Participation

Problems with functioning are often described related to the joints affected as gait problems in lower extremity OA and fine finger movements such as picking up objects in hand OA (82). HOA patients often describe activity limitations in performing tasks that require considerable grip strength combined with twisting, like wringing clothes, and opening jars and bottles (96).

Intensity of physical work in women has also been associated with HOA (94), and an association between chopsticks use and HOA has been identified (97). A French nationwide study showed that most patients (80%) with clinical hand, hip or knee OA report limitations in daily activities compared to controls. These limitations included work, leisure and basic tasks. As much as 64.4% of the employed patients had work limitations compared to 14.3% of the controls (98).

Personal Factors

Fatigue is another common symptom in OA (99) and can be described as an enduring generalized tiredness (100). Fatigue has been reported to be important both in HOA and RA (50), and in rheumatology care about 40% of patients with osteoarthritis report experiencing fatigue, and this symptom has also been associated with work dysfunction and health status (101).

Health-related quality of life

HRQOL is not directly covered by one of the dimensions of ICF, but is related to a combination of them. Health-related quality of life captures physical and mental aspects related to several of the ICF domains. It is reported that women with HOA in specialist care have poorer HRQOL (SF-36) scores compared to controls (50).

Patients with OA report increased co-morbidities (71) and cardiovascular and gastrointestinal risks in these patients are increased (102). The evidence for an increased mortality risk in patients with osteoarthritis can partly be explained by reduced physical activity, co-morbidities and side-effects of medical treatment (103). A review of mortality in OA independent of localization included seven studies of varying quality, and evidence of increased mortality in OA compared to the general population was moderate (103). Hand OA has been associated with cardiovascular mortality (94). A Finnish population-based study of people above the age of 30 found an association between radiographic HOA and death based on cardiovascular disease (Relative Risk 1.42; 95% CI 1.05 to 1.92) (94). There are indications that this risk is higher in patients with OA than the normal population, but lower than in inflammatory arthritis. The risk of death due to vascular disease has been reported to be lower in patients with OA than people without OA, but significantly lower than the risk in rheumatoid arthritis (104).

1.1.3 Pathogenesis

The aetiology of OA is unknown, and considered to be multi-factorial, as both genetic and environmental factors influence the disease. The risk factors for both radiographic and symptomatic OA increase with age. This can be related to increasing obesity, excess joint

loading, instability or impaired neuromuscular joint protection. Female gender is also a risk factor, especially after menopause, however the reasons for this is unclear (105).

The disease process in OA may relate to an error of the fine repair processes of the joint structures. Macrophages in the synovial tissue produce pro-inflammatory mediators and affect the balance of anabolic and catabolic processes of the cartilage (106;107). That OA involves inflammation has been known for years (21;80). One study examined DIP joints of diseased persons histologically and found that OA started with subchondral ossification without observable cartilage destructions (108). Structural degeneration such as increasing sclerosis and cartilage thinning (109), subchondral bone changes and synovitis (110) are linked to the OA process.

New assessment and imaging methods demonstrate that OA involves the whole joint, not just the cartilage (111), including changes of tissues around the joint such as musculature and the nervous system (8;112). Structural joint changes such as osteophytes, cysts, sclerosis and joint space narrowing can be detected by radiographs (14). Subchondral sclerosis of the cortical plate can lead to deformation of the articular surfaces of the joint, and has been associated with HOA progression. Sclerosis has been identified as developing earlier in the disease course in the hand than in the knee (113).

1.1.4 Epidemiology

The exact incidence of HOA is difficult to determine and varies with the population studied and the diagnostic methods in use (114). Radiographic, symptomatic and self-reported OA are criteria commonly used in epidemiologic studies. The prevalence of clinical OA is estimated to be about 12.1 among 25-74 year-olds in the USA (115), and in the general population, prevalence of symptomatic HOA was 8% (105). Symptomatic HOA significantly increases with age and the prevalence is higher in women than in men (78;116). HOA has been reported to be more common in certain occupations (117;118).

Self reported HOA

Numbers from Spain indicate that HOA following ACR criteria in the age group 60-69 years olds is 15.3%, for 70-79 years 23.9% and 17.3% in people above 80 (119). In Norway self reported HOA among individuals aged 24-74 years is 4.3% (120).

Symptomatic OA

Symptomatic OA is often defined as the combination of radiographic HOA with symptoms (78). To be classified as having HOA in the Framingham study, participants had to have joint pain, aching or stiffness on most days and mark the symptomatic localization on a schematic hand joint drawing. Prevalence of symptomatic HOA in people above 70 years was 26.2% in women and 13.4 in men (78). A study of persons from the general population in Greece found symptomatic HOA to be about 2%, among the less frequent in prevalence studies (121). In another study from the USA, disabled women above 65 years fulfilling the ACR criteria for HOA were 23% (122). A study from Italy indicates that HOA is present in 15.3% of persons above 65 years (123). Prevalence of symptomatic PIP and DIP HOA in Chinese was 5.8% in women and 3% in men, however numbers from the USA indicate 12.7% in men and 25.6% in women (124). In another population-based study from the USA prevalence of symptomatic HOA above 60 years was 8%. Women had more CMC-1 OA deformity than men (105). Age adjusted CMC-1 OA has been reported to be about twice as common for women (15%) as for men (7%) (95).

Radiographic OA

There are different radiographic scoring and grading systems (59). A literature review identified 21 different definitions of radiographic HOA. The Kellgren and Lawrence scoring system was used in 80% of the studies reviewed. Prevalence of radiographic DIP OA (defined as one or more DIP joint with Kellgren Lawrence grade 2 or more) in a Dutch population has been reported to be up to 76% in women and 64% in men, more prevalent than hip or knee OA (125). In another Dutch population aged 55 years and above, 67% of women and 54.8% of men had radiographic HOA (9). A study comparing Chinese and US American women and men found a lower prevalence of radiographic DIP and PIP OA in the Chinese population (47% women and 44.5% men, and USA 85% women and 75.2% men) (124). In a Danish study of people above the age of 45, 21% had CMC-1 osteophytes on radiographs (126). Several studies have indicated a higher prevalence of radiographic OA in women than in men (95;127;128).

1.1.5 Risk factors

Several modifiable and non-modifiable factors contribute to the risk of osteoarthritis, including age, gender, genetics, behavioural influences, obesity, injury, poorer muscular strength and occupation (10;129). Most patients are aged 55 years or older and the disease increases in prevalence with increasing age (114). Risk factors in OA can be divided into the different domains Body Function and Structure, Activity and Participation, Environmental and Personal Factors.

Body Function and Structure

Data from the Framingham study of people aged 71 years and older show that people with symptomatic HOA perform more poorly on maximum grip strength than those without HOA (78). However, high muscular strength in HOA may increase risk of CMC-1 OA and MCP (76) contradictory to the effect of quadriceps strength in knee OA (14). The mechanisms for these associations are not yet fully understood.

Hip dysplasia (130) and varus malalignment in the knee (131) increase the risk of OA. In HOA the saddle formed CMC-1 allows little bony stability, and forces affecting the thumb during use are high and may be a reason contributing to the frequency of CMC-1 joint affection (52).

There are suggestions from population studies that a higher bone mineral density (BMD) may protect against OA development (132). Women with HOA seem to have lower BMD than those without HOA (65). And it has been suggested that women with HOA have an increased risk of developing hand osteoporosis (133). Cross-sectional studies have also suggested that high BMD is associated with increased OA prevalence in HOA (134;135).

Chondrocytes are sensitive to vitamin D. There are indications that an optimal level of vitamin D intake can protect against hip and knee OA progression (136;137), but there is a lack of such information for HOA.

Activity and Participation

Work-related factors have been reported to affect the incidence of HOA (138). Repetitive tasks like pinch grip of the hand may influence OA (139). But there is no agreement whether the dominant hand is more at risk for OA than the non-dominant hand (140;141).

Injury has been known to predispose knee OA (14), and hypermobility may increase the risk of developing CMC-1 joint OA (142).

Personal factors

Age is an important risk factor in HOA (125), and with an increasingly aging population more individuals will get the disease (143). The associations between aging and OA can be influenced by factors like obesity, injury or work-related stress affecting joint symptomatology decades later than the exposure to the stress, possibly related to the summation of exposure to risk factors.

Overweight and obesity increases the risk of HOA (94;95;126). It has been shown that weight loss when overweight can reduce the risk of knee OA (144), and there are indications that the amount of weight loss is related to a reduction in OA symptoms (50). This has to our knowledge not been studied in the hand, thus it is still unclear whether weight reduction in HOA is associated with a symptomatic improvement.

Gender is an important factor; symptomatic HOA is generally more frequent in women. In the Framingham study 26.2% of women and 13.4% of men above 70 years had HOA (78). Hormones may play a role in the development of OA, as suggested by studies showing an increased incidence of OA after menopause in women. It is also supported by the suggested decreased OA incidence and prevalence when taking oestrogen pills during menopause (145), however these findings from cohort studies on knee OA are not consistent (146). A study on Chuvashian women reported a negative association between age at menopause and radiographic HOA, and the younger at menopause, the greater the OA risk (147). Other studies have not identified the risk of being young at menopause for hip (148) or hand (149) OA. The role of female hormones has been hypothesized as important but evidence is still unclear (150). An Italian population-based study identified musculoskeletal disease in general to be significantly more common in women than in men, and the most common musculoskeletal disease was peripheral OA (151).

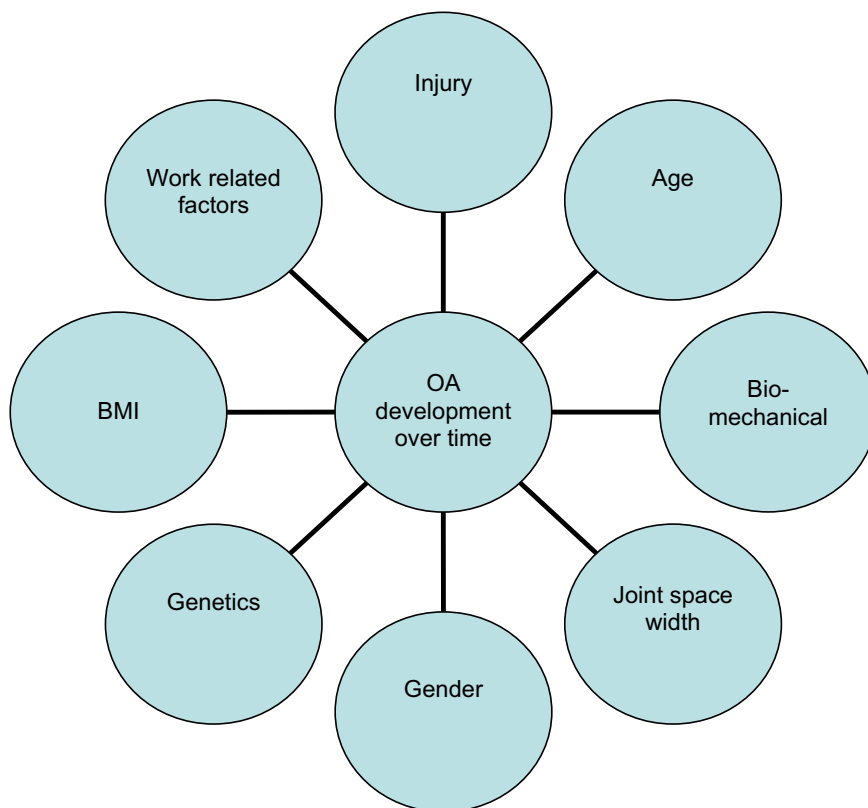
A family history of osteoarthritis may contribute to the risk of osteoarthritis (46). Genetic factors have been reported to contribute about 30-65% of the risk of radiographic HOA (152;153) and that radiological DIP osteophytes have positive predictive values for radiological hand and knee OA (154). The influence of genes on radiographic OA of the hand, hip, knee and disc degeneration has been examined in one study. The authors concluded that there is a strong genetic influence on radiographic HOA and degenerative disc disease (155). A HOA sibling study showed that radiographic HOA was more strongly associated with knee (51%) than hip OA (25%) (156). Another study included siblings with OA at different sites (40 -70 years). The most common combination of HOA (ACR criteria) with other localizations was spine-hand (59%) and hand-knee (25%) (157). In a UK study, siblings of patients with severe knee OA were at a higher risk for developing radiographic knee OA than controls (158;159). Another aspect of this is the presence of Heberden nodes that may increase the risk for knee OA threefold. The presence of Heberden nodes is also associated with knee OA progression (160).

Twin studies from the UK have shown that some genotypes can increase the risk for radiographic HOA threefold (12), and OA has been shown to be inheritable for all joint localizations, however evidence for predicting which joints should be affected based on genetic factors is lacking when comparing individuals with radiographs of the hand, hip and knee joints (161).

There is conflicting evidence for the role of ethnicity in OA: one study suggested that there were no differences in prevalence (162), another that Afro-Americans had hip OA 35% more frequently than whites (163). In HOA symptoms have not been strongly associated with ethnicity (164).

There is little high quality knowledge about risk factors related to HOA alone, this has been more frequently studied in other OA localizations. Knowledge about the contributions of risk factors and whether they can be altered is important (165), however the role of the different potentially relevant bio-psychosocial factors is not yet optimally researched in HOA. Thus, one could think of a number of factors which contribute to the development of HOA (Figure 2).

Figure 2. Factors associated with HOA development



1.1.6 Development over time

Pain and structural changes in OA are weakly associated, and predictive studies have assessed the progression of structural change and symptoms over time (8). The development of OA is dependent on various factors (Figure 2).

Symptomatic and radiographic progression of HOA over two years has been assessed. Only about half of the included patients completed the study. Self reported pain increased in 50% and decreased in 29.7%, and function increased in 52.9% and decreased in 35.5%. The mean magnitude of change (Standardized Response Mean, SRM) was 0.25 for pain, 0.23 for

function, 0.35 for osteophyte score and 0.34 for joint space narrowing. Mean scores for pain, function and radiographic features deteriorated over two years, radiographic progression being more responsive than self-reported pain or function (51).

Dieppe et al followed 500 patients with hip, knee and hand OA recruited from specialist care for eight years. They found that 6.3% reported improvement and 17.2% deterioration on pain and patient global change. The patients with knee OA and knee OA combined with HOA had worse follow-up outcomes (166).

