Distal radius fracture: Incidence, malunion and osteoarthritis

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Distal radius fracture

Incidence, malunion and osteoarthritis

MUHANNED ALI
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MUHANNED ALI was born in Iraq in 1979, received his medical degree from Baghdad University in 2002. He completed his specialty training in orthopaedic surgery at Kristianstad-Hässleholm Hospitals, Sweden in 2014. His thesis work explores different aspect about the most common fracture in humans, distal radius fracture.

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Distal radius fracture

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Muhanned Ali

DOCTORAL DISSERTATION

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Distal radius fracture: Incidence, malunion and osteoarthritis

Abstract

Background:
Fractures of the distal radius are the most common fractures in adults, mostly affecting women after the age of 50 years due to a strong association with osteoporosis. Programs for screening and treating osteoporosis have been implemented, potentially affecting the incidence. Two well-known complications after a distal radius fracture are malunion and osteoarthritis (OA). Little is known about how malunion affects the patient outcomes on long-term, and generally the evidence regarding the association between malunion and patient-reported outcomes is unclear. The diagnosis of radiocarpal OA, based on visual assessment of wrist radiographs, is a time consuming process and is subjeted to reliability issues. There is a lack of standardized reproducible and efficient methods to assess radiocarpal OA.

Objectives and methods
1. Compare the incidence of distal radius fracture in Northeast Skåne in Sweden in 2016 with that in the same region's adult general population in 2001 using radiographs to identify and verify fracture cases.
2. Investigate the association between malunion and patiet-reported outcomes 12-14 years after a distal radius fracture by assessing the change in the disabilities of the arm, shoulder and hand (DASH) score over time according to malunion.
3. Evaluate the current evidence regarding the association between distal radius fracture malunion and patient-reported outcomes by systematic literature review and meta-analysis.
4. Compare the ability of a novel computer software to identify radiocarpal OA with the assessment performed independently by two surgeons according to the Kellgren-Lawrence classification.

Results:
The overall incidence of distal radius fracture in Northeast Skåne in Sweden in 2016 was 24% lower than the incidence in 2001. Compared to patients without malunion, those with malunion had significantly worse DASH scores from baseline to 12-14 years; the adjusted mean difference was 11 points (95% CI 4 to 17; $p = 0.002$). The systematic review and meta-analysis showed that adults with a malunited distal radius fracture had significantly worse patient-reported outcomes compared to patients without malunion with an overall effect size of 0.58 (95% CI, 0.39 to 0.77; $p<0,0001$). The computer software had 46% sensitivity and 70% specificity with the area under the curve (AUC) of 0.58 (95% CI 0.43 to 0.73), indicating poor ability to identify radiocarpal OA.

Conclusion:
The incidence of distal radius fracture has decreased in Northeast Skåne during the last two decades. Patients who sustain a distal radius fracture and heal with malunion are more likely to have worse subjective outcomes including activity limitations and pain on long-term. There is evidence that malunion of distal radius fracture has a moderate negative effect on patient-reported outcomes. The computer software for detection of OA could not detect OA of the radiocarpal joint.

Key words Distal radius fracture, incidence, malunion, radiocarpal osteoarthritis

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MADE IN SWEDEN

To my family, friends and colleagues

Table of Contents

List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. **Ali M**, Eiriksdottir A, Murtadha M, Åkesson A, Atroshi I. Incidence of distal radius fracture in a general population in southern Sweden in 2016 compared with 2001. *Osteoporos Int*. 2020;31(4):715-20.

II. **Ali M**, Brogren E, Wagner P, Atroshi I. Association between distal radial fracture malunion and patient-reported activity limitations: a long-term follow-up. *J Bone Joint Surg Am*. 2018;100(8):633-9.

III. **Ali M**, Rosales RS, Brogren E, Atroshi I. Association between distal radius fracture malunion and patient-reported disability: a systematic review and meta-analysis. *Submitted*.

IV. **Ali M**, Brogren E, Atroshi I. Assessment of a novel computer software in diagnosing radiocarpal osteoarthritis on plain radiographs of patients with previous distal radius fracture. *Osteoarth Cartil Open*. 2020;2(4):100112.

Abbreviations

AI	Artificial intelligence
AO	Arbeitsgemeinschaft für Osteosynthesefragen. The comprehensive classification of fractures (type A, extra-articular; type B, partial intra-articular; type C, complete intra-articular)
AUC	Area under the curve
CI	Confidence interval
DASH	Disabilities of the arm, shoulder and hand
DDD	Defined daily dose
GEE	Generalized estimating equations
ICC	Intraclass correlation coefficient
ICD	International classification of diseases
OA	Osteoarthritis
PROMs	Patient-reported outcome measures
PRWE	Patient-rated wrist evaluation
QUIPS	Quality in prognosis studies
RoB	Risk of bias
ROI	Region of interest
SD	Standard deviation
SMD	Standardized mean difference
TFCC	Triangular fibrocartilage complex
VAS	Visual analog scale

Introduction

Distal radius fracture is the most common fracture in humans [1-3]. This is not surprising considering the automatic reflexes commanding the hand and arm to reach out when a person trips or falls for any reason, with the purpose of preventing the fall or minimizing the effect of injury by taking the impact with one's hand [4].

Fractures of the distal radius affect both females and males and occur in all age groups from children to elderly people [5]. In younger individuals, it is more common that the fracture is caused by high energy trauma such as traffic accidents and falls from heights, or to be the result of accidents during sport or leisure activities [6]. In middle-aged and elderly people, distal radius fracture is more common in women due to a strong association with osteoporosis [7]. A low energy trauma, like fall in the same plane, is the usual cause of a wrist fracture in this age group [8].

Treating distal radius fractures is challenging. Different patient groups may have different needs with different treatment objectives, making management of distal radius fractures a complex and demanding issue. Untreated, distal radius fracture probably leads to activity limitation, impaired function and to a deformed, stiff and painful wrist. For the society, the economic burden of managing fractures of the distal radius is substantial and it is expected to increase, especially when taking into account the increasing number of patients with this injury and the wide use of internal fixation devices [9].

There are several treatment options for this fracture. Non-operative treatment using cast or orthosis, with or without closed reduction, is still the most common treatment method [5]. Surgical options include closed reduction with pinning or external fixation, or open reduction and internal fixation, where volar locking plates and fragment-specific fixation devices have gained popularity over the last two decades [5,10]. The choice of treatment depends on several factors, including fracture type and degree of displacement, patient's age and level of activity, the available treatment options, the routine practice of the treating center, the surgeon's experience, and patients' preferences.

The goal of treatment should be to achieve fracture healing, so that the patient can regain function to preinjury level, without pain and without causing additional damage caused by the intervention. If that is not possible to achieve, the goal would be healed fracture with the best possible outcome that is acceptable to the patient.

One factor that may affect the outcome is whether the fracture heals in displaced position (i.e., malunion), or if the fracture heals in a near anatomical position. It is still debated whether and to what extent malunion leads to worse patient-reported outcome and poor function. The question is vital since various treatment methods differ in their ability to restore anatomy.

Another possible complication related to distal radius fractures is development of post-traumatic radiocarpal osteoarthritis (OA). There is uncertainty regarding to what extent post-traumatic wrist OA affects hand function, and therefore there is a need to explore the relationship between post-traumatic wrist OA and patient-reported hand function. The diagnosis of radiocarpal OA is made by visual assessment of the wrist radiographs, usually performed by a radiologist or by an orthopaedic- or a hand surgeon. The procedure is subject to reliability issues affecting the ability to establish a correct diagnosis [11]. With the advances made in using artificial intelligence (AI) in medicine, including programs to improve diagnostic accuracy, such programs could help in the diagnosis of radiocarpal OA.