There is not much evidence for the effect of postponing or avoiding surgery, however one small non-randomised study is published. Of thirty-three patients waiting for thumb base surgery for their OA complaints, 70 percent (n=23) indicated that they were improved after trying pharmacological and non-pharmacological treatments and no longer desired surgery. At seven years follow-up only two of the 70% refusing surgery were operated (167).

The presence of HOA is suggested to increase the risk for osteoarthritis at other localizations (91), including the risk for future hip or knee OA. Progression of knee OA is associated with progression in spine and hip OA (168), and in knee OA risk factors for progression can be located to bone marrow lesions, meniscal disease and joint malalignment (169;170). It is shown that many patients with knee OA remain stable over time for long periods of time (171).

Factors that could possibly modify HOA symptomatology are often not sufficiently tested in clinical care. People with hand limitations rarely consult their general practitioner, and are not frequently referred to physical or occupational therapy (172;173).

In sum, there are indications that symptomatic HOA can become asymptomatic, deteriorate or remain unchanged over time. Pharmacological and non-pharmacological treatment can possibly alter the disease course in severe HOA, but unfortunately only few patients with hand OA are offered non-pharmacological care.

1.1.7 Disease impact in HOA compared to other localizations

OA of the different localizations differs in anatomy, function and risk factors and the response to the same intervention may vary between the sites. Therefore different recommendations exist for hip, knee and HOA (12). Risk factors vary in strength for the different OA localizations, i.e. the role of BMI is strong for knee OA, and female gender has a stronger bias for knee than hip OA (22). When managing and developing interventions for people with OA, it is important to know to what extent disease impact is affected by the different localizations. At the beginning of this study, little information about disease impact in HOA compared to hip, knee and generalized OA was available, and only one international recommendation for managing HOA had been developed (12). A few studies have assessed the differences between localizations in single factors (Table 3).

Body Function and Structure

The AMICA study from Italy compared patients with hand, hip, knee and generalized OA with respect to pain. They found that the median pain on a visual analogue scale was higher for patients with hip and generalized OA than for patients with hand and knee OA (71).

A Norwegian population-based study found that obesity (BMI>30) was associated with knee (OR 2.81) and hand (OA 2.59) but not hip (OR 1.11) OA (92). A study from Germany (174) assessed overweight in patients elected for hip and knee joint surgery grouped into hip, knee and generalized OA; and compared them. They found that overweight was strongly associated with knee OA, but not with hip or generalized OA.

Activity and Participation

HOA has in one study been associated with difficulties performing daily activities both in upper- and lower-extremities. As a result of this finding, authors have suggested including assessment of functioning at other localizations than the diagnosed OA (164).

Table 3. Studies on contributors to disease impact of hand, hip, knee or generalized OA

Author, year	Comparisons	Results
Bijkerk, 1999 (155)	The influence of genes on radiographic OA of the hand, hip, knee and discus degeneration.	Authors conclude that there is a strong genetic influence on radiographic HOA and degenerative discus disease
Sturmer, 2000 (174)	Obesity in hip, knee or generalized OA	Overweight is strongly associated with knee OA, but not with hip and generalized OA
Cimmino, 2005 (71)	Pain in hand, hip, knee OA in general practice	VAS pain was significantly higher in the hip and generalized disease groups compared to knee and HOA
Grotle, 2008 (92)	Effect of obesity (BMI >30) 10 years population based study	Obesity was associated with knee OA OR 2.81, HOA 2.59 but not hip (OR 1.11) OA
Elliott, 2007 (164)	Comparing assessed, self-reported and performance based functioning in HOA	Symptomatic HOA is associated with impaired lower extremity performance

1.1.8 Evidence-based treatment

The burden of OA is expected to increase, possibly due to an increasing proportion of elderly (7), less active (175) or obese (176) individuals. Due to the increasing number of people with OA, there is a need for evidence-based information about how to assess, treat and live with the disease (7;11;143). Prospective studies have generated knowledge about how OA progresses over time within various groups, but it is not clear whether the group progression is affected by a few fast-progressing patients. Another argument relevant to this is also the low proportion of OA patients who are in need of joint replacements (22).

Evidence-based knowledge

Evidence-based practice combines knowledge from clinical experience, patient knowledge and scientific research (177), and includes using the best currently available research-based evidence in deciding about the care of patients (178). It can be defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about

the care of individual patients” (179). Research-based evidence is a part of evidence-based clinical reasoning, and is available at different levels; through published primary studies, narrative or systematic reviews, or overviews. Reviews sum up evidence from primary studies and overviews sum up evidence from systematic reviews. Narrative reviews are not as systematic or transparent as systematic reviews, and the criteria for avoiding bias are lower (180). Systematic reviews use predefined criteria for evaluating the evidence, and sum it up systematically, but narrative reviews often lack descriptions of systematic methods used and sum up qualitatively (180). Guidelines or recommendations use evidence from all knowledge levels.

Evidence-based medicine implies systematically examining the evidence, following a transparent, pre-set methodology and applying it to clinical practice (181). This process includes a judgement about the hierarchy of evidence used in the medical literature, which considers overviews as the highest quality data available (178). Some argue that the top of the evidence hierarchy should consist of systems continuously updated with the latest research-based evidence: below this level are treatment recommendations, overviews, systematic reviews, and at the bottom of the hierarchy are primary studies. The higher up in the hierarchy, the less chance for challenges to validity (182).

There are various systems developed for assessing quality of studies based on the questions whether and to what extent we can trust the results. Search strategy, design and validity of included studies like the Jadad scale (183), and methods for combining, analyzing and reporting results in reviews and overviews can be assessed based on different methods like GRADE (184) or AMSTAR (185;186).

Being up to date with the results of primary studies is time-consuming, and results of primary studies can be conflicting. Systematic reviews summarize the best available evidence within a topic using transparent methods, comprehensive literature searches, rating of data quality and interpretation of graded results (180). As systematic reviews are often narrow, focusing on one aspect of a topic, overviews include results from systematic reviews summarizing a wider perspective on the evidence available. Therefore overviews may be more easily accessible and more feasible for the clinician and health care politician.

Treatment recommendations

Treatment recommendations are developed based on different formats; some include research evidence and clinical experience, and others include opinions and patient experiences. The European League Against Rheumatism (EULAR), ACR and Osteoarthritis Research Society International (OARSI) have developed recommendations for treating OA. Available treatments include pharmacological, non-pharmacological and surgical care, and are mainly aimed at alleviating symptoms.

EULAR has developed specific evidence-based recommendations for HOA (12) based on systematic reviews of research-based evidence and expert opinion. They state that the management of HOA should include both pharmacological and non-pharmacological treatments, is mainly aimed at alleviating symptoms and should be individually tailored. Based on a multidisciplinary consensus providing joint protection, education and hand exercises with thermotherapy and CMC-1 orthoses is recommended in the non-pharmacological treatment of patients with HOA.

Exercise improves pain and function in hip and knee OA and is recommended by the OARSI (75), but in hand OA, exercise has been studied combined with patient education compared to a group that received patient education in the format of RCT only (187). There was no published high quality study on HOA exercises alone, so the combination of patient education and exercise was recommended by the EULAR for the management of HOA (12).

Evidence-based management is dependent on many factors, especially the extent to which medical doctors, health professionals (188) and patients (189) adhere to research-based evidence and guidelines. Non-optimal adherence to recommendations for OA management (190-192) is frequent among health professionals. It has been reported that patient information needs are not optimally met (193;194). Many patients do not receive recommended interventions (195), and patients often lack a correct perception about their disease (196). A lack of knowledge about the disease can influence adherence to treatment (197). Another major barrier to the success of implementing recommendations in hip and knee OA has been identified as the continuous change in evidence and recommendations over time (188). It is suggested that only about 90% of a guideline's content remains correct after three years (198). The literature on adherence in health care in general is extensive (199) and beyond what is addressed in this thesis.

Some argue that resources should be used on implementation of already existing recommendations rather than developing new ones. An overview detected 34 clinical treatment and diagnostic recommendations for osteoarthritis published between 1993 and 2005, many of them overlapping in content (200).

Evidence from systematic reviews

Clinicians are asking for summaries of the evidence supporting treatment recommendations (189). Systematic reviews are based on clearly formulated questions that use systematic methods to search for, select, and assess relevant research (201). The quality of evidence from systematic reviews can be graded, and the quality can indicate to what extent one can believe that the estimated effect is true, and to what extent it is likely to change if new studies are added to the evidence base (184).

Non-pharmacological treatment

Due to the increasing proportion of patients with osteoarthritis, there is a need for effective non-pharmacological treatments to be developed (202), especially because there are no effective disease modifying drugs available(203).

A systematic review of pharmacological and non-pharmacological therapies in 2005 detected only few published RCTs on HOA. These were of low quality, among other factors due to the lack of standardized outcome assessments (204). Systematic reviews about non-pharmacological therapies for HOA available at the initiation of this thesis are shown in Table 4. Splinting and exercise for CMC-1 OA has been combined in different studies. Towheed et al found that there was some evidence for yoga, splint, spa and occupational therapy for HOA (204), and systematic review on laser therapy in HOA included one study where laser therapy was not superior to placebo for improving pain, stiffness or function (205).

Table 4. Systematic reviews including non-pharmacological therapies for HOA at the beginning of this project

Author, year	Inclusion	Conclusion
Towheed et al., 2005 (204)	31 RCTs on treatments	Some evidence: CMC-1 splint, yoga, spa and occupational therapy
Zhang et al., 2007 (12)	309 studies on treatments	Recommend: joint protection, thermotherapy, exercise, CMC-1 splint
Brosseau et al., 2007 (206) (Withdrawn)	7 RCTs	Low level laser for HOA
Egan, Brosseau, 2007 (207)	7 studies, varying design	CMC-1 splint “may help relieve pain”

Evidence from primary studies

Keeping updated on results from primary studies is time-consuming. But as systematic reviews and overviews exist, one can limit updating to searching for newer trials from the years after the existing review included their systematic search. Studies of non-pharmacological effects in HOA are up until now best answered by RCTs (208). This type of trial can be used as guidance where there is doubt about the most optimal (or harmful) treatment (179). There are results from RCTs on efficacy of different interventions for HOA like yoga, joint protection and exercise (Table 5).

Two studies not included in the systematic reviews were about yoga and exercise. Yoga has been examined in 25 patients with a method difficult to understand from the article, but the authors state that it can improve HOA pain (209). Different exercise regimens combined with CMC-1 splints were assessed in 40 patients with HOA. Neither regimen was superior to the other (210) but after 6 weeks both groups improved on pain, strength and function.

Table 5. Management of HOA, non-pharmacological studies

Author, year	Comparisons	Results
Garfinkel, 1994	Yoga RCT crossover design, 11 men/14 women, method is difficult to understand, high dropout percentage	Authors state that yoga has promising pain relief
Buurke, 1999	RCT crossover design n=10 examined three different CMC-1 splints	No difference in pain, but patient preferences varied between the splints
Stamm T, 2002	RCT Joint protection education and exercise compared to information leaflet (n=40), 3 months follow-up	Modest benefit of combination of joint protection and exercise
Weiss, 2004	The effect of two different CMC-1 splints, custom made or prefabricated, n=25.	“Both pain and function were improved by splinting...”
Wajon, 2005	RCT, 2 types exercise regimen + splint for CMC-1 OA, 6 weeks, n=40,	Neither regimen superior to the other

Relevant non-randomised trials

Interviews with OA patients have indicated that exercise (55.7%) and the use of assistive devices (29.6%) are common self-management methods (211). One study was detected that was not included in any of the reviews above. A pre-post test study of 55 persons with HOA who received training and strengthening exercises three times a week indicated that grip strength had the potential to increase and pain decrease during a two-year follow-up period (212).

Pharmacological treatment

At present there are no effective disease-modifying interventions available (213), and treatments are aimed at improving pain and function (112). Several attempts to disease modification in OA have been tested, however it is not certain that a reduction of structural damage would equal symptom relief and improve quality of life. Whether structural damage is the main cause of OA symptoms is unclear (22).

The EULAR guidelines for the treatment of HOA recommend paracetamol as the first line drug, and NSAID if the response to paracetamol is unsatisfactory or if there are signs of

inflammation. Intra articular injections of corticosteroids can also be applied. Opioids are recommended when all other pharmacological treatment options have failed (12). Evidence for the effect of pharmacological treatments in HOA is often based on studies of patients with knee OA.

There is evidence that non-steroidal anti-inflammatory drugs (NSAIDs) and cyclogenase-2 (COX-2) inhibitors are more effective for treating hip and knee OA pain than paracetamol, and more patients preferred COX-2 to the other compounds (214;215). However, COX-2 has been reported as inducing a high risk of cardiovascular disease (216). This, in addition to the increased risk of gastrointestinal, cardiovascular and renal complications associated with the use of NSAIDs (217;218) makes pharmacological options for optimizing pain control especially challenging.

EULAR (12) and NICE guidelines (219) recommend trying topical NSAIDs before oral use. The topical NSAIDs where the active compounds are absorbed locally by the skin have lower plasma concentrations than when orally administered. The evidence of effect of the topical NSAIDs is not convincing (220). There is evidence that oral NSAIDs are more efficient than topicals (221). Topical capsaicin can reduce pain and tenderness in OA (222) and is recommended for use on HOA. High quality consistent independent studies on the effects of glucosamine and chondroitin are lacking (12).

Intra-articular injections are also used to treat OA. Hyaluronic acid is costly but has shown efficiency in knee OA with a possible pain reduction of up to 4 months, and corticosteroid injections can reduce knee pain for 4-8 weeks (223-225) but not convincingly in thumb base OA in a placebo controlled RCT with 40 patients (226).

Surgical treatments

Surgery in OA is most commonly applied in hip and knee OA. It has been suggested that when patients with hip and knee OA have constant pain, indicating advanced structural disease, surgery in the form of joint replacements may be indicated (27). Others argue that surgery should be considered when the non-pharmacological and pharmacological core approaches have failed (75;219). The EULAR guidelines for treatment of HOA recommend surgical examinations in patients with severe OA where other pharmacological and non-pharmacological treatments have been considered (12).

Surgery is available in HOA, and various methods are in use. The most commonly recommended procedures studied are trapeziectomy, trapeziectomy with interpositional arthroplasty, ligament reconstruction, trapeziectomy with ligament reconstruction and tendon interposition, and joint replacement. A Cochrane review has assessed the effect of surgery on pain and function and found that none of the five surgical methods above were superior to the others (227). Joint prosthesis is also possible in hand joints (228;229). Joint replacement has been rated among the most effective interventions for severe hip and knee OA (8).

1.1.9 Philosophy of science

Positivism

Fundamental positivism acknowledges that there is a reality of existence that can be studied and believed to be true, assuming that reality exists also when it is not observed. Methods for collecting information about reality within positivism can be hypothetic deductive and include systematic procedures for observation and the use of statistical analyses typical for quantitative research. Quantitative, often numeric, empirical observations are used to understand and explain different phenomena within this tradition (230).

The quantitative approach to get an overview on RCT-based evidence for non-pharmacological and non-surgical treatments for OA based on RCTs includes hypothesis testing, assessment of quality and summarizing results. Assessing outcome measures for functioning in hand osteoarthritis is a quantitative approach within the same tradition, especially inspired by Galilei who introduced the thought of measuring what could be measured to make the yet not measurable measurable (231). Describing and comparing quantities of disease impact in patients with HOA is also a quantitative explorative approach using the hypothetic deductive approach inspired by Karl Popper's falsification theory (232).

Bio-psychosocial theory

The project is influenced by a bio-psychosocial way of thinking introduced by the medical doctor Engel in 1977 (233). Bio-psychosocial can be explained as: "A view that health and

illness involve the interplay of biological, psychological, and social factors in people's lives" (2). It is assumed that all factors are affected and can affect a person's health. Bio-psychosocial theory assumes that people, behaviours and the reasons for behaviour are complex. Important biological factors can be genetic (inherited materials and processes); physiological factors can be organs, cells and structural defects; and psychological factors can be self-efficacy, cognition, emotions and motivation; and social factors are those of family and friends as well as the societal and health care systems (2). The ICF is based on bio-psychosocial theory. In this PhD project, Body Function, Structure, Activity and Personal factors were addressed, whereas Participation and Environmental factors were not included. Study I and II addresses the outcomes function, pain and stiffness specifically, while study III additionally studies Personal or other factors not yet classified, like HRQOL.

OA is a chronic disease, characterized by complex biological, psychological, pathological and environmental mechanisms. The philosophy of understanding, treating and measuring functioning in patients with OA needs a wider than a pure biomedical perspective. For example, explaining the level of pain as pure nociception arising from the affected joint makes it difficult to understand why people with similar levels of joint affection have very different levels of pain. Qualitative interviews have shown that OA and its consequences are greatly affected by the patient herself, and Personal factors like control and negative emotions (234).

The needs of people with OA change throughout the life span. Parallel to the impact of the condition, bio-psychosocial systems change with time and the biological factors can be influenced by age which again can influence physiological decline. Similarly, personal cognitive factors may also play important roles to health behaviour, i.e. knowledge and health cognition can affect health-related action. Health-related cognition and behaviour can also change during a life span development as social relationships change over time. For instance, the role of being a son or a boyfriend demands different skills and actions than being a great-grandfather. People are also affected by their life span roles attached to education, employment or retirement (2). These differences are important to help understand disease impact, function and health behaviour in people with OA.

Pain theory

One of the most important symptoms in HOA is pain. It can be explained as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (235). It thus includes a complex sensory and emotional experience, perceived and described by an individual (236), and can be captured by the biopsychosocial model. It includes the pain mechanisms in the format of an updated gate-control theory by Melzack and Wall from 1965 (236). This theory explains nociceptive and neuropathic mechanisms of the peripheral and central nervous system (236-238).

Nociceptive stimuli from the innervated joint structures (except from the cartilage which is a-vascular and a-neural) are potential sources of OA pain. Structures with good nerve supply are capsule, synovium, ligaments, bone and musculature (22). The pain process can be explained as nociceptive stimuli ascending along the spinal cord up to the brain, where it can be inhibited or facilitated and perceived. The brain sends a response to the spinal cord where the noxious stimuli can be modulated. Central nociception and dys-regulation can also generate pain through the central nociception. Local cell destruction or inflammation can sensitize nociceptors and increase sensitivity by lowering the thresholds of pain. Long-lasting pain states are often characterized by enhanced pain perception (hyperalgesia), and a condition where normal stimuli become painful (allodynia) (22;239). Central sensitization can be explained by a hyper-response to prolonged or repeated periods of noxious stimuli and increased thresholds of pain transmission(239). Peripheral pain sensitization may be relevant in HOA pain (240).

The perception of pain can be modified by the cognitive and affective state including Personal factors of the individual (22). This theory takes into account that OA pain can be modulated not only by affecting noxe and inducing other competing stimuli, but also by addressing the perception of pain by the individual. This way many of the non-pharmacological and non-surgical interventions may help to modulate pain in HOA. The theory opens up for the possibility that a purely educational intervention can reduce HOA pain.

1.2 Assessments in HOA

1.2.1 Patient reported outcomes (PROs)

In addition to the value of capturing the patient perspective, there are some questions only patients themselves can answer, such as the degree of pain (241). The simplest form of patient reported outcome measure (PROM) consists of one question, for example a simple visual analogue scale (VAS) or numeric rating scale (NRS). Numerous items assessing single characteristics are often combined into a total or composite score (242). Transforming a final score and comparing it to standard or population norms can make comparisons across diseases and populations possible, for example as for HRQOL (243). When PROs are developed they are subject to testing such as reliability, validity and responsiveness.

Reliability

Reliability reflects the error of measurement and the actual stability of repeated measures in stable study subjects. It includes, for example, measurement error, expected variability, interclass correlation (ex. Pearson correlation coefficient between different variables), intraclass correlation (within variable), and internal consistency of the score. Test-retest reliability for assessing measurement error can be expressed through intra-observer reliability as a measure for variations within one observer during a series of observations, and inter-observer reliability indicating variability between observers (242).

Validity

Validity refers to the degree to which an instrument captures and measures what it is supposed to measure. Criterion validity reflects how well scale scores relate to actual performance of a task it was originally developed to predict. The scale is often compared to another comparable test or a 'golden standard'. Criterion validity captures concurrent and predictive validity. Content validity reflects the relevance of the content of the items judged by experts. This type of validation is not based on the items or scales or performance during a test. Content validity captures face validity. Construct validity reflects underlying abstract variables or mini-theories that cannot be directly observed about the relationship between phenomena or observable behaviours (242).

Responsiveness

Sensitivity to change can be seen as the ability to measure change in a state, but some argue that responsiveness reflects the ability to measure clinically important change. In both cases one can assume that change in the construct studied occurred over time and responsiveness is an expression of the measurement's ability to capture this change (242).

A minimally clinically important difference (MCID) has been defined as “smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management” (244). When assessing clinical effects in a specific patient group, the MCID should therefore be group-specific. There are similar constructs related to MCID, some of them named Minimum Important Difference (245) and Smallest Worthwhile Effect (208). These are relevant to interpreting effects in trials. The RCTs referred to in this thesis include expressions related to significance, such as clinical significance including meaningful change and not necessarily clinically meaningful statistical significance.

Choosing outcome measures

The OMERACT III conference recommended that four domains should be included in hip, knee and HOA trials in the future; pain, physical function, patient global assessment, and in addition imaging in longitudinal studies (246). Two reviews of trials and outcome measures in HOA were published in 2000 which concluded that better outcome measures and high quality trials in HOA were needed (190;247).

An overview of the orthopaedic literature from 1991 to 2001 has reported increased interest for PROs, both generic (patient's view of their overall health state), disease-specific and joint-specific (248). The advantages of joint-specific measures are that they have the ability to detect very specific outcomes while generic PROs can capture capture unexpected effects. These types of PROs are often complementary, and contrast with patient-specific measures that are individualized where patients choose the items to be assessed.

Disease specific outcome measures are important to assess the effect of treatment and compare different types of treatment for specific diseases. Subjective information, for example, about pain, requires that this information is translated into objective measures for

it to be communicated (249). Scales with sumscores are often used for parsimonious reasons and make results as simple as possible for the user, based on the assumption of a simple true explanation about effects (250).

1.2.2 Disease-specific measures

A group of researchers has initiated work on developing a consensus-based checklist and standards for the selection of health status outcome measures (251). There is not yet consensus on optimal criteria of good measurement properties (251). Not all measurement properties are equally important in each case, so agreeing on a set of criteria for health status instruments is challenging (252). Different standards or guidelines for measurement instruments have been published, e.g. about quality of life (253) or function (254). The latter served as a basis for the OMERACT filter (255).

Valid outcome measures are important in clinical research on patients with HOA, and the OMERACT (246) and the OARSI initiatives have recommended that functioning should be measured in patients with HOA, but there is no consensus on choice of instrument based on rigorous testing of their performance in trials or clinical practice (256-258), and only few of the instruments used to assess functioning in HOA have been evaluated for reliability, validity, and responsiveness. The OMERACT also developed a set of domains to be fulfilled for outcome measures in rheumatology. These domains include the concept of truth, including issues of validity, discrimination including reliability, sensitivity to change and feasibility indicating practical concepts of using the outcome measures (255). Outcome measures in osteoarthritis usually describe clinical status, detect change and assess response to treatment.

Since 2002, the OMERACT has included patients to ensure that the measures used in rheumatology capture concepts important to patients (259). It is important that patients have taken part in developing outcome measures and scales so that they are applicable and express meaningful domains.

Disease-specific measures in HOA

A survey of patients consulting for OA revealed that 74% of patients with HOA had difficulties with functioning (98). This emphasizes the need for instruments measuring HOA functioning. There are several measures available for assessing function in OA which includes the following domains: clinical examination, patient's assessment of pain, patient's and physicians' global assessments of disease activity and patient's assessment of physical function. When evaluated together, these measures sample the broad range of improvement in OA (have content validity), and all are at least moderately sensitive to change, i.e. they have discriminant validity.

Patient-reported HOA-specific outcome measures of hand function have been developed such as the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) (260) and the Functional Index for Hand osteoarthritis (FIHOA) (261;262). These are location specific and disease specific measures developed with for patients with HOA. A systematic review of measurement scales in HOA concluded that AUSCAN was among the measures most highly rated with regard to conceptual framework, feasibility, reliability and validity. However, the authors of the systematic review concluded that the properties had not been sufficiently tested to make any definitive conclusion about a preferred instrument (256). Table 6 summarizes the available clinimetric characteristics of PROs for hand functioning in HOA at the start of the project.

PROs for assessing hand functioning have been mapped to the ICF showing the differences in their contents (263). In content analyses AUSCAN (260), Cochin scale (264), FIHOA (261) and SACRAH (265) captured items specific for hand functioning in OA. The FIHOA primarily captures Activity and Participation, and AUSCAN additionally captures Body Functions like pain and stiffness. The other PROs described were more generally used within the field of rheumatology and covered wider areas of general functioning that included hand function (82). HAQ (266), the modified HAQ (267) and AIMS2 (268) are all primarily developed for rheumatoid arthritis, and regional specific outcome measures as the Disability of the Arm, Shoulder and Hand (DASH) (269) integrating shoulder, elbow and hand function, and Michigan Hand Outcomes Questionnaire (MHQ) which was originally developed and tested for hand surgery (270;271).

FIHOA was developed after interviews with affected patients to ensure that the patient reported outcomes measure areas of interest relevant to patients. AUSCAN was developed by health professionals based on existing measures, but patients chose the most important ones among a list of selected items (260). Both AUSCAN and FIHOA were tested in a test-retest approach during the original development process to ensure consistency of the results, and estimates were made for internal consistency and homogeneity of the measures and associations between the scales (260;261). The AUSCAN was tested as self-report questionnaire (260), while the FIHOA was originally tested as an investigator-administrated scale (261;262). In Norway there was to our knowledge no available outcome measure for assessment of functioning in HOA free of charge before FIHOA was introduced with this thesis.

Assessments beyond disease and location specific function have been suggested by others (164) based on a study detecting that HOA has been associated with difficulties performing daily activities both in upper and lower extremities.

Table 6. Available clinimetric characteristics of PROs for hand functioning in HOA at the start of the project

Instrument evaluation	Patients (response rate), setting and data collection methods	Data collection	Missing data	Cronbach's alpha/ item-total correlation (range)	Test-retest correlation	Construct validity (correlations unless otherwise stated)	Responsiveness
AUSCAN & FIHOA:							
Bellamy et al. (260) Canada, Australia	50 (87.72) patients, ACR criteria; mean age 60.4 (sd=7.8), 80% female. Test-retest at 1-week (n=44) Responsiveness following a washout and reuptake with NSAIDs; mean age 59.9 (sd=8.0), 86.36% female.	Self-completed Self-completed at home	7 patients had incomplete assessments	Pain 0.90 Physical 0.94	Pain 0.70 Stiffness 0.77 Physical 0.86	Comparisons with Grip strength, Pinch grip, Doyle, Global pain, Global function, Severity, Morning stiffness, FIHOA, HAQ	SRMs: AUSCAN Pain 0.53-0.74; Stiffness 0.23-0.31; Function 0.52-0.72. SRMs: FIHOA 0.27-0.31
AUSCAN:							
Allen et al. (272) USA	Participants of OA genetic study with radiographic HOA. 700 (79.73) of 878 patients completed strength measurements; mean age 69 (sd=9) years, 80% female.	-	-	Total 0.96 Pain 0.93 Physical 0.94	-	Factor analysis supported two AUSCAN multi-item scales. Inter-scale 0.63-0.79 A Comparisons with Grip strength, Pinch strength, Pain severity	-
Allen et al. (273) USA	Participants of OA susceptibility genes study with radiographic evidence for HOA. 1730; median age 61, 65% female.	Self-completed	-	Total 0.96 Pain 0.94 Physical 0.95	-	Factor analysis supported the two AUSCAN multi-item scales for most subgroups. Comparisons with Grip strength: Pinch strength, AUSCAN subscales	-
Mac Dermid et al. (274) Canada	121 patients post-hand-surgery with clinical OA diagnosis, mean age 65.4 (8.1), 81.7 % female	Self-completed	-	-	-	Factor analysis supported two AUSCAN subscale factors Correlations with SF-36 MCS & PCS	-

S-Christensen et al. (275) Norway	199 patients with clinical HOA referred to a rheumatology outpatient department: mean age 61.7 (5.7) yrs 91% female.	Self-completed	Pain 2.0% Stiffness 2.5 Physical 1	Pain 0.93 Physical 0.95	-	Inter scale 0.64-0.83 B	-
FIHOA:							
Dreiser et al. (262) France	RCT of ASU. 261 patients meeting ACR criteria for HOA: mean age 61.1 (sd 7.5), 91.6% female.	Clinician interview	-	-	-		SRM 0.58
Dreiser et al. (261) France	Patients with active (n=100) and inactive (n=100) OA. Mean age 65.95 (8.9) years, 84.34% female. Intra-observer reliability assessed in active OA patients at 24 hrs.	Clinician interview	3% (active OA)	0.85	Intra-observer (24 hrs) 0.95 Kappa (items) 0.68-0.87	Principal component analysis supported uni-dimensionality. ANOVA and pair wise comparisons: significant differences between active, inactive OA and controls for FIHOA scores (p<0.001). MANOVA: significant differences between active, inactive OA and controls for all ten items (p<0.001).	-

SRM: Standardised Response Mean = mean change in scores divided by the standard deviation of change scores. Short Form-36 scales: from 0-100 where low scores indicate poor health. The Physical Component Summary (PCS) and Mental Component Summary (MCS) are represented here.