Background

Incidence of distal radius fracture

The incidence of distal radius fracture increases with age. In men, the increase in incidence is gradual, while in women the incidence increases rapidly after the age of 50 with a peak incidence after the age of 80 [12].

Several factors affect the incidence. In young adults, distal radius fracture is usually associated with high-energy trauma or sport and leisure activities [6], and an increase in outdoor activities would increase the incidence. In middle aged and elderly individuals, distal radius fracture is more often the result of a low-energy trauma due to a strong association with osteoporosis [7,8]. With a more fragile bone there is an increased risk of sustaining a wrist fracture when stretching out the hand trying to stop a fall. Osteoporosis increases with age, and women after menopause are more affected [13]. Therefore, the incidence of distal radius fracture increases with age and women are more vulnerable, especially after the age of 50 years [12]. When life expectancy increases the burden of distal radius fracture is expected to subsequently increase. Thus, demographic changes in a region, country or globally would have a direct impact on the incidence. Lifestyle can also affect the incidence. A more sedentary lifestyle increases the risk of osteoporosis and subsequently the incidence of distal radius fracture [14]. Physical activity and a more active lifestyle can improve bone mineral density, muscular strength and balance which would decrease the risk of sustaining a fracture [15]. In addition to lifestyle changes, fracture liaison services including pharmacological interventions to treat osteoporosis have been shown to decrease the fracture risk [16]. Thus, the implementation of programs for screening and treating osteoporosis would result in a lower incidence of osteoporotic fractures.

The incidence of distal radius fracture has shown a large variation worldwide [2,12,17-22]. Different incidence rates have been reported from different countries with the variation in incidence even evident across different regions within the same country. The Scandinavian countries have reported the highest incidence rates of distal radius fractures. In Bergen, Norway, the incidence of distal radius fracture in 1988 in persons aged 20 or older was 38 per 10,000 person-years [23]. In Reykjavik, Iceland, the incidence of distal radius fracture in residents aged 16 or older in 2004 was 27 per 10,000 person-years [24]. Similar incidence rates were reported from Sweden and Finland with a nationwide study from Sweden showing an incidence of 28 per 10,000 person-years in adults during 2010 [5], while a study from Oulu in Finland showed an incidence of 26 per 10,000 person-years in persons aged 16 and older during 2008 [20]. On the other hand, lower incidence rates of distal radius fracture have been reported from Asia. The incidence of distal radius fractures in people aged 20 or older in Taiwan between 2000 and 2007 was 15 per 10,000 person-years [22]. Even lower incidence rates were reported from Sakaiminato, Japan with an incidence of 8 per 10,000 person-years in persons aged 50 or older during the period 2010 to 2012 [25].

The incidence of distal radius fracture is changing over time. A population-based epidemiological study from Rochester, Minnesota, estimated the incidence of distal radius fractures in residents aged 35 or older over a 50-years period from 1945 to 1994. That study found an increase in incidence when comparing the periods 1945 to 1954 and 1955 to 1964 with the periods 1965 to 1974 and 1975 to 1984, then the study found a slight decrease in incidence during the period 1985 to 1994 [17]. Similarly, the incidence of distal radius fractures increased in Malmö, Sweden, when comparing two periods of time with 25 years apart, 1953-1957 and 1980-1981 [26]. A follow-up study in the same region during 1991-1992, showed a decrease in incidence, mainly due to a decreased incidence among women [27].

Seasonal variations in the incidence of distal radius fracture have also been observed. A study from Rochester, Minnesota about the effect of weather on the incidence of distal radius fracture found a strong seasonal pattern with increase in fracture risks in winter compared to summer. The study also found an association between adverse weather, such as in snowy and icy conditions, and increased fracture risk [28]. Another study of the incidence of distal radius fracture in patients aged 16 or older living in Oulu in Finland during 2008 found a clear seasonal variation with an increased fracture risk during winter and slippery conditions [20]. Furthermore, a study about the relationship between the incidence of distal radius fractures and mean annual temperature analysed data from Leicester, UK from 2007 to 2014, and concluded that the incidence of distal radius fracture increases with low temperature [29].

The studies that have reported the incidence of distal radius fracture have varied in study designs. While some studies used prospectively collected and radiograph-verified data to estimate the incidence [21,30], other studies retrospectively searched medical records to identify fracture cases which were then verified by examining the wrist radiographs [24]. On the other hand, some studies relied on register data only to estimate the incidence [12,19]. The variation in study design may also to some extent explain the difference in reported incidence rates.

In summary, the reported incidence of distal radius fracture varies between different regions and seems to change over time, which could be contributed to demographic, lifestyle, and climate differences as well as availability of fracture and osteoporosis prevention and treatment programs. The variations in study design could also explain some of the differences in reported incidence rates. New incidence estimates, preferably from the same geographical regions where previous incidence rates were calculated, using comparable study designs, are necessary to monitor the change in incidence and to assess the effectiveness of fracture prevention programs.

Treatment considerations

The aim of treating a distal radius fracture is to achieve fracture healing with optimally restored function and without symptoms or disability, or at least acceptable function and symptom state for the patient, and at a reasonable cost to the society. To achieve these goals different treatment methods, both non-surgical and surgical, are used [5]. The choice of treatment is a result of several considerations. Patient characteristics and preferences, the cause of the fracture and its characteristics, the surgeon's experience and preferences, the routines used at the treating center and the available resources may all play a role when deciding how to treat a distal radius fracture.

The age of the patient is an important factor influencing the preferred choice of treatment [31]. In elderly patients with a more fragile skeleton, it is more difficult to maintain good fracture alignment until healing, which might require a more stable fixation [32]. At the same time, the functional demands and level of activity in elderly patients may differ from that in younger patients [33], which also needs to be considered during the decision-making process regarding type of treatment. The patients' health status and comorbidities might also play a role. Comorbidities have been shown to slightly decrease the patient's odds of having surgical treatment [34]. When surgery is considered, comorbidities have been found to increase the chance of having open reduction and internal fixation and to decrease the likelihood of having percutaneous fixation [31]. The patient's socioeconomic or insurance status may in some countries influence the choice of treatment, depending on the healthcare system. Data from the federal health insurance (Medicare) in USA showed that as median household income increased, the odds of receiving open reduction and internal fixation increased [34]. Patients, after thorough information about the pros and cons of the different treatment methods, might prefer not to undergo surgical intervention, despite being recommended such treatment. Patient preferences need to be taken into account and respected. Parents and relatives may also in specific circumstances influence the choice of treatment, especially in patients unable to make own decisions, such as those with severe mental illness or dementia . In such situations, a discussion with relatives about the choice of treatment would be important.

The type of fracture (open or closed, intra-articular or extra-articular, displaced or non-displaced, degree of displacement and comminution), carpal alignment, the status of the soft tissues and skin, and possible other associated injuries may all influence the choice of treatment. Non-displaced fractures are usually treated non-surgically with cast [35], while displaced fractures need to be reduced and the reduction maintained until healing. Displaced intra-articular fractures more frequently need open reduction and internal fixation to restore joint congruity compared to extra-articular fractures [36]. Open fractures or presence of skin blisters need special management. Associated injuries such as fracture of the distal ulna, injury to the triangular fibrocartilage complex (TFCC) or injury to the scapholunate ligament may need special management and can influence the choice of treatment [37].