Performance tests in HOA

Performance tests assess different domains than PROs. Performance is observed, as opposed to self-reported. It can be argued that performance measures can be more objective, less affected by individual Personal factors; however patient opinion is not a part of this way of measuring and thus the results of performance measures can mask the actual problems of the patient. The correlations between performance and self-reported measures can never be optimal due to the assessment of different perspectives used in assessment. The use of correlation between different measurement methods can be misleading. Correlation

measures the strength of agreement and it is unlikely that two different methods will agree, indicating perfect agreement for all patients (276). Also, if one of the methods has poor repeatability the agreement between the two methods will be poor as well (276). A sumscore that increases the true variance could increase reliability of the different tests and correlation between them (242). It could be discussed whether it is adequate that these different methods for measuring the same phenomenon really are considered unsatisfactory regarding what we could expect when comparing these different categories. There is a difference in how specifically a picking-up test like the Moberg picking-up test (MPUT) and grip strength measured by a dynamometer may be compared to answers to scale items like the AUSCAN.

The MPUT (277) assesses the efficiency of fine finger movement. The task is to pick up and place 12 small objects one by one and put them in a container as fast as possible. The outcome is time-use in seconds. The Jebsen-Taylor Hand Function test (278;279) and Sollerman Hand Function test (280) are different tests developed for hand disorders. The Button Test is also used and tested for Rheumatoid Arthritis (281;282) as performance measures of grip strength (283). Grip strength is often used in HOA measured by a dynamometer, either by the instruments Grippit or Jamar. High grip strength has been associated with increased risk of CMC-1 OA and MCP (76).

Other disease-specific outcome measures often used in osteoarthritis

Outcome measures in osteoarthritis are needed to describe clinical status, detect change and assess response to treatment.

Western Ontario McMaster Osteoarthritis Index (WOMAC) is a scale comprised by 24 items on the dimensions pain (5 items, scored 0-20), stiffness (2 items, scored 0-8) and physical function (17 items, scored 0-68). The WOMAC is presented to the populations studied as VAS (0-100) or Likert (5-point) scales. There are various ways of displaying the results of the subscores and the sumscore. Some studies report the raw scale where the sumscore is related to 0-96, but due to the difficulties interpreting the results when comparing them to other outcomes, the results can be normalized to 0-100 or 0-30 scales (284-286). The WOMAC is a regional disease-specific patient-reported outcome measure designed for both hip and knee OA and a very common PROM for physical function in osteoarthritis.

The WOMAC results can be influenced by other factors or joint pains like low back pain, depression and fatigue (287).

Other joint-specific PROs also exist but are not as commonly in use as WOMAC, and not available in Norwegian at the beginning of this project. Based on the content of WOMAC, the Knee injury and Osteoarthritis Outcome Score (KOOS) and Hip disability and Osteoarthritis Outcome Score (HOOS) were developed for hip and knee injury and osteoarthritis (288-290). These scales are self-assessed and can be applied without extra costs. KOOS (42 items) addresses five outcomes: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. HOOS (39 items) addresses pain, activity limitations, sport and recreation, and hip-related quality of life.

1.2.3 Generic measures

The Short Form 36-item (SF-36) Health Survey is a widely used generic instrument assessing HRQOL (291). The SF-36 is used to assess HRQOL in the general population and in different diseases (scored 0-100, where 100 is best). It has eight health scales (physical functioning (10 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), bodily pain (2 items), social functioning (2 items), mental health (5 items), vitality (4 items) and general health perceptions (5 items) that contribute to two higher order health scales. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores have a mean value of 50 and standard deviation of 10 based on normative data from the general population (291).

The instrument is self-assessed and commonly used in rheumatology. The English version has been translated into Norwegian and validated (292). It is found valid and reliable for the use in the general population and for patients with RA (293). There is evidence suggesting that OA impacts HRQOL (SF-36) comparably to rheumatoid arthritis (50).

1.2.4 Needs for research in HOA

The background describes evidence-based knowledge about the understanding of management, assessment and disease impact in HOA at the beginning of this project. Studies have shown that HOA is a prevalent disease that can affect activity, participation, work and quality of life. OA guidelines for pharmacological approaches recommend treating OA patients in general, but evidence for treatment with non-pharmacological and surgical approaches is mainly joint-specific. Evidence-based knowledge about OA is mainly based on studies on knee OA. Overviews of high quality research-based evidence for knee (294) and hip (295) OA have been performed but not for HOA.

As shown above, there are indications that there are insufficient high quality studies concerning therapies for hand osteoarthritis, compared to those for knee (294) and hip osteoarthritis (295;296). An overview is a practical and efficient guide to the direction of effects and reveals where high quality research is lacking.

In order to perform high quality research, valid and reliable outcome measures are needed. As shown above, there is one outcome measure which has been developed for evaluating the effect of treatments in HOA is available, however it is not properly tested, nor freely available in Norwegian. The lack of validated outcome measures restricts the possibility of assessing and comparing effects of different treatments, and thus limits research in the field of HOA. A few instruments measuring function in HOA are available internationally and could be translated and validated.

As shown above, there is also limited evidence about the disease impact of hand OA compared to hip, knee and generalized OA (129), and knowledge about functioning in joints other than the primary localization is seldom addressed in studies. This information is important for tailoring treatments to the patients and developing more targeted treatment strategies for these patients.

The background indicates that HOA is an under-investigated disease with respect to efficacy of various interventions, validated outcome measures and disease impact, compared to OA in other localizations.

- I. There is little research-based evidence available for knowledge about the effect of different treatments for HOA.
- II. Available outcome measures to evaluate management and compare effects are lacking for HOA.
- III. There is little knowledge about the disease impact of HOA compared to hip, knee or generalized disease.

2. General aim and specific research questions of this thesis

2.1 General aim

The overall objective of this thesis is to improve understanding about management, clinical assessment and disease impact in HOA.

To accomplish this, an overview of systematic reviews on the effects of non-pharmacological treatments in HOA was performed; outcome measures to assess functioning were translated and validated, and disease impact in patients with HOA was described and compared to hip, knee and generalized OA.

2.2 Specific research questions

I: What is the existing evidence for effect of non-pharmacological and non-surgical interventions in HOA? (Paper I)

II: Are AUSCAN and FIHOA valid and reliable self-report instruments for assessment of hand functioning in patients with HOA? (Paper II)

III: What is the disease impact in patients with hand OA compared to patients with hip, knee or generalized disease? (Paper III)

The objectives are answered in the following way:

Objective I: To perform an overview of systematic reviews on the effect of treatments for hand osteoarthritis.

Objective II: To translate and validate outcome measures for functioning in hand osteoarthritis.

Objective III: To describe disease impact in patients with HOA compared to hip, knee and generalized OA.

3. Materials and methods

3.1 Study designs

The results of this thesis are based on I) an overview of high quality systematic reviews, and II) and III) observational cross-sectional data from two patient populations in specialist care. The designs of the studies are described in Table 7.

Table 7. Study characteristics

Article	Theme	Design
I	Overview of HOA interventions	Overview of systematic reviews, systematic literature search, quality assessment
II	Concurrent evaluation of FIHOA and AUSCAN	Cross sectional, test-retest reliability and validity
III	Comparing disease impact in hand to hip, knee or generalized OA	Cross sectional

3.2 Study populations

Assessing disease impact in HOA and comparing it to OA at other localizations was not possible in the HOA population because there was no information about OA in other localizations than the hand. As a consequence, it was necessary to include another patient population originating in the OA clinic to answer the research questions raised in this thesis (Table 8).

Table 8. Basis for the three studies

Article	Patients / Publications	Sample
I	173 potential reviews	4 systematic reviews, HOA
II	n = 128, retest n=40	HOA
III	n=408	Hand, hip, knee or generalized OA

The patients contributing to Paper II and III are originated in two different populations. The Oslo Hand Osteoarthritis Population was initiated (50) to evaluate the burden of disease in HOA, and the OA population was recruited from OA patients referred to a specialist care clinic in Oslo between 2005 and 2010. The two populations are described below.

The study was conducted in two patient populations (Table 9):

- A. The Oslo Hand Osteoarthritis Population was initiated in year 2000-2003 at Diakonhjemmet Hospital.
- B. The OA population was recruited from all patients with hand, hip, knee and/or generalized OA referred to specialist care between 2005 and 2010.

Table 9. Patient populations included in this thesis

Population	Paper I	Paper II	Paper III
HOA population		X	
OA population			X

3.2.1 Oslo Hand Osteoarthritis Population

For her PhD, Barbara Slatkowsky-Christensen established a HOA population and performed baseline examinations in 2001/2003 with HOA according to the ACR criteria as inclusion criterion (N=209, 190 were women). These patients were recruited to the current study on validation of outcome measures for hand functioning initiated in August 2008.

At inclusion patients reported on a wide spectre of disease related variables, including socio-demographics, work and health status, physical activity, treatment strategies, medication and some standardized instruments for pain, functioning and HRQOL. Pain,

fatigue and disease activity were evaluated on visual analogue scales. In this part of the follow-up study, self-reported physical functioning was assessed by FIHOA and AUSCAN for patients with HOA. Performance-based measures of physical functioning were assessed by the Moberg Picking Up Test (277) and Jamar Dynamometer (297). Grip strength of both hands was measured with a JAMAR hand dynamometer (kg). The patient was sitting by a table with the shoulder in a neutral position and the elbow 90 degrees flexed while squeezing the dynamometer as hard as possible. Health-related quality of life was addressed by SF-36 (291).

All patients received written information about the follow-up and gave a written consent to continue participating in the study. All patients who were examined during the follow-up were asked to participate in the validation study. Patients who agreed to participate received oral and written information about the method and aims of the study. They were also informed that participation was voluntary and could be terminated at any time without stating a reason and without it affecting their care. All patients who gave their informed consent received a self-report questionnaire on physical functioning (FIHOA and AUSCAN, three pages) one week after meeting for the follow-up. The questionnaire also included a health transition item: “Since you were examined a week ago, how is your HOA now – much better, somewhat better, about the same, somewhat worse, much worse?” Respondents who stated that their HOA was about the same were included in the test-retest reliability analysis. The level of association between the two sets of scores was assessed using the intraclass correlation coefficient. To be acceptable for use in groups of patients the estimates of reliability should exceed 0.70 (250).

3.2.2 OA Population

To compare disease impact according to OA localization 408 patients with clinical OA in hands, hips, knees or generalized OA (at least two different extremity localizations (44), not assessing the spine) were recruited after being referred to the specialist rheumatology clinic at Diakonhjemmet Hospital.

At inclusion all patients were asked to fill in self-report questionnaires including questions on socio-demographic variables, work and health status, physical activity, questions on

treatment strategies for their condition, medication and a few standardized instruments for assessing pain, functioning and HRQOL. Pain, fatigue and disease activity were evaluated on numeric rating scales. Physical functioning was assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (284) for patients with hip or knee OA and AUSCAN (260) for patients with HOA. HRQOL was addressed by the SF-36 (298;299).

A rheumatologist and a project coordinator read all referrals to the multidisciplinary OA clinic at Diakonhjemmet Hospital. Patients aged 18-80 years were recruited to the study by a telephone-based screening-form for OA based on the American classification criteria of OA in hands, hips or knees. Patients with difficulties understanding the Norwegian language, who had been severely traumatized, who had recently gone through surgery, or who had diseases like rheumatoid arthritis, current cancer, etc., were excluded from the study. Patients who fulfilled these criterias received oral and written information about the study. They were also informed that participation was voluntary and could be terminated at any time without expressing a reason and without it affecting their care.

3.3 Data collection

When normal the functioning of a body part is impaired, it can result in disability; an altered capacity to meet personal, societal or occupational demands (48). Hand function based on the ICF definition is included in all three papers included in this thesis.

Paper I considers function as a main outcome measure for evaluating the effect of HOA interventions. Paper II includes self-reported and performance-based measures of physical function. Grip strength is a performance-based measure that correlates well with physical function, and can be measured with a hand dynamometer (300;301). Paper III includes disease impact consisting of factors such as physical function, stiffness, pain, fatigue, disease activity, HRQOL and psychosocial factors.

The outcome measures included in this thesis are sorted according to the International Classification of Functioning, Disability and Health (3) in Table 10.

Table 10. Categorization of outcomes in this thesis according to the ICF

Domain	Outcome	Paper I	Paper II	Paper III
Body Function	Pain	X	X	X
	Stiffness	X	X	X
	Strength	X	X	X
	BMI			X
Body Structure	Hand	X	X	X
	Hip			X
	Knee			X
	AUSCAN	X	X	X
Activity & Participation	AUSCAN	X	X	X
	FIHOA	X	X	
	WOMAC			X
	Grip strength		X	
	Picking up test		X	
Personal Factors	Age		X	X
	Gender		X	X
	Education		X	X
	Employment			X
	Comorbidities			X
	Fatigue			X
HRQOL	SF-36	X		X

HRQOL=Health-related Quality Of Life

For the purpose of the current study it was decided that instruments for use should preferably be simple, validated, translated versions developed for the target group. It has been proposed that the selecting outcome measures in HOA should be evidence-based (302). In this study, the AUSCAN and FIHOA were chosen to assess hand function in HOA because they were developed specifically for this, and have shown evidence related to important criteria for evaluation of PROs including data quality, reliability, validity and responsiveness (250). They are both short instruments and hence are acceptable to patients and have clinical feasibility, but have undergone limited concurrent evaluation. Two studies that included some concurrent evaluation of the AUCAN and FIHOA were detected.

All patients included in the HOA and OA population were clinically examined, and contributed with demographic and disease related information. The OARSI has recommended assessing HRQOL in patients with HOA (257), a motivation for inclusion in the current studies. Table 11 describes the most important outcomes included in the studies.

Table 11. Outcome measures in the studies

Outcome	Paper I	Paper II	Paper III
Demographic characteristics	X	X	X
<i>Disease-specific PROM</i>			
AUSCAN	X	X	X
FIHOA		X	
WOMAC	X		X
<i>Generic PROM</i>			
SF-36			X
VAS/NRS pain	X		X
VAS/NRS fatigue			
VAS/NRS patient global			X
HSCL-25			X
<i>Performance tests</i>			
Grip strength (Jamar)		X	
Moberg pickup-test		X	

PROM= patient reported outcomes, VAS=Visual Analogue Scale, NRS= Numerical Rating Scale, AUSCAN sum 0-10, 0 is best, WOMAC (0-30, 0 is best), HSCL-25= Hopkins Symptom Checklist – 25, (1-4, 1 is best), SF-36= SF-36 Health Survey (0-100, 100 is best), PCS= Physical Component Summary, MCS= Mental Component Summary

Paper I was based on a comprehensive literature search for systematic reviews on “hand osteoarthritis/osteoarthritis or OA” published in English, Dutch or Scandinavian languages between the year 2000 up until week 40, 2008. Publications were identified by a computerized search in Cochrane, Medline, MBASE, PEDro, Cinahl, and PsychINFO databases. Two reviewers independently assessed the relevance of all references based on titles and abstracts. Methodological quality was then assessed using eleven criteria from the Measurement Tool to Assess Systematic Reviews (AMSTAR) for assessing quality of evidence for each review. AMSTAR is a reliable and valid measurement tool for assessing systematic reviews based on assessments of quality of primary studies, design of primary studies, consistency, and directness, rated as “met,” “unclear/partly met,” or “not met” with overall scores ranging from 0 to 10 (185;186).

3.3.1 Demographic and disease related variables

All patients included in Paper II and III received a questionnaire containing demographic and disease-related variables by mail, after consenting to participation in the study approximately one week prior to the clinical examinations at the specialist clinic. They brought the questionnaire to the clinical examination.

The clinical examinations serve as a basis of diagnosing and treating HOA, and excluding other differential diagnoses (303). Clinical examinations are affected by both the clinician and patients experience and beliefs, and usually include anamnesis, and a general observation and assessment of the affected joint(s). Physical examinations in OA usually includes BMI, joint movement range, the degree of pain during movement, soft tissue swelling and joint tenderness, structural joint deformity, muscular strength, and observation of different activities (22).

3.4 Statistics

All statistical analyses in this thesis were undertaken using the Statistical Package for the Social Sciences for Windows, versions 14-17 (SPSS, Chicago, IL, USA). Unless otherwise stated, a 5% level of significance was chosen for all analyses.

Reliability captures quantification of error of measurement and repeatability of the results across conditions. It includes measurement error, expected variability, interclass correlation, intraclass correlation, test-retest reliability and internal consistency of the scale (242).

Principal Component Analyses (304) were used to assess scale structure. Internal Consistency was assessed using Cronbach's alpha for assessing associations between scale items and the remainder of the scales. Intra Class Correlations were used for assessing test-retest agreement, and external construct validity was assessed by correlation statistics.

T-tests were used for one-to-one comparisons of continuous variables between two groups. One-way analysis of variance (ANOVA) was used for assessing difference between groups for continuous variables for, and Chi square tests were used to compare groups for

categorical variables. Plots of residuals were examined. Regression analyses were used to explore possible relationships between variables in hand, hip, knee and generalized OA and to compare groups adjusted for variables described to be possible confounders selected a priori (305). The normal residual assumption of the fitted models for continuous variables were checked using residual plots.

Univariate ANOVA analyses of clinically important variables were performed, and covariates with p-value <0.05 were included in the multivariate analyses testing null hypothesis of no mean difference between the groups.

3.4.1 Descriptive and explorative analyses

To describe the populations included in the studies and to display an overview of the data, detect errors or outliers, descriptive analyses such as frequencies, means, standard deviations, cross-tabulations and graphs were performed. Descriptive statistics were given as median (interquartile range) or mean (95 % confidence intervals) where appropriate, and percentage for counts. ANOVA statistics was used for group comparisons. The level of significance was set at $p < 0.05$. Descriptive analyses were completed using SPSS Statistics (version 17.0; SPSS Inc., Chicago, IL).

Two authors independently assessed methodological quality of each of the reviews retrieved in Study I according to the criteria list of 11 criteria from AMSTAR, a reliable and valid assessment instrument where each review is rated on based on assessments of quality of primary studies, design of primary studies, consistency, and directness on a scale from 0-10.

3.5 Legal and ethical aspects

All studies were conducted according to the principles of the Declaration of Helsinki. All patients gave informed consent before participation. Each study was evaluated and approved by the Regional Committee for Medical Research Ethics.

There are several guidelines for ethics for research on humans; some important issues (306) are addressed below. For patients the value of the project consists in their contribution to valid outcome measures that may serve others and themselves. This project has not involved high technology and expensive tools, but the minimum human resources possible to ensure valid results. The study was independently reviewed by several instances before it was initiated. One example of this was the review by the ethical board. The selection of subjects took place both from the OA population and the HOA population, on a pragmatic basis. All participants were invited to participate when they were referred to a specialist clinic. There were minimal risks and potential harm in this project. Patients were assessed and filled in PROs.

All participants were informed verbally in lay terms and in writing about the risks and benefits of their participation. Informed consent is available from all subjects in both populations. The patients were told that they could withdraw from the studies any time without stating a reason and that their health care would not be affected in any way by their doing so.

This project fulfils the official goal for medical research in Helse Sør-Øst as stated in the research strategy for South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF 2008-2011): ” Medisinsk og helsefaglig forskning er virksomhet som utføres med vitenskapelige metoder for å frembringe ny kunnskap og erkjennelse som på kort eller lang sikt kan være relevant for pasientbehandling og for helsetjenesten... ”, that is to say that adequate medical research should be relevant for treating patients. All patients involved in the project signed an informed consent and were informed according to the Helsinki declarations. The studies were approved by the Regional Ethical Committee (REK) and data inspectorate. *The OA population:* REK ref 156-06073 1.2006.598 and 14442. *The HOA population:* REK ref. 106-00056 404-00056 127-01-00056.

4. Summaries of results

In order to contribute to the insights about management, clinical assessment and disease impact in HOA, the following actions were taken. An overview of high quality systematic reviews about non-pharmacological and non-surgical interventions for HOA was performed. PROs for hand function in HOA were translated and tested, and disease impact in HOA was described and compared to hip, knee and generalized OA in patients in specialist care.

4.1 Paper I

There is inadequate evidence to determine the effectiveness of non-pharmacological and non-surgical interventions for hand osteoarthritis: an overview of high-quality systematic reviews

A total of 173 reviews were identified in the systematic literature search, of which eight were assessed in full-text by two independent reviewers using a previously validated quality assessment form. Four systematic reviews were finally included.

In overviews, results are dependent on available published systematic reviews. They are important tools to guide directions in choice of interventions and locate areas where more research is needed, but they might not be useful for deciding specifically how interventions should be carried out, especially when primary studies and systematic reviews in the field of research are few. Based on single randomized controlled trials, there was some evidence for the effect of pain relief from topical capsaicin compared with placebo; the number needed to treat was three to achieve 50% symptom relief. There were conflicting results regarding the effect of different splints on pain, and no significant difference between the effects of thermal vapour treatment and those of topical ibuprofen. There were favourable functional outcomes for exercise and education compared with osteoarthritis information alone equivalent to two number needed to treat to achieve more than 50% improvement on “patient global function”. Desire for surgery after splinting or no treatment was equal for both groups in a small RCT.

In conclusion, there is currently insufficient high-quality evidence regarding non-pharmacological and non-surgical interventions for HOA. Considering the limited research evidence and the prevalence and impact of the disease, there is an urgent need for more trials of non-pharmacological and non-surgical interventions for HOA.

4.2 Paper II

Concurrent evaluation of data quality, reliability and validity of the Australian/Canadian Osteoarthritis Hand Index and the Functional Index for Hand Osteoarthritis

In order to concurrently evaluate the data quality, internal consistency, test-retest reliability and validity of two patient-reported outcome measures (PROs): Australian/Canadian Osteoarthritis Hand Index (AUSCAN; 15 items) and the Functional Index of HOA (FIHOA; 10 items) for measuring functional impairment in HOA, the FIHOA was translated. Patients from a HOA population [n=128, mean age 68.6 years (standard deviation 5.8), 91% women] completed PROs and performance measures during routine follow-up in specialist care. One week later, a subsample (n=40) reporting no change on an HOA-specific transition question contributed test-retest data.

Both instruments had satisfactory levels of data quality, internal consistency, test-retest reliability and construct validity. The AUSCAN performed slightly better than the FIHOA relating to levels of missing data (0 vs. 5%), floor effects, principal component analysis loadings (0.62–0.83 vs. 0.52–0.83), item-total correlation (0.77–0.91 vs. 0.45–0.76) and Cronbach's α (0.94–0.96 vs. 0.90), respectively. AUSCAN items had slightly lower test-retest κ -values (0.29–0.77 vs. FIHOA 0.41–0.77) and AUSCAN scales lower intra-class correlations (0.80–0.92 vs. FIHOA 0.94). Correlations between the two instruments ranged from 0.58 to 0.88 for the AUSCAN scales of stiffness and physical function, respectively. The AUSCAN physical function scale was generally slightly stronger correlated with the other PROs and performance measures.

In conclusion, there is evidence for the reliability and validity of AUSCAN and FIHOA; they are suitable for measuring physical functioning in HOA. The FIHOA had higher test-retest reliability and is shorter, but the AUSCAN performed slightly better concerning data quality and construct validity.

4.3 Paper III

Disease impact of hand osteoarthritis compared to hip, knee and generalized disease in specialist rheumatology health care

To improve understanding about disease impact in HOA compared to hip, knee and generalized disease in specialist rheumatology care, disease impact was described and compared in a cross sectional design. Patients with OA referred to a specialized rheumatology clinic (408 patients, 86% women) were included in the study. They were examined by a rheumatologist and classified into primary hand, hip, knee and/or generalized (<2 joint localizations) OA.

The results indicate a considerable disease impact across all localizations: patients scored above 5 on NRS pain (range 0–10), had on average 2 co-morbidities, and scored above 1.5 on emotional distress (HSCL-25, range 1–4). Patients with hand OA scored poor on disease-specific functioning of the lower extremities, and patients with lower extremity OA also scored poor on disease-specific hand functioning. Patients with hand OA scored better on pain ($p=0.001$, ANOVA) and SF-36 physical component ($p<0.001$), whereas no major differences were observed for the mental component ($p=0.07$).

In conclusion, OA patients referred to specialist care reported considerable levels of disease impact across localizations. Regardless of functional impairments related to the primary OA localization, patients generally reported high levels of impaired disease-specific functioning at other sites. In the management of OA, clinicians should also consider functioning in other joint sites than the primary OA localization.

5. General discussion

5.1 Methodological aspects

Methodological limitations of the studies in this thesis may contribute to various forms of bias, and a discussion of how these limitations may affect the results is addressed in this section.

5.1.1 Study design

A summary of results of systematic reviews on non-pharmacological interventions for hand OA was performed using a systematic method for conducting overviews of such reviews. Overviews have prior to this study been performed on non-pharmacological interventions for hip (295) and physical therapy interventions for knee (294) OA. A similar method was applied for the overview concerning hand OA.

Including and assessing the studies following the literature search revealed many methodological weaknesses of the retrieved reviews. To resolve contrasting data from systematic reviews, it was necessary to consult some primary studies as well. After assessing the quality of the retrieved systematic reviews, only four reviews could be included in the overview. In the present overview, the small number of and few high quality primary studies available limited the clinical value of the systematic reviews included in the overview. Due to the a priori decided design, and the possibility of comparing results across overviews of the different localizations with similar design, the authors decided not to include reviews of lower quality.

The validity of the evidence available from RCTs is dependent on numerous factors (307). Well known strategies for overcoming bias are randomization and blinding, and this was evaluated in the systematic reviews included in the overview. Blinding could be evaluated based on the patients, therapists, assessors or the statisticians. In non-pharmacological trials

it can for example be difficult to blind the therapist to which treatment he or she is giving with the purpose of controlling for the placebo effect. And if two similar active interventions are compared in one study, it is not certain that blinding the therapists to their interventions would improve the quality of the study (308), but it can still reduce the possibility for evaluation bias. Non-pharmacological RCT's are criticised for their non-optimal blinding procedures, among other methodological weaknesses. This has recently been brought up in the scientific literature. Pragmatic trials assess effects of real-world clinical interventions (309), and have their own CONSORT statements, which allows assessment of the methods, based on their own terms, alongside those of other experimental trials (310).

The primary outcomes of the overview were pain, stiffness and function. Pain and physical function are two of the core measures recommended by the OMERACT (246). The method as described a priori was followed throughout the study with a few adjustments. 'Desire for surgery' was added as an outcome for the effect of splinting as it was found important in one included trial. The performance-based outcome grip strength was also additionally reported. In one of the systematic reviews, outcomes for comparisons were not specified, and it was then decided to report the authors' conclusions (204) for the comparisons in the results section. None of the included trials reported results on 'stiffness', so there were no results for this outcome. Two of the included systematic reviews reported conflicting quantifications and directions of effects of splints (12;207), and therefore the results from the primary studies were reported (311;312).

The results of studies can be rated based on statistical or clinical significant differences between the groups, however some argue that the smallest worthwhile effect is what really matters to the patient. This idea captures the magnitude of the beneficial effect of an intervention including costs, risks and negative consequences of the treatment. It considers that the intervention should be based on the perceptions of the patients receiving the intervention, and is therefore intervention-specific (208). No trials including smallest worthwhile effects were assessed.

A strength of the study was the comprehensive literature search and the use of a validated quality checklist (AMSTAR) developed and tested for assessing quality of systematic reviews. Several other quality assessment tools for assessing systematic reviews have been

published (185) and considered during the development of AMSTAR. All systematic reviews were assessed with the AMSTAR checklist.

A classical psychometric method to analyse measurement of human characteristics was applied to validate the two PROs AUSCAN and FIHOA. A weakness of this study was the absence of a classical golden standard for comparison; however as a result of a missing golden standard, various measures were included to increase the external construct validity where the PROs were compared with each other and other instruments, including performance-based measures.