The management of distal radius fractures should always follow the concept of evidence-based medicine. When evidence is lacking or unclear, the surgeon's preferences and experience, in combination with local treatment traditions, become more influential [38]. While one surgeon may prefer, and is more familiar with, the volar locking plate when considering surgical treatment of a distal radius fracture, another surgeon may be more comfortable with the external fixation devices, and a third is used to pin fixation of the fracture. In some parts of the world there are no other options than closed manipulation of the fracture and fixation with a cast, regardless the type of the fracture [39]. There might be no fluoroscopy to assess quality of reduction and the treating surgeon or personnel rely only on their clinical judgment.

In summary, the choice of treatment of distal radius fractures depends on patient- and fracture related factors, the surgical experience and the treating facility's internal resources, as well as the level of the existing evidence.

Outcome measures

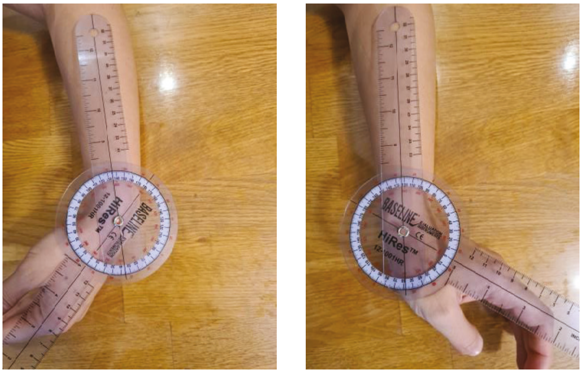
Traditionally, outcome measures after distal radius fractures have relied on surgeon-assessed measurements such as wrist and forearm range of motion, grip strength and on radiological outcome measures such as the dorsal angulation, ulnar variance, radial tilt and articular step-off and gap. However, these outcome measures do not necessarily reflect how patients perceive their function after the fracture and its management. Therefore, there has been a shift during the last decades towards using patient-reported outcome measures (PROMs) to assess treatment results.

Functional outcome measures

The physical outcome measures of distal radius fractures include wrist and forearm range of motion and grip strength of the hand. These outcomes were measured in *Paper II* in a standardized manner.

Flexion and extension of the wrist

Flexion and extension of the wrist are measured with the elbow joint flexed and the forearm in neutral position on the examination table with relaxed fingers. The patient is asked to actively flex and extend the wrist to the maximum possible position. With a Goniometer the degree of flexion and extension is measured by applying one arm of the Goniometer radially on the forearm, parallel to the radius bone while the other arm is placed radially parallel to the 2nd metacarpal bone (Figure 1).



Flexion Extension

Figure 1. Measuring flexion and extension of the wrist

Pronation and supination of the forearm

With the elbow in 90° of flexion next to the body and the forearm in neutral position, the patient is asked to maximally pronate and supinate the forearm. The examiner measures the pronation and supination by applying one arm of the Goniometer along the humerus and the other arm on the dorsal and volar aspect of the distal forearm respectively, proximal to the ulnar styloid process parallel with the wrist joint (Figure 2).

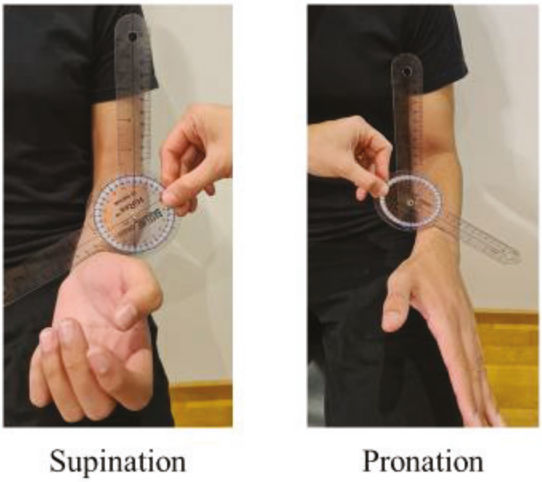


Figure 2. Measuring pronation and supination of the forearm

Grip strength

With the patient's elbow in 90° flexion, forearm in neutral position, and wrist in 0-30° extension, the examiner asks the patient to grip the handle of the dynamometer as hard as the patient can and then to relax. The procedure is repeated three times and the mean of the three measurements (in kg) is registered for each hand (Figure 3).

Figure 3. Grip strength measurement

Radiological assessment

A standard radiographical examination of the wrist joint includes a posteroanterior and a lateral view. Although plain radiographs of the wrist are usually sufficient to diagnose a fracture of the distal radius, CT scans may be needed, especially when planning for surgery in cases with complex intra-articular fractures. MRI might also be helpful, particularly, in diagnosing associated ligament injuries. The radiographic parameters usually assessed on standard plain radiographs include dorsal angulation, ulnar variance, radial inclination, intra-articular step-off and gap and the fracture type. The type of fracture is commonly classified according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) system, which is a comprehensive classification system with three main categories (type A, extra-articular; type B, partial intra-articular; type C, complete intra-articular) and 27 subgroups. The AO classification has been shown to be the most reliable fracture classification system when restricted to its three main types [87].

In this thesis dorsal angulation, ulnar variance and radial inclination were measured in a standardized manner.

Dorsal angulation

Dorsal angulation of the articular surface of the radius was measured on the lateral view as the angle between a line connecting the dorsal and palmar lips of the radius and a line perpendicular to the central axis of the radius [40] (Figure 4).

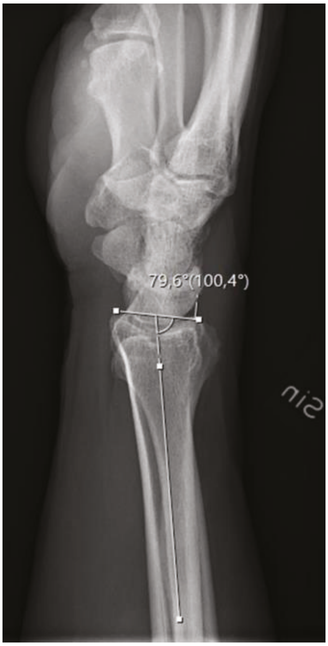


Figure 4. Measuring dorsal angulation

Ulnar variance

Ulnar variance was measured on the posteroanterior view as the distance between two parallel horizontal lines, one drawn from the mid-articular surface of the ulnar side of the radius toward the ulna and the other drawn along the carpal surface of the ulnar head [41] (Figure 5).

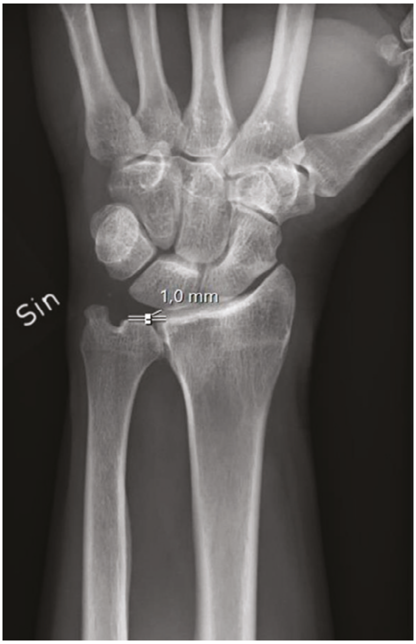


Figure 5. Measuring ulnar variance

Radial inclination

Radial inclination was measured on the posteroanterior view as the angle between a line drawn from the distal tip of the radial styloid to the mid-articular surface of the ulnar side of the radius and a line perpendicular to the long axis of the radius [40] (Figure 6).

Figure 6. Measuring radial inclination

Patient-reported outcome measures

PROMs are tools intending to assess the patient's perceived status of health or function at a specific time, through questionnaires or scales. When assessed before and after an event or an intervention, PROMs can give information about how a patient perceived these events. There are different types of PROMs, generic health status outcome measures and condition-specific, region-specific, or joint-specific outcome measures. In this thesis, results of the following PROMs are reported:

The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire

The questionnaire was developed by the American Academy of Orthopaedic Surgeons (AAOS), the Council of Musculoskeletal Specialty Societies (COMSS), and the Institute for Work and Health (Toronto, Ontario) [42]. The DASH is a 30-item self-administered region-specific questionnaire designed to assess upper extremity disability and symptoms. The items ask about the degree of difficulty in performing specific physical activities because of the arm, shoulder or hand problem (21 items), the severity of symptoms, including pain, activity-related pain, tingling, weakness and stiffness (5 items), as well as the problem's effect on social activities, work, sleep and the psychological impact of the upper extremity problems (4 items). Each item has 5 response choices, scored from one point (no difficulty or no symptom) to five points (unable to perform activity or very severe symptom). The item scores are then used to calculate a scale score ranging from 0 (no disability) to 100 (worst disability) [43]. The DASH score has previously shown to have good validity, reliability, and responsiveness in assessing various disorders of the upper extremity, including the assessment of recovery after distal radius fracture [44,45]. The Swedish version of DASH has also proven to be a reliable and valid instrument in assessing patient-reported outcomes in patients with upper-extremity musculoskeletal conditions [43].

QuickDASH

The QuickDASH is a shortened version of the DASH questionnaire comprising 11 items that measure the degree of difficulty in performing various physical activities due to a shoulder, arm, or hand problem (6 items); the severity of pain and tingling (2 items); and the problem's effect on social activities, work and sleep (3 items). Similar to the DASH, the QuickDASH has five response options with a scale score ranging from 0 (no disability) to 100 (worst disability) [46]. The QuickDASH has been shown to be reliable and valid [47].

The Patient-Rated Wrist Evaluation (PRWE) questionnaire

The PRWE is a 15-item patient-reported, wrist-specific outcome measure that assesses patient-rated pain and disability. The PRWE allows participants to rate their level of wrist pain (5 items) and disability during a variety of activities of daily living (10 items). Each item could be rated from 0 to 10 for a total possible score of 100 (0=best possible score, 100=worst possible score) [48]. The PRWE questionnaire, including its Swedish version, has been shown to be reliable, valid and responsive in patients with distal radius fracture [49,50].

The visual analog scale (VAS)

The VAS is a measure that has been used in different disciplines, including orthopaedic research [51-53]. Patients rate their symptoms, experiences, or attitudes by marking the point representing their perception of the severity of the measured construct on a straight line of fixed length. The ends represent the extreme limits of the parameter to be measured. In *Paper II* the patients were asked to rate the severity of wrist pain during the past month on a VAS from 0 (no pain) to 100 (worst possible pain). The patients also rated their satisfaction with their hand function on a VAS from 0 (fully satisfied) to 100 (very dissatisfied). The VAS has been shown to be reliable and valid in patients with musculoskeletal pain [54,55].

Malunion

Malunion is a term used to describe a fracture that has healed with abnormal alignment (Figure 7). While some studies have shown that healing of a distal radius fracture in non-anatomical alignment does not necessarily result in activity limitations or pain [56-58], other studies have found that malunion leads to greater patient disability and functional impairment [59-61] and that with increased deformity, the patients are more likely to suffer from worse symptoms and impaired function [62]. The level of activity and functional demands of the individual may influence whether malunion is tolerated by the patient.

As the literature yields conflicting results, no consensus exists, and there is still controversy regarding whether malunion is associated with worse functional outcomes and pain. This issue is important because it may influence the choice of treatment, as treatment methods differ in their ability to restore anatomy. In a previous study, malunion defined as dorsal angulation of >10° and/or ulnar variance of >3 mm, has been predicted to occur in 27% of minimally displaced fractures and in 60% of displaced fractures if treated with closed reduction and cast alone [63]. On the other hand, displaced distal radius fractures are less likely to heal with malunion if treated with open reduction and fixation with volar locking plate compared to closed reduction and cast or percutaneous pin fixation [64-66].

Guidelines from different countries have been developed and cut-off values of 10-20° in dorsal angulation, 2-3 mm in ulnar variance, 15° radial inclination and/or 2-3 mm intra-articular step-off have been proposed as cut-off values for “acceptable” alignment [67-71]. However, the evidence is still insufficient to demonstrate an association between these radiological parameters and patient-reported outcomes, and high-quality studies are needed to improve the evidence.

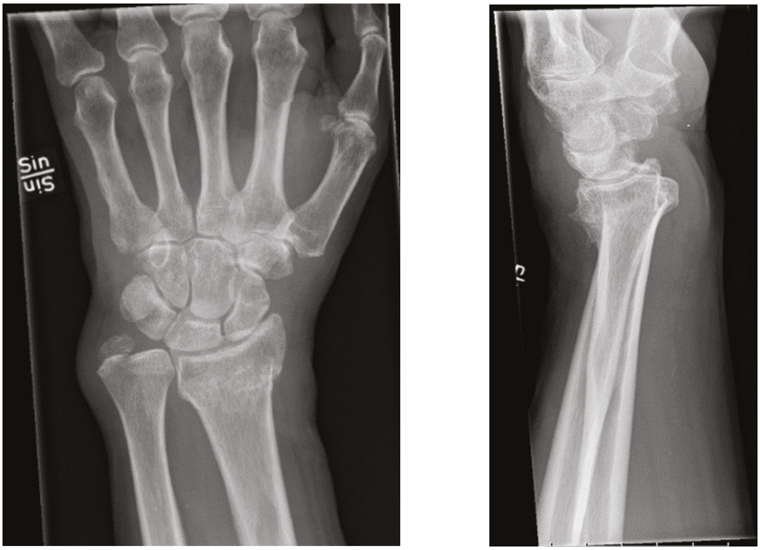


Figure 7. Malunited distal radius fracture

Osteoarthritis of the radiocarpal joint

Osteoarthritis is a degenerative joint disorder in which there is a progressive loss of articular cartilage, intra-articular synovial inflammation, deterioration in the architecture of the subchondral bone associated with new bone formation and capsular fibrosis. It can be classified as primary, when no obvious cause can be identified, or secondary when it follows a specific condition such as fracture and trauma, joint infection, ligamentous instability, congenital deformities or other disorders involving the joint as avascular necrosis of the lunate or scaphoid bones [72].

Osteoarthritis ranks among the 50 most common diseases and injuries globally, with OA of the knee affecting over 250 million people or about 4% of the world's population [73]. However, OA of the radiocarpal joint is uncommon and in most cases is post-traumatic, although a minority of patients develop primary wrist OA [74].

Although radiocarpal OA may be present without symptoms for many years, it can cause severe functional impairment [74]. Patients may develop wrist pain, stiffness, and weakness. Initially these symptoms occur intermittently in association with activities involving the wrist but as OA progress the symptoms may become constant. Radiocarpal OA is usually diagnosed on plain wrist radiographs based on joint space narrowing, subchondral sclerosis, and the presence of osteophytes and cysts. Radiographic criteria for the diagnosis were proposed by Kellgren and

Lawrence [11]. They classified OA of the radiocarpal joint into 5 grades (0, no osteoarthritic changes; 1, possible sclerosis and minimal osteophytes without joint space narrowing; 2, slight joint space narrowing and osteophytes; 3, moderate joint space narrowing, osteophytes, and possible cyst formation; 4, severe joint space narrowing, osteophytes, and sclerosis) (Figure 8). Beside being time-consuming, assessment of plain radiographs for OA may not be sensitive enough in detecting early OA. Artificial intelligence (AI) is being increasingly used in medicine, including applications for diagnostic purposes. It has been proposed that changes in the microarchitecture of subchondral bone can be detected in early OA, before cartilage degradation and subsequent joint space narrowing are visualized on radiographs [75,76]. Computerized software algorithms that use AI to assess the orderliness of the subchondral trabecular bone have been developed [77-80]. One such computerized texture algorithm (Image biopsy lab©, Vienna) has been shown to be capable of distinguishing knee joints with OA on plain radiographs, based on the changes seen in the microarchitecture of the subchondral bone, from those without OA with an accuracy of 84% [78]. The use of this software has been reported to increase the consistency between physicians when grading radiographic features of OA [81]. This novel computer software has not been assessed with regard to OA in the wrist joint. A software that can detect OA in the wrist joint in a standardized manner and with good accuracy can be of benefit in clinical research about wrist OA.