The quality of PROs is based on the idea of a sound measure of truth meaning whether the measures measure what they are intended to measure, whether the results can be trusted, and can capture change over time. The ICF model, OMERACT or Cochrane collaboration checklists can be used as examples of what should be measured (313). The COSMIN checklist consisting of criteria about measurement properties such as validity, reliability and responsiveness; interpretability and generalizability of results has recently been published (314) and could have made the design of this study easier. According to these criteria there are various methods recommended for validating and comparing PROs, including the methods used in this thesis. Evaluating how instruments perform over time is recommended by the COSMIN; this was not assessed in this study due to the absence of longitudinal data, but will be on a future research agenda.

One week recall was chosen for the test-retest analyses. There is no consensus on an optimal recall period for these instruments, so the authors decided to perform retest assessments at one week based on prior comparable publications (260), and the assumption that this allowed sufficient time for the patients to forget details of the scorings one week prior to the recall. Keeping the time between test and retest short was also considered important to minimize possible disease fluctuations that could influence PRO scorings. The scoring of PROs is also dependent on Personal factors like motivation, perception of normality and education; this may contribute to the explanation of lower levels of correlation with performance-based measures. It is shown that the personal reference frames when scoring PROs can reach magnitudes regarded as clinically relevant (315).

Challenges using total scores can be that some items may be more important than the others, and mask important results. In these cases, items can be weighted to contribute more or less significantly to a total score. Secondly, the different scales use different metrics and therefore cannot be directly compared (242). If items are missing from a scale, this is also a challenge when the total score is dependent on all the items; this can be treated in different ways. The patient may have skipped the question by coincidence or intentionally; they may have perceived it as not applicable or difficult to understand. Missing items are often included in the calculation of the scale scores. The missing item can be replaced by the mean score of the completed items, or one could calculate a mean score of all completed items, however both possibilities affect the total score (242). Data quality in terms of levels of missing data and score distributions at the item level have seldom been systematically assessed in earlier studies on AUSCAN or FIHOA, but is a criterion that has been recommended in the evaluation of PROs (24;33). In the current study, acceptability to patients was supported by the low levels of missing data, as the majority of items had five or fewer missing responses.

Comparable studies have used different methods for validation, i.e. assessments of homogeneity by Bland-Altman plots to visualize the distribution of the differences (316) that could have been used to display test-retest scorings, where in this study Kappa was chosen. A more extensive 'Rash analysis' could alternatively have been applied to evaluate the scales, however this non-classical method was considered more difficult to apprehend, and was performed later in a separate study (317).

The assessments included in Paper II and III were influenced by previous studies. To assess hand function in HOA, both self-reported and performance-based measures are recommended. AUSCAN and FIHOA are recommended PROs, and the Moberg picking-up test is a recommended performance test (263). Self-reported and performance-based instruments measure different constructs (82); thus finding a perfect correlation between them would be unlikely. The choice of preferred instruments for measuring the impact of OA is not agreed on, but the results of PROs are used to make important decisions about patient care, an important reason for assignment if the measures are valid and relevant (313).

Two important studies assessing the PROs for functioning in HOA were performed prior to Paper II. Dreiser et al. tested the FIHOA in French while developing the scale that was based on patient interviews (261;262), and Bellamy et al. evaluated the scale they had developed themselves in English (260). This highlights the need for an external evaluation of these PROs. The Flemish version of the AUSCAN and FIHOA were tested and published after the beginning of this thesis (316) using a similar methodology as the current study. Both scales were tested in patients with HOA recruited from specialist care (260;261). It is possible that these patients are not representative for HOA patients in general, however all studies used comparable populations developing and testing the PROs, and this facilitates comparisons between the studies.

Comparing disease impact across disease localizations was made possible using a cross-sectional approach. A cross-sectional design examines relationships between different phenomena at one point in time. However, when associations are measured concurrently, it is unclear which phenomena influenced the others. The method thus limited the results to being hypothesis-generating only. It would be interesting to observe these patients in a longitudinal design to follow how disease impact changes over time.

Another challenge is that when multiple comparisons are performed; there is a risk of multiple testing biases. The more comparisons made, the greater the chance that statistically significant differences can occur by chance. It was important to stay true to the hypotheses stated a priori. Since applying the Bonferroni test did not change the main results significantly and the study was explorative and thus only hypothesis-generating, these corrections were not applied in Paper III. Consensus on recommended outcomes in HOA can contribute to reducing the risk of multiple comparison bias in future research.

5.1.2 Representativity of study population

A major problem in all observational studies is the selection of subjects, because if the sample is not representative of the population, then, according to Altman, “the results will be unreliable and of dubious worth” (318). The possibility of extrapolating the results is dependent on the representativity of the study population. This problem is a form of

selection bias, an error as a result of the conduct or design of the study, alongside other problematic factors like non-random sample, hard to trace patients omitted, number of non-participants, and systematic differences between those who consent to participate and those who do not. Additionally, there is a chance of publication bias, where RCTs with positive results tend to be reported and published more frequently than studies with negative results. Systematic reviews frequently include only published studies, and this may therefore have influenced the results of the overview.

The systematic reviews in Paper I (12;204;207;319) included results of comparisons based on 27-318 patients. The patients included had hand OA defined by different methods because the primary studies did not use the ACR criteria. HOA is a clinical diagnosis and all patients in Paper II fulfilled the ACR clinical criteria for HOA with both pain and structural signs, which indicate that the patients included had a well- established disease. This may have excluded early HOA and has implications for extrapolating the results to this group of patients. The patients included in Paper III had HOA confirmed by a rheumatologist. Psoriatic arthritis, rheumatoid arthritis and haemochromatosis were not included in the studies; however it may be possible that these diagnoses will appear in a future follow-up of this population due to differential diagnostic challenges.

The health care systems are different across the world, in some countries patients with OA are treated in primary care, in others patients with OA are not treated at all. The Norwegian health care system is organized in such a way that patients with hand problems primarily seek help with their general practitioner, and if indicated they are referred to specialist care. Especially if symptoms are difficult to treat in primary care, are too persistent, or if there are other present complex factors, patients can be referred to specialist care for evaluation. Study II and III included only patients recruited from specialist care and it should be considered whether this population is representative for patients with OA in general. It is predominantly plausible that patients in specialist care are more severely affected, have a higher degree of hand-related disease, have more complex problems or co-morbidities, and may be more perceptive about their disease than the selection of patients in general practice. Therefore it would have been especially interesting to compare disease impact in a population based in specialist care with that of one based in primary care.

In Papers II and III elderly and female patients are overrepresented (Table 12). Despite only slightly more frequent radiographic HOA among women than men (116), symptomatic OA is about twice as common in women (116). Age-standardised prevalence of erosive and symptomatic OA is also higher in women (9.9% vs. 3.3%, and 15.9% vs. 8.2%) than in men (116) and these may thus also be more frequently referred to specialist care. Women live longer, and consult general physicians for OA-related problems in Norway almost 75% more often than men (320). In general practice, the median pain score of hand, hip and knee OA has been reported to be higher in women than in men (71), comparable to other musculoskeletal diseases (321). There are indications that women generally report a higher chronic pain prevalence than men (322). A Canadian population-based study showed that a higher percentage of women than men reported having been diagnosed with arthritis, they were older at a higher percentage, more often physically inactive and more frequently reporting functional limitations (323). Patients seeking help for hip and knee OA in primary care in a Spanish study were 74% women and mean 71 years old, thus older than the patients in the current study from specialist care (324). Age and female gender have both been found to be associated with OA (325). Due to the knowledge about these factors, a significantly higher representation of elderly and women was expected prior to the study. In Paper II, the population was older and had an established disease also because patients were recruited among patients diagnosed in 2001-2003, thus not representing early HOA. In Paper III, for example patients with HOA were mean 63 years old, and patients with knee OA mean 61 years old (Table 12), thus age and gender were included as possible confounders in the analyses due to the possibility of the factors being risk factors.

It is known that European populations are more physically active than other populations from the USA, Canada or Australia (326), and this may imply lower BMI values, as found in our populations, possibly due to more physical activity like walking or cycling in European countries (326) due possibly also to the frequency of winter activities like cross-country or downhill skiing, very frequently performed in Scandinavia. The current population may thus not be representative for patient populations from other continents.

Data on ethnicity was not collected in Paper II or III but this factor might influence disease impact and localizations affected. Studies show that hand and hip OA is less common in Chinese than Americans (124), and that African Americans may be less likely than

Caucasians to have radiographic HOA but more likely to have radiographic knee OA (327). Generally most individuals included in this thesis were of Norwegian origin.

In Paper III, all patients referred to a specialist outpatient clinic for their OA who fulfilled the inclusion criteria were asked to participate, and 77% of those invited were included in the study. In Paper II, 76% (209 of 275) of potential patients were included. The reasons for refusing inclusion were not recorded or assessed and thus serve as a potential bias for the representativity of these patient populations, so there is no possibility of knowing if the individuals who declined were significantly different from those who consented. Paper III showed that a high percentage of patients referred to the OA clinic had HOA.

Due to the clinical approach of the study, the localization groups did not represent a normal distribution of the OA diagnosis from the population (120). A reason for this may be that the study was performed at a rheumatology department. In a similar study with OA patients referred to a specialist rheumatology clinic in United Kingdom, knee OA was more common (41.2%), while hand (30%) and hip (19%) OA were less frequent (328). Another reason for the high representation on HOA complaints in the current population may be that general physicians refer these patients to specialist care due to little accessible knowledge about the evidence of effect of various treatments for HOA (329;330) in addition to a lack of physician treatment options such as disease-modifying drugs. HOA is however increasingly suggested to be the most common localization of OA in specialist care (331), and it is more common than previously thought. A recent systematic review indicate that HOA may be the most prevalent peripheral OA joint localization (332).

Paper III was also limited by the lack of consensus on criteria for the diagnosis of generalized disease, and due to the cross sectional study design, the associations between the localization groups could not be confirmed over time, which restricts the ability to draw conclusions on the directions of the associations examined. Some of the associations may also be explained by factors not studied, this will be examined in future studies.

Table 12. Demographic characteristics of the two patient populations

Factor	Paper II		Paper III			
	HOA n=128 population	HOA n=40 test-retest patients (of the n=128)	OA n=270 population hand	OA (n=33) population hip	OA (n=75) population knee	OA (n=30) population generalized
Age (years)	68.6 (5.8)	67.5 (4.3)	63.2 (0.5)	61.0 (1.4)	60.8 (1.1)	63.2 (1.5)
Female no. (%)	117 (91)	37 (93)	240 (89)	26 (78)	50 (67)	27 (90)
Pain	41.7 (23.8) *	44.4 (25.2) *	5.2 (0.1) **	6.1 (0.4) **	5.2 (0.3) **	5.1 (0.4) **
Fatigue	45.2 (29.0) *	46.4 (31.2) *	3.9 (0.2) **	4.9 (0.6) **	4.8 (0.3) **	4.5 (0.6) **

*VAS=0-100, 0= no pain **NRS=0-10, 0=no pain

In sum, the populations available for these studies included mainly patients with moderate to severe HOA recruited from specialist care. The representativity of the populations studied is limited by an overrepresentation of women and elderly, but this may be generalized to other OA patient populations from specialist care.

5.1.3 Clinical assessment

Being female and having multiple joints radiographically affected are reported as possible predictors for functional impairments measured by both FIHOA and AUSCAN (333). However, the relationship between function and radiographic symptoms is not strong (9).

The populations studied in Paper II and III were on average above 60 years and scored significantly on pain. Age and pain severity have been reported to be among the features strongly associated with limited hand functioning in older people with hand problems (334).

PROs in HOA assess the domains they have been developed for, however new information about other important domains of disease impact in HOA have been published recently. These include Personal factors like psychological changes and aesthetic discomfort (335). It has become known that aesthetic discomfort is a challenge for many patients with HOA, especially in women (336) and has been linked to erosive disease, anxiety, depression and

poor HRQOL (337). Unfortunately, aesthetic discomfort is not included in the PROs assessed in Paper II. Considering the focus on patient-centred outcomes and patient reports over the last years, assessing aesthetic damage should have been included in Paper III as well. It could have added to the knowledge about what to measure, and how to measure function and disease impact.

Assessing the presence of nodes formally could also have been included in papers II and III and possibly added information about structural damage and future disease impact. A recent study found that the presence of multiple nodes in the interphalangeal joints was associated with an increased risk of total hip and knee replacements compared to patients without multiple nodes (338), but this was not in the scope of this thesis.

Hand strength is important for hand function, however the method of use of the Jamar dynamometer in studies varies considerably, i.e. how many attempts the patients get at performing the task, reporting maximum or using either hand or the dominant hand (339). The Jamar dynamometer is reported to have high levels of test-retest reliability ($ICC > 0.85$) for trial one, mean values of two trials, or the best out of three trials (340). In this study we used the best trial out of two attempts for each hand. The patients in Paper II performed mean 19 kg on grip strength, comparable to another female OA population from specialist care (50). A study of change in grip strength in 32 healthy and 10 disabled women showed that the change should be at least 6 kg to be clinically meaningful (341), which may be large in a group with reduced levels of hand strength at baseline such as the current population. A 20% change has been used as an important change in studies on grip strength using another hand dynamometer (Grippit) which is a comparable assessment instrument to the Jamar (342).

All patients in Paper II fulfilled the ACR criteria. They are classification criteria developed for selecting patients for trials, and symptoms most days of the prior month is mandatory, in combination with structural change for fulfilling these criteria. EULAR published their recommendations for diagnosing HOA during the years spent on this thesis and were thus not used in the current project. These recommendations are less complex than the ACR criteria and do not warrant long term symptoms; they include the presence of Heberden nodes, family history of nodes, age above 40, and joint space narrowing (46), which may capture people with milder disease.

There is no agreement on criteria for generalized OA. Several of the definitions of generalized OA include the presence of nodules, which would indicate that patients with nodular HOA have generalized OA. HOA may be an indicator of a more generalized disease which may involve other joints in addition to the hand (343). HOA and generalized disease seem closely linked. HOA is some times hypothesized to be the beginning of generalized disease since HOA is associated with OA at other localizations (344). The long-lasting character of persistent pain in OA over time may change normal pain processing (239), and OA pain may be less localized in advanced disease or in combination with other factors like distress, co-morbidity or negative emotions. It is known that emotions can change the perception of pain (345). Further, radiographic OA is more common than symptomatic OA, and it is possible that a more generalized pain, negative emotions and sensitisation process may result in a more generalized pain pattern in advanced OA, leading to a more generalized pattern of symptomatology. It seems plausible that generalized OA includes HOA; however HOA does not necessarily include generalized disease, but it seems as if the two may be interrelated on several levels. Consensus on criteria for generalized OA may facilitate comparisons of the impact of different OA sites in the future.