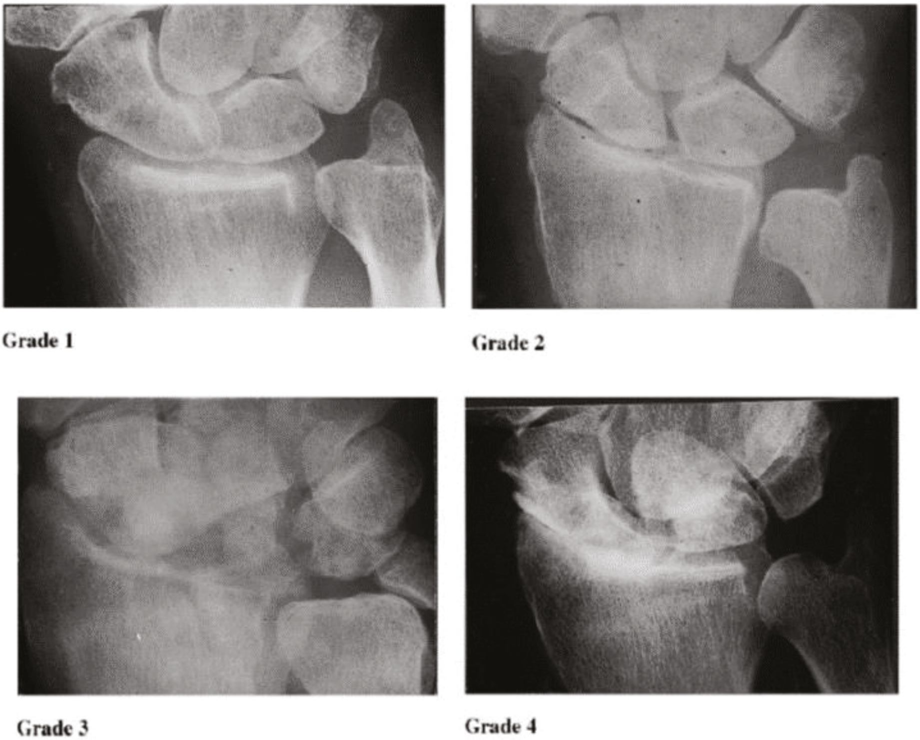


Figure 8. Kellgren-Lawrence grading of wrist osteoarthritis. *Ann Rheum Dis,* 1957. Reproduced with the permission of BMJ publishing [11]

Ulnar styloid fracture

A fracture of the ulnar styloid is commonly associated with a distal radius fracture [82]. Although, these fractures can be associated with a slower recovery of wrist flexion and grip strength [83], studies with up to three years follow-up time have shown that fractures of the ulnar styloid do not affect wrist function or patient-rated outcomes [83-86].

Aims

The general aim of this thesis was to contribute to current knowledge about distal radius fractures in adults and to the evidence-based care of patients with these fractures. The specific aims were:

1. To estimate the overall incidence of distal radius fractures and the incidence according to age, sex, and fracture characteristics in the adult population of Northeast Skåne in Sweden during 2016 and compare the incidence to that estimated in the same population during 2001.

2. To investigate the association between distal radius fracture malunion, and radiocarpal osteoarthritis and activity limitations, pain, satisfaction, and functional outcomes in the long term.

3. To assess the evidence regarding the association between distal radius fracture malunion and patient-reported disability by systematic review of the literature and meta-analysis.

4. To assess the ability of a novel computer software to diagnose radiocarpal osteoarthritis in patients with a previous distal radius fracture.

Patients and Methods

Design

Four different study designs were used in this thesis. *Paper I* was an epidemiological study designed to estimate the overall incidence of distal radius fracture and the incidence according to age, sex, and fracture characteristics in the adult population of Northeast Skåne in Sweden during 2016 and to compare the overall incidence with that estimated in the same population during 2001 using the same methodology. *Paper II* was a cohort study with long-term follow-up of patients who sustained a distal radius fracture 12-14 years earlier, aimed to investigate the association between fracture malunion and patient-reported disability and pain. *Paper III* was a systematic literature review with meta-analysis to assess whether distal radius fracture malunion is associated with greater patient-reported disability. *Paper IV* was a diagnostic study to assess the ability of a novel tool, a computer program trained using AI, to detect radiocarpal OA in patients with a previous distal radius fracture.

Data source

Paper I, II and *IV* were based on data from patients who were residents in Northeast Skåne in Sweden. Northeast Skåne is a region in southern Sweden with a population of about 187 000 inhabitants (2021). The region has only two hospitals; Kristianstad and Hässleholm hospitals, and these are the only health care facilities that manage acute distal radius fractures. Patients with acute distal radius fracture seek the emergency departments of Kristianstad or Hässleholm Hospitals. These patients are prospectively registered in the orthopaedic department's register, by an orthopaedic specialist or a resident, according to the International Classification of Diseases (ICD) as S52.50, S52.51, S52.60, and S52.61. Medical records of these patients can be easily retrieved using the unique personal identity number. All radiographs performed at Kristianstad Hospital and Hässleholm Hospital are stored in the radiology department's electronic database (common for the two hospitals).

Paper III was a systematic literature review and thus, data were extracted from the individual included studies.

Methods

Paper I

A previous prospective population-based study in the region of Northeast Skåne in southern Sweden, estimated that the overall incidence of distal radius fracture in the adult population in 2001 was 26 per 10,000 person-years [30]. In *Paper I*, a similar study was conducted with the aim to identify adults in the same region with a distal radius fracture during the period January 1 to December 31, 2016, to compare the incidence in 2016 with that in 2001. The inclusion criteria were acute fracture of the distal radius and age above 18 years. The exclusion criterion was residence outside the region at the time of fracture according to the National Population Register. Patients were identified in two steps. In the first step, the hospital's orthopaedic department's register was searched, using the ICD codes to identify cases that fulfilled the eligibility criteria. The radiographs of the identified fracture cases were retrieved from the radiology department database to verify the diagnosis. In a second step, all radiographs of the wrist performed for any reason at Kristianstad and Hässleholm hospitals during the study period were retrieved from the radiology department electronic database and examined to identify possible additional cases that might not have been registered in the orthopaedic department's patient register. The search in the orthopaedic department register and in the radiology department electronic database, extended from January 1, 2016 to January 31, 2017 to account to fracture cases from December 2016 that might had sought and thus, been registered during January 2017. Medical records of all identified fracture cases were reviewed to ascertain that they fulfilled the eligibility criteria, and to extract demographic data including, age, sex, fracture side and fracture date. The posteroanterior and the lateral radiographs of all identified cases were examined, independently by two reviewers, an orthopaedic surgeon and a radiologist, to confirm the diagnosis, to measure the dorsal angulation and ulnar variance and to classify the fracture according to the AO classification (type A, extra-articular; type B, partial intra-articular; type C, complete intra-articular) [87]. The interrater reliability of the two examiners' measurements was evaluated with the intraclass correlation coefficient (ICC). As in the previous study [30], fractures with dorsal angulation of − 20 to 5° and/or ulnar variance of up to 1 mm were considered as nondisplaced or minimally displaced, and fractures with greater displacement were considered as displaced.