The main approach in Paper III was to focus on the clinical disease impact, but additional radiographic data on structural joint damage could have brought a new dimension to the comparisons. Imaging was a part of the clinical examination when clinically indicated. Many patients were referred after imaging had been performed in primary care. Radiographic assessments should if optimal be assessed in all joints to contribute to the knowledge about the association between symptomatic and radiographic OA, but this would have warranted other aims, another set of ethics and judgements of possible side-effects; and was not the focus in this thesis. The development of imaging methods in HOA has increased knowledge about HOA while this project was ongoing. Studies have shown that ultrasound and MRI can detect synovitis in HOA, and MRI can detect bone marrow lesions. Both synovitis and bone marrow lesions seem to be associated with pain in HOA (346). Ultrasound and MRI can detect more joints with erosions than conventional radiographs, i.e. possibly indicating that erosive HOA can be more frequent than reported in studies up until now (116;346).

Disease duration could not be exactly recorded in the patients; disease onset is difficult to assess in OA, and it is unlikely that data on disease duration from a clinical setting would be

reliable; however including this feature in Paper III could have been valuable. Also, it was not systematically registered which hand joints were involved in the studies. Recent studies have suggested that this feature could be relevant to future disease impact. CMC-1 OA has been reported associated with higher levels of impairments and disability than DIP and PIP OA (347).

Frequent co-morbidities were assessed in Paper III, and the patients had on average two other diseases. More knowledge about co-morbidity and mortality risk in OA has emerged recently. Mortality has been associated with co-morbidity and side-effects of pharmacological treatments (303;348;349). Still, there are indications that many patients with OA treated for known gastrointestinal and cardiovascular co-morbidities receive pharmacological treatment known to affect these comorbidities negatively (324). Thus, assessing co-morbidity may be important to risk reduction and modifying future disease impact in OA (350).

More knowledge about the patient perspective in HOA research has become available after the start of the PhD project. Patients have expressed a lack of information about the impact of HOA (351). This study has contributed with more knowledge concerning this issue.

5.2. Main results

The results of the studies will be discussed in the light of the current evidence base.

5.2.1 Non-pharmacological management of HOA

There is an increasing amount of research-based evidence available through publications, indicating a need to sum up and make evidence more easily accessible for the different stakeholders. An overview comprises evidence from several reviews into one simple user-friendly table easily accessible to busy clinicians. A systematic transparent method was used to summarize research-based evidence of non-pharmacological and non-surgical management of HOA. The overview was based on systematic literature searches, assessment of study quality and synthesis of results. This method also ensured the possibility

of comparing results with the existing overviews on hip and knee OA. It was confirmed that the evidence base for the management of HOA was thinner than for hip and knee OA.

The results of the overview of evidence for the effectiveness of non-pharmacological and non-surgical interventions for HOA showed that there was insufficient high-quality evidence available. There was some evidence from single RCTs indicating a beneficial pain relieving effect of capsaicin and improved function from the combined intervention of exercise and education. The paucity of primary studies available about non-pharmacological management of HOA limits the scope of the systematic reviews, and this again limits the content of overviews in the field. It is therefore important to emphasize that there is an important difference between 'no existing evidence' on a certain scientific level, and 'evidence of no effect'.

Only evidence from systematic reviews was reported, and if no systematic review existed for a type of intervention, it was not included. Primary studies were only consulted in the overview due to unclear and inconsistent reporting of the results in the systematic reviews. A limitation of such an overview is the possibility of excluding the most novel evidence from primary studies. The review by Zhang et al. is the most recent of the included reviews that addresses all non-pharmacological treatments. They included studies published up until January 2006, and could only identify a few relevant primary studies (RCTs and CCTs). For example, they identified only one study on education, two on exercises/yoga, one on TENS, one on laser and three on splint/gloves. It is unlikely that a substantial number of new studies published between the most recent systematic review we have included, and the overview, would have altered our findings.

The systematic reviews included were of variable quality and included heterogeneous trials that limited the possibilities of quantitative pooling; in addition only a few systematic reviews were available in the field of research. This led to a weaker general contribution to the knowledge about treatment effects, but important areas for future research were detected. This is not an unusual finding in evidence-based practice that prefers knowledge from high quality studies over other types of evidence. Evidence-based practice acknowledges bias and aims at minimizing this in studies, but when the theoretically best available studies are absent, one can use the best research-based evidence available. Other types of studies, patient and clinician knowledge are also valued. Clinicians need to make

use of the various forms of evidence when meeting an individual patient. Overviews may be important tools to guide directions in choice of interventions, but they might not be useful for deciding how interventions should specifically be carried out on the individual level. Deciding on the type, dose and timing of interventions should be a shared decision between the clinician and patient in each clinical setting. Additionally, the patient that exactly represents the average population in a RCT probably does not exist (352).

Systematic reviews of non-pharmacological care often include complex interventions with more than one simple intervention affecting and being affected by the specific question of the systematic review (353). There is thus not just a problem of heterogeneity of included patients but also of the interventions applied. However, overviews provide information on a “mean” effect, regardless of the amount of responders or non-responders.

The results of Paper I show that the same evidence from primary studies could be presented differently and possibly also in conflicting ways by different systematic reviews. Detecting and clarifying this is therefore an important task for overviews.

Two relevant recently published systematic reviews add to the evidence of the overview in this thesis: they both included newer primary studies; one included studies of varying designs, and one included samples with other forms of arthritis (330;354). They both found support from the literature for applying exercise, thermotherapy, orthoses and joint protection.

In addition to a small amount of high quality evidence-based knowledge about managing HOA, there are indications that the little knowledge which does exist is not being used optimally by clinicians. This hinders optimal information, advice and management in clinical care. A recent qualitative study show that patients report being confused by contrasting advice in the health care system, they are, e.g. concerned that exercising and moving their hands may impact OA development negatively (351). Research about what facilitates and limits the use of recommendations for good clinical practice in OA is among studies currently being performed by the EU and EULAR in cooperation (the EUMUSC.NET project) (355).

Posterior to this paper the evidence-based knowledge about managing OA has increased and this is the focus of the discussion below.

Guidelines

The recently published ACR recommendations added HOA to hip and knee OA in the new advice for non-surgical management of OA (356). The recommendations for both pharmacological and non-pharmacological management of HOA were however only conditionally offered based on the meager high quality evidence. The results of Paper I was included in this recommendation. Assessments, joint protection, assistive devices, thermotherapy and splints were conditionally recommended, based mainly on expert opinion. There were strong recommendations for non-pharmacological management for hip and knee OA, however, due to considerable available evidence, but pharmacological management was also only conditionally advised for HOA.

Systematic reviews

Paper I concluded that there was insufficient high-quality evidence regarding non-pharmacological and non-surgical interventions for hand osteoarthritis. Systematic reviews have been conducted after the initiation of this thesis and could be assessed for inclusion in an update of the overview (Paper I).

Most of the newer systematic reviews still seem to conclude in agreement with Paper I that the evidence base for non-pharmacological treatments in HOA is weak. Two systematic reviews including different non-pharmacological trials for HOA reported that most studies included had major methodological weaknesses, and lacked proper outcome measures, methods for randomization, and description of blinding (204;357).

A systematic review on the effects of splints and exercises in HOA published in 2011 found that splinting reduced pain on short and long term through combining two RCTs in a meta-analysis, additionally there was some evidence for pain reduction, improved flexibility and strength related to hand exercises and promising results of combining splints and exercises (358). Including these results in an update of Paper I would strengthen the results of applying splints in the management of HOA.

A review by Valdes and Marik (354) concluded that literature supports the use of orthoses, exercise, thermotherapy and joint protection in HOA. A review on the effect of spa, mud and magnetic therapy compared to none or other interventions for OA included small trials with small samples that included multiple testing were included, increasing the risk for bias (319). Another review about the effect of spa therapy on hand and knee OA was conducted by Francon & Forestier (359), they reviewed RCTs only and concluded that these therapies could be beneficial; but that evidence was too weak to allow definitive conclusions.

A very recent review on rehabilitative interventions for people with HOA by Ye et al. (330) however, concluded differently than the other reviews, possibly e.g. due to the inclusion of different types of primary studies, such as RCTs, quasi RCTs and crossover trials. Their assessment of methodological quality was based on the PEDro scale with a cut-off of 6/10 points to allow inclusion. The 10 studies included were on exercise (n=3), on thermotherapy (n=2), low level laser (n=2), splint (n=1), massage (n=1), and acupuncture (n=1). The authors concluded that a night splint can improve pain, function, strength and range of motion; exercise can improve strength based on data from three conflicting studies; and that laser can improve the range of motion of the CMC-1 joint. One study showed beneficial effects of education combined with exercise (330). Several of the included primary studies that served as basis for this review were published after the systematic search for reviews in Paper I. This emphasizes the need for updating the overview.

Primary studies

Paper I pointed out the limited research evidence for different HOA interventions and concluded that there was a need for more trials of non-pharmacological and non-surgical interventions. The overviews are limited to evidence from systematic reviews, and systematic reviews usually include high quality trials only, so it is important that the primary studies are of high methodological quality.

The conclusions in Paper I about the effect of splinting the thumb base were based on weak studies with only few included patients. The evidence base continuously increases and conducting systematic reviews opens up the possibility of combining results from smaller studies. There is some evidence from RCTs not yet included in systematic reviews, for example one randomised crossover trial on the effect of two different splints, with twice as many included patients as the other primary studies, has recently been published which

includes data from 56 patients with the primary outcome AUSCAN function. The results showed no statistically significant differences between the splints, but pain decreased slightly more with the custom-made splint, while the prefabricated one was most preferred (360). Paper I did not include any results for assistive devices or balneotherapy. Recently, the use of assistive devices has shown improved performance and satisfaction with performance in patients with HOA (361). A recent small single blind study on the effect of balneotherapy on HOA from Hungary (362) did not present any quantitative pooling of data, but authors concluded that 38 degrees thermal water in combination with magnetotherapy, compared to 36 degrees thermal water 3 times a week for 5 weeks can improve pinch strength and HAQ.

New high quality studies are awaited shortly that may contribute significantly to the evidence-base for non-pharmacological management of HOA (363;364).

Alternative and complementary medicine for OA in general

Alternative and complementary interventions specifically for the hand joint are rarely studied. Paper I detected some evidence for pain relief from topical capsaicin compared with placebo. The efficacy of topical Capsaicin, with ingredients from red hot chilli peppers has been studied in different OA joints (365;366) and found to relieve pain. Several RCTs with positive results on symptoms and pain have been conducted on avocado soybean oil (ASU) for osteoarthritis in the hip or knee (365;367;368). Rosehip powder (*Rosa Canina*) has also been suggested to be beneficial (366;368;369).

Regardless of the methods used, most studies conclude in concordance with the results in Paper I, emphasizing the need for more high quality studies about the effect of treatments in HOA.

5.2.2 Assessing PROs for HOA

With the purpose of improving the access of PROs measuring functioning in HOA in clinical care and studies, AUSCAN and FIHOA were assessed for data quality, reliability and validity. Research on PROs has developed through the years spent on this thesis. Including the patient perspective in outcome measures like the impact of living with a

disease has led to a greater reliance on PROs (370). This is especially important in evaluating the effect of complex interventions often used within the field of rheumatology where there are several treatments used in combination with each other tailored to the individual patient (371).

Concurrent evaluation of instruments is recommended when there is a lack of evidence for the comparative performance of two potentially appropriate instruments (33). In the Norwegian setting, AUSCAN and FIHOA had comparable evidence for data quality, internal consistency, test-retest reliability as well as internal and external construct validity. Both instruments showed evidence for reliability and validity for measuring function in HOA. These results add to the findings from other studies from the literature, which were not sufficient for determining the most appropriate instrument due to differences in design, methods and limited concurrent evaluation.

Items scores were more normally distributed for the AUSCAN. There was evidence of a floor effect for the FIHOA items with mean scores between 0.53 and 1.32 on the four-point scale. The AUSCAN has earlier been found to be more responsive in a comparative evaluation of the two instruments (16) which has potential implications for responsiveness. Both instruments had adequate evidence for internal validity based on the findings of classical Principal Component Analyses (PCA). The instrument scales also had satisfactory internal consistency based on the results of item-total correlation and Cronbach's alpha. High levels of Cronbach's alpha however may also be an indication of item redundancy which could have been further explored. In general, test-retest reliability was satisfactory for both instruments and similar to other studies (16;17;24).

The development of new measures may sometimes be tempting, but when some measures in an area are in use there is a great advantage that results can be compared across populations and time. A few of the items in the included PROs may be less relevant in our population due to cultural issues and environmental factors. Especially "turning doorknob/handle" and "turning taps" in AUSCAN and "sewing or using screwdriver" in FIHOA are less relevant in a Norwegian setting than where the items were developed. Doorknobs and taps are overall not designed to be turned but lifted or pressed, and the gender differences related to sewing or using screwdrivers are not evident in our cultural environment anymore. The

Norwegian research group suggested that patients could choose themselves which of the gender specific items they would answer.

The items 'clench your fist' and 'accept a handshake' performed more weakly than the other items of the FIHOA (PCA 0.52 and 0.64 respectively). This may suggest that these tasks are different from the others. Clenching a fist is a Body function, while the other items represent activities, and the degree of clenching the fist is important in determining if it is problematic or not. Acceptance of a handshake could depend on other factors than a disability of the specific functioning of the hand, and has previously been reported as difficult to link to the ICF (372). However, at the item level the FIHOA generally performed better than AUSCAN.

There are indications that the content of the FIHOA may be slightly more detailed including more precision items than the AUSCAN (317); AUSCAN captures pain and stiffness in addition to functioning, while the FIHOA is a purely functional scale. Higher FIHOA scores have also been associated with HOA-related structural damage through MRI (373), this has to our knowledge not been detected for AUSCAN. In another validation study, using Rasch analysis, the AUSCAN subscales, and FIHOA were both shown not to be uni-dimensional. However, deleting misfitting items improved the scales performance. The revised AUSCAN physical function subscore and the FIHOA both correlated well with performance measures such as the Moberg picking-up test and grip strength (317), which strengthens the validity of the scales. The exact time used for the administration of the scales are not reported, but the investigator administrated version of the FIHOA takes approximately 2.5 minutes to complete (262). Recording how much time patients used filling in the questionnaires would also have been relevant to feasibility, but was not included in the current study.

Forty patients were recruited for the test-retest analysis; this number is comparable to validations of the same outcome measures in other languages performed by other research groups (261). The low test-retest reliability for some of the items in AUSCAN may be explained by the fact that few sinks have turnable taps, and doorknobs are seldom found in Norwegian homes; that fastening jewellery may be mainly gender-specific, and lastly, that people with hand OA may often use both hands when carrying a pot. The results of test-retest also show that for real change to occur beyond measurement error, AUSCAN total

scores must change more than 0.76 on the 0–4 scale and FIHOA more than 5.55 on the 0–30 scale.

Strong correlations between FIHOA and AUSCAN total score as well as the subscales pain, stiffness and physical function suggest that both instruments measure similar constructs in this population. External construct validity based on the correlations with the other PROs and performance measures were also comparable for both instruments. In general, slightly stronger correlations were found for the FIHOA with the other functioning measures than with the AUSCAN total score due to the inclusion of the subscales pain and stiffness. The AUSCAN physical subscale and the FIHOA had similar levels of correlation for the majority of the comparisons. Instruments measuring a combination of ICF domains or constructs may mask true treatment effects in one domain because they capture several domains. On the other hand, assessing function in patients with HOA, which is a complex disease is not easy, and no single instrument can reflect all aspects of the disease. Strengths and weaknesses of including subscales from different domains in one total score should be considered when choosing outcome measures in studies or clinical care.

It is important to examine instruments in other settings than the one they were developed in, and by other research teams than the ones who developed them. In summary, both instruments are suitable for application. The brevity of the FIHOA makes it potentially more acceptable to patients. The FIHOA had higher test-retest reliability, but performed slightly more poorly than the AUSCAN in tests of data quality and external construct validity.

Due to the low proportion of men (9%) the discriminant capacity of the gender-specific FIHOA question could not be assessed in this study. Further comparisons of AUSCAN and FIHOA with respect to responsiveness in randomized controlled trials should be performed. The possibility of item redundancy should be further assessed for both instruments. Finally the appropriateness of the AUSCAN and FIHOA should be evaluated in the different subtypes of OA, including their ability to discriminate according to HOA severity.

Responsiveness was not included in the study. Self-reported measures of health status are often used in rheumatology research and clinical practice. However, they may not always correlate with more objective measures of disease activity, and may be influenced by other factors than the disease itself, such as mood, motivation and co-morbidity. Even the

simplest PROs like self-reported VAS, NRS or Likert scales of pain, fatigue and patient global disease activity may provide important information, although it is known that these measures show considerable variation over time (374).

Studies about outcome measures, and various treatment effects detected by these have been published since the beginning of this project, however, an updated review (204) concluded that there is still a lack of use of standardized outcome measures, and this still limits the results and possibilities for quantitative pooling (357) in meta-analyses and reviews.

5.2.3 Comparing disease impact in HOA to other localizations

Woolf et al. addressed how to measure the impact of musculoskeletal conditions (375) with health state, or disease impact as a part of the burden of disease. The burden of disease often includes personal, demographic, societal and economical factors, and disease impact can be understood as individual burden (7;129;325).

From the beginning of this project, only a few relevant results on the comparisons between localization groups in OA had been published in this field. In Paper III OA patients referred to specialist care reported considerable levels of disease impact across localizations. Patients scored above 5 on NRS pain, had on average 2 co-morbidities, and scored above 1.5 on emotional distress (HSCL-25, range 1-4). The patients reported high degrees of pain regardless of OA localization. On the other hand, this may be attributed to a general finding of chronic hand pain. A systematic review of hand problems in elderly adults found that age was associated with increased hand pain severity (334), this may also be applicable to the current population.

Despite a general focus on assessing HRQOL over the last years, a recent systematic review concluded that data on HRQOL in HOA is still limited (79). In Paper III, HRQOL was compared across OA localizations and showed that patients with hand OA scored better on pain ($p=0.001$, ANOVA) and SF-36 physical component ($p<0.001$), than the other localization groups, whereas no major differences were observed for the mental component ($p=0.07$). This may be the case because patients with HOA have better health-related physical functioning, or that the physical summary score (PCS) of the SF-36 mainly focuses

on lower extremity functioning. Research on knee OA has shown that female gender and comorbid conditions are associated with poorer HRQOL, and increasing age has been associated with poorer PCS, but improved mental component summary (MCS) (376). On the MCS, HOA patients in Paper III scored slightly poorer than the other groups, however the difference was minor, with an adjusted difference between the hand and hip group of β (95% CI) 2.39 (0.2, 4.6). Busija et al. (377) published a review on the burden of osteoarthritis in general. They concluded that patients with different chronic conditions generally score poorer than the population norm on the physical component of the SF-36 (PCS), but that there are only small differences for the mental component (MCS). These findings are in concordance with the results of Paper III.

In our study, the mean number of self-reported painful joints was 10 in hand OA, seven in patients with hip and knee OA, and 14 in patients with generalized disease. Joint pain comorbidity has been associated with higher levels of pain and distress, and impaired functioning and HRQOL in hip and knee OA (378) in a Dutch population.

The current sample of patients with HOA reported cardiac events in 9% and hypertension in 26%. The association between HOA and cardiovascular disease is currently under further exploration (94;344;379), and may have impact on future disease management.

Many patients in Paper III had a high BMI, especially the knee OA patients. Patients with generalized disease had a lower BMI (<25) than the other localization groups. The association between low limb osteoarthritis and overweight is well established, and reducing overweight can improve pain (ES 0.20 (95% CI 0.00, 0.39) (368). A systematic review has shown that there is an association between HOA and overweight (380), but there is yet no high quality evidence that weight reduction decreases hand symptoms in HOA (356). The mechanism that causes the relationship between OA and overweight is unknown. Biomechanical factors may play a role (381) as well as factors like cytokines and adipokines (382;383). The patients in Paper II and III were not as overweight as comparable populations in other studies; this may impact the generalizability of the findings.

Patients with HOA scored poorly on disease-specific functioning of the lower extremities and patients with lower extremity OA also scored poorly on disease-specific hand

functioning. This location and disease specific impaired functioning at other sites than the symptomatic OA is difficult to explain. Some patients with knee OA as their primary complaint could have HOA or hip OA as well, and vice versa. Why patients with HOA score poorer on WOMAC could also represent a more generalized response to localized disease, activity and participation restrictions that could affect symptom perception and report. There is also the possibility that the location-specific outcome measures may be less specific than originally accounted for. AUSCAN and WOMAC have to our knowledge not been tested to discriminate between different OA localizations. On the other hand, the Johnston County OA project also found that people with HOA had difficulties performing activities involving both upper and lower extremities, independent of hip or knee diagnoses (164). Since many people with OA seem to have multiple painful joints or affected joint areas, it would be helpful to have an instrument which captures functioning to detect more generalized OA. The latter will be on the future research agenda.

The frequency of patients with HOA included in Paper III may be a reflection of many referrals to specialist care, one explanation possibly being a lack of patient satisfaction with primary health care. Data from Portuguese OA patients and their physicians have been analyzed regarding priorities for treatment. While 41% of patients rated fine hand and finger movement as one of their top priorities for management, only 5% of the physicians rated this domain as a priority for treatment in clinical practice (384). The involvement of multidisciplinary teams or other health care professionals than physicians contributing to both an OA-specific and bio-psycho-social approach in primary care has been suggested as a promising approach for treating people with OA more optimally (385).

In Paper III, stiffness was considerable, and mean values varied between 5 and 6 on NRS between the different localization groups. Considering the significant impact of stiffness, it was surprising that none of the included reviews in Paper I reported on the outcome stiffness as a separate outcome. Addressing stiffness as an outcome in trials should be on the future research agenda.

The EULAR has initiated the development of measures of disease impact including domains perceived as important by patients. Rheumatoid Arthritis Impact of Disease (RAID) is an instrument including pain, function; sleep quality, coping and physical and emotional wellbeing (386). A comparable instrument for OA has not yet been developed but it is an

interesting method for establishing the perceived content of disease impact among patients and assesses what is rated most important for them.

Due to the clinical approach and the absence of longitudinal data, study III is only hypothesis-generating. It would however be interesting to follow these patients over time. Paper III show that patients with HOA have comparable disease impact regardless of localization, indicating a need for equal care between the sites affected. Patients scored poorly on disease-specific functioning in regions not diagnosed with OA, indicating a need for examining both upper and lower extremities in clinical practice.

6. Conclusions

Responding to the specific research questions posed the following answers can be given: Based on an overview of available systematic reviews, Paper I indicated insufficient high-quality evidence regarding non-pharmacological and non-surgical interventions for hand OA. Considering the limited literature in this area and the prevalence and impact of the disease, more primary studies and updated systematic reviews are warranted.

Despite the relative paucity of high quality evidence available, there was some evidence for the pain relieving effect of topical capsaicin as compared to placebo, and favourable functional outcomes for exercise and education compared to OA information alone. There was also some but limited evidence that splinting of the thumb CMC-1 joint reduces pain. However, the most striking finding was the paucity of available systematic reviews.

The results from Paper II show evidence for reliability and validity of two self-report instruments, AUSCAN and FIHOA, for measuring hand functioning in OA. As such they are both suitable alongside other generic and disease-specific PROs and performance measures for the comprehensive evaluation of patients with HOA.

Paper III demonstrates considerable disease impact for OA regardless of joint localization. Patients had high levels of pain, physical and mental disability, presence of several co-morbidities and increased BMI in localized disease. Further, the majority of patients

reported symptoms also at other sites than their primary OA localization. Health-related physical functioning was poorer in patients with hip and knee OA, but there were no major differences with respect to mental functioning between the groups.

6.1 Answers to research questions

I What is the existing evidence for effect of non-pharmacological and non-surgical interventions for HOA?

There is insufficient high-quality evidence regarding non-pharmacological and non-surgical interventions for hand OA. Considering the limited literature in this area and the prevalence and impact of the disease, more primary studies and updated systematic reviews are warranted.

II Are AUSCAN and FIHOA valid and reliable instruments for assessing hand functioning in patients with HOA?

There is evidence for reliability and validity for both AUSCAN and FIHOA for measuring hand functioning in OA. The versions need to be tested further with respect to responsiveness in RCTs and in different subtypes of HOA and localizations of OA.

III What is the disease impact in patients with hand OA compared to patients with hip, knee or generalized disease?

Patients with HOA, hip, knee and generalized OA experience considerable disease impact regardless of which joint region is affected. The majority of patients also reported symptoms also at other sites than the primary OA localization.

6.2 Clinical implications

For effectively treating symptoms in HOA, the best evidence-based interventions must be identified. This depends on access to good quality outcome measures. Valid outcome measures for HOA need to be applied in trials to bridge the gap of evidence-based knowledge between upper and lower limb OA. Knowledge about disease impact is relevant for what to treat and what to measure, in addition to identifying areas of future research.

The results of Paper I indicate that there is a lack of high quality evidence for the non-pharmacological management of HOA due to a paucity of high quality published papers and a lack of accessible validated outcome measures. Conducting trials on HOA functioning is easier with the presence of an easily accessible validated version of FIHOA.

The available evidence should further be considered for application and information in clinical care for people with HOA. One way of increasing the knowledge about evidence-based management of HOA is teaching the teachers. In Norway a patient education programme for osteoarthritis is developed and implemented, and it includes an overview of evidence-based management strategies that the teachers keep updated (387). This ensures that the knowledge is accessible to both clinicians and patients in OA educational settings and may increase use of evidence-based interventions evaluated with positive results. Diakonhjemmet Hospital now offers an education programme to patients as an indirect consequence of the current PhD project.

The validated PROs for functioning in HOA are implemented in HOA research projects, and the responsiveness is currently being assessed in a RCT. These PROs should also be considered for evaluation in the different localizations of OA and subtypes of HOA.

Considering the findings from Paper III, functioning in other sites than the primary OA localization as well as the level of emotional distress should be taken into account in the assessment and management of patients with OA.

6.3 Future perspectives

Currently, the field of rheumatology is preparing for effective drugs to improve the disease burden in OA. Having knowledge about disease impact and valid outcome measures to use for assessing the effects of new treatments is important. This also highlights the need for developing an instrument for assessing the disease impact perceived by patients in OA, as has been developed for RA (RAID) and probably also an easily accessible and valid instrument for disease outcomes (386).

This thesis has increased the insights about management, assessment and disease impact in HOA. An overview of high quality systematic reviews about non-pharmacological and non-surgical interventions for HOA was performed. PROs for hand function in HOA were translated and tested, and disease impact in HOA was described and compared to hip, knee and generalized OA in patients in specialist care. Hopefully this knowledge will be useful in clinical practice and future research.

Studying disease impact in one HOA population over time would contribute important knowledge about disease impact and progression, and is a part of the future research agenda. One study that followed patients with HOA over six years showed that pain and function improve over time in about 26% of cases, and deteriorate in up to 50% (388). A longitudinal approach may help detect factors predicting disease course and associations with clinical improvement or deterioration important to targeting future treatment.

The data collection from this thesis will continue, including a focus on imaging, and will hopefully contribute to answering other research questions in the future than the ones currently presented as well as contribute to improved understanding about management, assessment and disease impact in HOA. Using the validated outcome measures will contribute to increasing knowledge about disease impact and effect of various treatments in the future. Assessing the responsiveness of AUSCAN and FIHOA and performance measures are on the research agenda.

In order to contribute to the knowledge about the disease impact of HOA, studies examining co-morbidities, cardiovascular disease, how to alter stiffness, and the role of overweight related to functioning are needed. More knowledge about different phenotypes of OA, their

different outcomes and the impact of localization on functioning in HOA could help target treatment. Indicators for HOA progression are needed to better understand how to live with, assess and treat HOA.

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8. Erratum

In Paper II, errors have occurred in the paragraph ‘Health-related quality of life’ p. 5, referring to Table 2. 70.6 (19.2) should be 68.8 (1.3), 49.2 (21.0) should be 50.0 (2.5), 41.2 (7.4) should be 38.5 (0.7), 34.3 (8.8) should be 37.5 (1.8), 45.7 (5.5) should be 46.5 (0.5), and 48.7 (6.2) should be 47.5 (1.3). The numbers are correct in the table but not in the text.

9. Papers I – III