To calculate the incidence, the age- and sex-specific general population data were obtained from Statistics Sweden (complete population data are reported for December 31 each year) [88]. The overall, age-specific (3 groups; 19-49, 50-79 and ≥80 years) and sex-specific incidence rates with the 95% confidence interval (CI) were calculated. Incidence rates according to fracture AO type and displacement were also calculated. The incidence rates were calculated as the number of individuals with fracture divided by the 2016 mid-year population and expressed as incidence per 10,000 person-years. The 2016 mid-year population was calculated, using exactly the same method used to calculate the 2001 mid-year population ([population on December 31, 2015 + population on December 31, 2016]/2). This was done for the total population and for the age- and sex-specific population subgroups. The overall and the age-specific incidence rates in 2016 and 2001 adjusting for age (5-year groups), sex and at-risk population were compared using Poisson regression analyses. A p-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp, Armonk, NY), and Stata Release 15 (Stata Corp College Station, TX).

Paper II

Residents of Northeast Skåne in Sweden, who presented with an acute distal radius fracture at Kristianstad and Hässleholm hospitals from January 2001 through Mars 2002 were previously enrolled in two prospective cohort studies to investigate the association between distal radius fracture malunion and patient-reported disability and impaired function up to two years after the fracture [62,89]. In *Paper II* an extended follow-up of the original cohort, 12-14 years after the fracture was performed to investigate the association between fracture malunion and the change in patient-reported activity limitations over time. The secondary objectives were to investigate the relationship between malunion, radiocarpal OA, and ulnar styloid nonunion at 12 to 14 years after the fracture, and patient-reported activity limitations, pain, satisfaction, range of motion and grip strength. The inclusion criteria for this long-term follow-up study were patients with a distal radius fracture who had been treated with cast, closed reduction and cast, or closed reduction and percutaneous surgical fixation, who had participated in the initial study, and patient age 18 to 65 years at the time of the fracture. The exclusion criteria for this long-term follow-up were current severe medical illness or cognitive disorder, subsequent refracture of the study wrist, and initial treatment with open reduction and internal fixation (due to the very small number of such patients).

From October 2014 through April 2015 (ie, 12 to 14 years after fracture), all living patients who met the study's inclusion criteria were sent a letter with information about the study, a written consent form, and a questionnaire consisting of the DASH questionnaire and the VAS for pain and satisfaction. The responders were then contacted by telephone by a research nurse and asked to attend a radiographic examination of the injured wrist and a physical examination including wrist and forearm range of motion and grip strength. The medical records of the study participants were reviewed for information about possible subsequent surgical procedure on the injured wrist and other fractures sustained after the distal radius fracture.

A study researcher, blinded to the fractured side, method of fracture treatment, patient's responses to the questionnaires, and results of the radiographic examination, measured the range of motion in both forearms and wrists, and the grip strength of both hands.

Posteroanterior and lateral radiographs of the injured wrist were obtained. Dorsal angulation, ulnar variance, and radial inclination were measured. Radiocarpal OA was classified according to Kellgren and Lawrence (5 categories ranging from 0 [none] to 4 [severe]). The presence of ulnar styloid nonunion was recorded. All radiographs were assessed independently by an orthopaedic surgeon and a hand surgeon who were blinded to the outcome data. The interrater reliability of the measurements of the two surgeons was evaluated with the ICC. Malunion was defined as dorsal angulation of ≥10° (measured from 0°), ulnar variance of ≥3 mm, and/or radial inclination of ≤15°. These cut-off values were chosen based on previous research showing that distal radius facture malunion, defined as dorsal angulation of >10°, ulnar variance of ≥3 mm, or radial inclination of <15°, was associated with a higher level of pain and disability in patients younger than 65 years of age [90]. Other research has also shown that malunion with a dorsal angulation of ≥10° was associated with difficulties in performing everyday activities and work [60,91].

Based on the previous 1-year results [89], it was assumed that patients with malunion would have a mean DASH score of >25 points and a standard deviation (SD) of 17 points at the long-term follow-up. The minimum clinically important difference (MCID) for the DASH score has previously been estimated to be 10 points [92]. To detect a mean DASH score between patients with malunion and those without malunion larger than MCID, a sample size of at least 21 patients in each group would be needed. Based on the number of patients who participated in the initial study and the prespecified eligibility criteria for this long-term follow-up, approximately 100 patients estimated to be eligible, and a 70% participation rate was expected. In the previous study, approximately 30% of fractures had healed with malunion [89], which would meet the estimated sample size.

For the primary analysis (change in DASH score over time according to malunion), generalized estimating equations (GEE) were used, adjusting for baseline factors (age, sex, dominance of the fractured side, fracture AO type, and method of treatment). The DASH scores at baseline, 2 years, and the long-term follow-up were used in the GEE analyses. The GEE utilizes data for all patients including those with missing values for the dependent variable (DASH score) at ≥1 measurement times. To investigate the relationship between malunion and activity limitations in younger patients, a similar analysis on the subgroup (n = 30) of patients who were ≤67 years of age (extended retirement age in the population) at the long-term follow-up was performed. Because the definition of malunion implies the use of cut-off values for radiographic variables, the relationship between the DASH score and each of the radiographic variables (dorsal angulation, ulnar variance, and radial inclination) was also analysed as continuous variables (i.e., without cut-off values), adjusting for baseline factors using a GEE (for the change in DASH score over time) and linear regression (for the DASH score at the long-term follow-up). The DASH, pain and satisfaction scores, range of motion, and grip strength at the long-term follow-up were also analysed according to malunion using linear regression analyses adjusting for baseline factors. The correlations between the radiographic parameters at the long-term follow-up and the 1-year follow-up examinations were analysed using the Pearson correlation coefficient. The patients were categorized as having no radiocarpal OA (grade 0) or radiocarpal OA (grade 1 or higher) and according to the presence or absence of ulnar styloid nonunion. The DASH, pain, and satisfaction scores, range of motion, and grip strength at the long-term follow-up according to radiocarpal OA and ulnar styloid nonunion were compared using linear regression analyses adjusting for baseline factors and, for range of motion and grip strength using the uninjured side's values. The association between malunion and the presence of radiocarpal OA at the long-term follow-up was analysed using the chi-square test. Significance was set at $p < 0.05$.

Paper III

A systematic review with meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [93], and the study protocol was registered in PROSPERO (February 11, 2021).

A systematic literature search in PubMed, EMBASE, and Cochrane databases was performed on January 3, 2021, to identify eligible studies. The search strategy was constructed with the assistance of a clinical librarian (Appendix I). After removal of duplicates, title and abstract of retrieved records were screened and potentially eligible articles were assessed in full text for eligibility in a standardized manner, independently by two reviewers. Disagreements were resolved by discussion and consensus. If disagreement persisted, a third reviewer was consulted. The reference lists of all included studies were screened for additional studies of relevance to this systematic review.

The inclusion criteria were cohort studies and randomized controlled trials assessing patient-rated disability after malunited distal radius fractures in adults, using one or more of these validated PROMs; the DASH, QuickDASH, and/or the PRWE scales, measured at a minimum of 12 months after fracture. Since no formal definition of malunion after distal radius fracture has been established in the literature, the definition used by the included studies was applied. If the definition was not provided but data regarding patient-reported outcomes according to radiological parameters were available, dorsal angulation ≥10º, ulnar variance ≥3 mm, and/or radial inclination ≤15º was used as a definition of malunion. Similar cut-off values have been used in guidelines regarding management of distal radius fracture from different countries [67,68]. The wrist radiographs should have been performed at a minimum of three months after the distal radius fracture to ensure union. No restriction regarding date of publication was applied, but only studies published in English or Spanish were searched.

The exclusion criteria were studies reporting on skeletally immature individuals, studies not reporting on malunion and/or patient-reported outcomes according to malunion, follow-up time shorter than 12 months, radiographs performed earlier than three months after fracture, other study design than cohort studies and randomized controlled trials, and studies judged to have low quality.

Data extraction from the included studies was performed by one reviewer using a standard data collection form. A second reviewer audited the extracted data. Disagreements were resolved by discussion. In case of missing data, authors were contacted by e-mail and asked to provide the additional data. The data extracted from the articles included first author, publication year, number of patients, patient sex, mean and range of patient age, type of fracture (extra-articular or intra-articular), type of treatment, mean and SD of DASH, QuickDASH and PRWE scores, number of patients in the malunion and in the no-malunion groups, mean and range of follow-up time, and definition of malunion.

Two reviewers independently assessed the quality of the included studies. Assessment of risk of bias (RoB) was performed using the Quality In Prognosis Studies (QUIPS) tool, recommended by the Cochrane Prognosis Methods Group [94]. The QUIPS tool consists of six main domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Each domain includes multiple items that are assessed separately. For each domain the RoB can be classified as low, moderate, or high. To judge the overall RoB for each study we used the method described by Grooten el al [95]. A study that had low RoB in all six domains, or low RoB in five and moderate in one domain was classified as having low RoB. A study that had high RoB in at least one domain or moderate RoB in three or more domains was classified as high RoB. All other combinations were classified as moderate RoB. Any disagreement between the two reviewers was resolved by discussion and in case disagreement persisted, a third reviewer was consulted, and consensus was reached. Studies with high RoB were subsequently excluded from the systematic review and meta-analysis.

If more than one PROM was presented in a study, these were included as different inputs in the quantitative synthesis. The Heges'g was calculated as the standardized mean difference (SMD) with its 95% CI to express the overall size of the effect of malunion on patient-reported outcomes using a random effect model with a restricted maximum likelihood method. A p-value of <0.05 for the overall effect size indicated statistically significant difference. An effect size of <0.5, 0.5-0.8, >0.8

were considered as small, moderate and large clinical effect, respectively [96]. A forest plot was constructed. The Cochran Q (Chi2) test and the I^2 statistics were used to assess heterogeneity; a p-value of <0.1 on the Q test indicates significant heterogeneity [97]. The I^2 describes the percentage of variation across studies that is due to heterogeneity rather than chance with I^2 value of 25%, 50% and 75% reflecting low, moderate and high heterogeneity, respectively [97]. Egger regression test, Begg rank correlation test and a funnel plot were used to assess publication bias. A p-value of <0.10 in the Egger test and a p-value of <0.05 in the Begg test were considered to indicate a significant publication bias [98,99]. The statistical analyses were conducted in STATA version 16.0 (Stata Corporation, College Station, TX, USA).

Paper IV

This study included patients who had participated in a prospective cohort study of patients with acute distal radius fracture conducted 2001 to 2002, in Northeast Skåne in Sweden [62]. From October 2014 through April 2015 (12 to 14 years after the original study), 63 patients treated with casting, closed reduction and casting or closed reduction and percutaneous surgical fixation, were included in *Paper II* and attended a radiographic examination. Radiocarpal OA was classified according to Kellgren-Lawrence (five categories ranging from 0 [no OA] to 4 [severe OA]) [11], independently by an orthopaedic surgeon and a hand surgeon. In 12 patients (19%), there were discrepancies regarding the presence or absence of OA, which were resolved by discussion and consensus. Of the 63 patients, 25 were classified as having no radiocarpal OA (grade 0) and 38 as having radiocarpal OA (grade 1 or higher) [100].

A novel computer software (Image biopsy lab©) has previously been developed to identify knee OA. The software is an automated system that analyses the subchondral trabecular bone on plain radiographs in two rectangular bone regions, called regions of interest (ROIs), for detection of OA (Figure 9). The placement of the ROIs at the subchondral bone of the distal radius radiographs was performed using the proprietary software IB Lab TX Analyzer and was consistent across the cases.

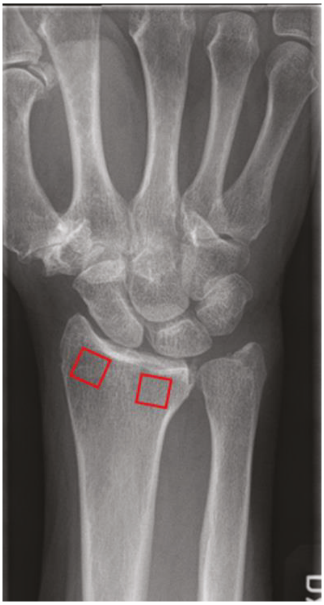


Figure 9. Radiograph of the wrist with the 2 selected regions of interest (ROI) marked (red squares)

In a first step, the computer software (previously trained to identify knee OA) assessed the radiographs of the 63 study patients for detection of radiocarpal OA. Two radiographs could not be assessed by the software due to technical issues. Thus, 61 radiographs were used in the analyses. In a second step, and in order to train the computer software to detect radiocarpal OA, we used 196 consecutive wrist radiographs (37 bilateral) for patients attending our orthopaedic department at Kristianstad and Hässleholm hospitals for any reason. These radiographs were examined and graded according to the Kellgren-Lawrence classification independently by the two surgeons. In 164 (84%) of the radiographs (28 bilateral), the surgeons agreed on the classification and these radiographs (75 OA and 89 no OA) were used as a labelled dataset to train the software to recognize radiocarpal OA. According to the software's developers a sample size of 75 radiographs per group (OA and no OA) would be needed for this purpose. Of the 164 radiographs, 20 could not be used due to technical issues, leaving 144 radiographs that were used for training the software. In a third step, the trained computer software reassessed the radiographs of the 63 patients with previous distal radius fracture. In this analysis 58 of the radiographs could be reassessed.

Sensitivity, specificity, and the area under the curve (AUC) were calculated before and after training to determine the computer software's ability to distinguish between OA and non-OA wrists.

Ethics, funding source and conflicts of interests

All studies included in this thesis have been under ethical consideration. *Paper I*, *II* and *IV* were approved by the regional ethical review board in Lund, Sweden. *Paper III* was a systematic literature review without patient involvement and thus, no application to the ethical board was required. The studies were conducted in compliance with Helsinki Declaration. Participants in *Paper II* were given verbal and written information about the study, and they provided written consent before inclusion. The research was supported by grants from Region Skåne and Södra Sjukvårdsregionen. The author of this thesis reports no conflicts of interests.

Results

Paper I

During 2016, an acute distal radius fracture was sustained by 314 adult residents of the Northeast Skåne (276 identified through the orthopaedic department's patient register and additional 38 through review of all wrist radiographs). An additional 22 fracture cases who were not residents of the study region were identified and were thus excluded. The mean (SD) age of the 314 individuals included in this study was 66 (19) years (range, 19 to 103 years); 245 (78%) were women with a mean age of 68 (18) years (range, 19 to 103 years) and 69 (22%) were men with a mean age of 57 (21) years (range, 20 to 93 years). The fracture involved the left wrist in 187 patients (60%), the right wrist in 122 (39%), and both wrists (bilateral) in 5 patients (1.6%). One patient had a subsequent new fracture of the same wrist during 2016. There were no missing data.

The mid-year population above 18 years of age in the study region during 2016 was 142,214. The overall incidence of distal radius fracture in 2016 was 22 (95% CI, 20 to 25) per 10,000 person-years. The incidence in women was 34 (95% CI, 30 to 39) and in men 10 (95% CI, 8 to 12) per 10,000 person-years. The women:men ratio of the incidence rate was 3.4:1. The overall incidence in 2016 was 0.76 (95% CI, 0.70 to 0.82; $p<0.0001$) of the incidence in 2001. The age-specific incidence in 2016 was 0.91 (95% CI, 0.69 to 1.20; $p=0.502$) for individuals 19-49 years, 0.67 (95% CI, 0.55 to 0.82; $p<0.001$) for individuals 50-79 years and 0.49 (95% CI, 0.25 to 0.97; $p=0.042$) for those ≥80 years, of the incidence in 2001 respectively.

The incidence in 2016 increased with age in both women and men (Figure 10). Among individuals below 45 years of age the incidence did not differ substantially between women and men. After the age of 45 years the incidence rate in women increased more rapidly with largest increase occurring after the age of 85 years. In men the incidence increased gradually, with highest incidence of 36 per 10,000 person-years seen in those above 90 years of age.

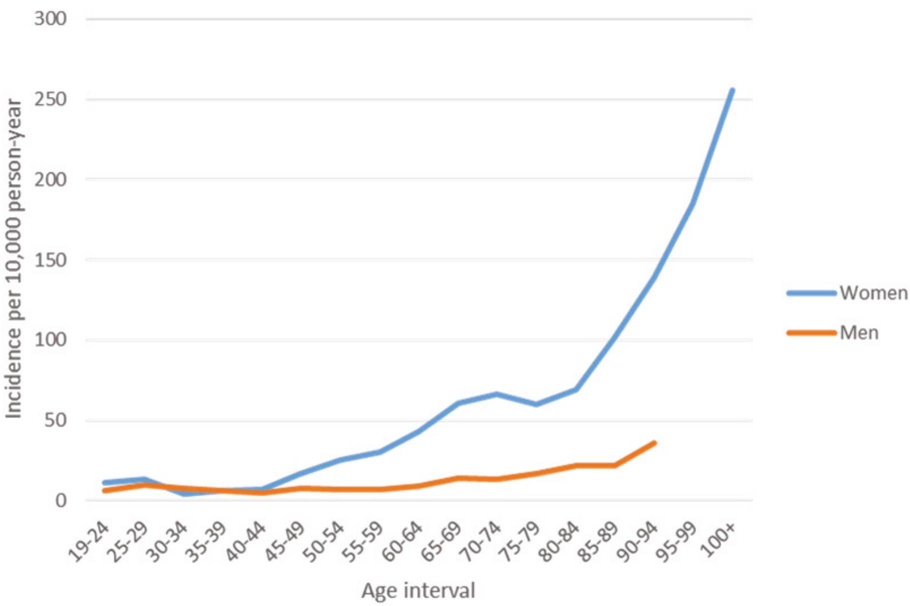


Figure 10. Incidence of distal radius fracture in Northeast Skåne in Sweden during 2016 according to age group and sex

The radiographic measurements assessed by the two examiners showed high interrater reliability with the ICC (95% CI) for dorsal angulation was 0.97 (0.96 to 0.97), for ulnar variance was 0.87 (0.84 to 0.89), and for AO classification was 0.80 (0.75 to 0.83). Therefore, the measures of one examiner were used in the analyses regarding fracture AO type and fracture displacement.

Of the 314 individuals with distal radius fracture in 2016, 163 (52%) had type A (extra-articular), 28 (9%) type B (partial intra-articular) and 123 (39%) had type C (complete intra-articular), compared to 79%, 5% and 16%, respectively, in 2001. The ratio of A:C fracture in 2016 was 1.3:1, compared to 4.9:1 in 2001. The incidence of type-A fracture during 2016 was 12 (95% CI, 10 to 13) and of type-C fracture 9 (95% CI, 7 to 10).

There were 197 (63%) individuals with displaced fracture and 117 (37%) with non-displaced or minimally displaced fractures; the values among women were 162 (66%) and 83 (34%) and among men 36 (52%) and 33 (48%) respectively. The ratio of displaced:non-displaced fractures in 2016 was 1.7:1, compared to 1.9:1 in 2001.

Paper II

97 potentially eligible patients for the long-term follow-up were identified, nine of them had died. Of the remaining 88 patients invited to participate, six declined and two did not respond. Of the 80 patients (61 women) who accepted participation, 66 patients (50 women) attended the examination and completed the questionnaires, while 14 patients only answered the questionnaires but did not attend examinations. Three of the 88 invited patients were subsequently excluded because at examination they were found to have refractured the study wrist. Thus of 85 eligible patients (Table 1), 63 (74%) patients (47 women [15 with intra-articular fractures]) responded to the questionnaires and attended examinations. The mean follow-up time (SD) was 13.2 (0.4) years (range, 12.1 to 14.0 years). The mean age at the time of follow-up was 66 (10) years (range, 36 to 79 years). Patients who completed questionnaires without attending examinations had similar patient-reported outcomes as those examined (Table 1).

Table 1. Characteristics of eligable patients for the long-term follow-up

Characteristics	Patient-Reported Outcome Measures and Examinations[a] (N = 63)	Patient-Reported Outcome Measures Only[a] (N = 14)	Nonparticipants (N = 8)
Sex[b]			
Female	47	11	4
Male	16	3	4
Age at fracture[c]	53 (9)	54 (13)	53 (14)
Fracture involving dominant hand[d]	27 (43%)	6 (43%)	4 (50%)
AO fracture type[b]			
A	48	9	4
B	2	0	1
C	13	5	3
Treatment[d]			
Nonoperative[e]	39 (62%)	9 (64%)	5 (62.5%)
Operative[f]	24 (38%)	5 (36%)	3 (37.5%)
DASH score[c]			
Baseline[g]	3.8 (9.2)	4 (6.9)	1.3 (2.3)
2 years[h]	12 (8.)	8.6 (10.8)	3.4 (3.3)
12-14 years	11 (15)	11 (12)	NA
VAS score 12-14 years			
Pain	10 (18)	9 (17)	NA
Satisfaction	17 (29)	7 (18)	NA
Radiographic variables at 1 year			
Dorsal angulation (deg)	1.3 (9.3)	1.5 (9.3)	5.8 (8.2)
Ulnar variance (mm)	0.9 (2.8)	1.9 (2.2)	1.1 (1.7)
Radial inclination (deg)	19 (4)	19 (5)	20 (6)
Radiographic variables at 12-14 years			
Dorsal angulation (deg)	-0.1 (11)	NA	NA
Ulnar variance (mm)	1.0 (2.2)	NA	NA
Radial inclination (deg)	20 (4)	NA	NA

[a] Patient-reported outcome measures are the DASH questionnaire and VAS for pain and satisfaction; examinations are physical and radiographic.

[b] The values are given as the number of patients.

[c] The values are given as the mean and the standard deviation.

[d] The values are given as the number of patients, with the percentage in parentheses.

[e] This treatment involves cast with or without closed reduction.

[f] This treatment involves closed reduction and external fixation or percutaneous pinning.

[g] Scores were missing in 15 patients in the patient-reported outcome measures and examinations group, 4 patients in the patient-reported outcome measures-only group, and 5 patients in the nonparticipants group.

[h] Scores were missing in 4 patients in the patient-reported outcome measures and examinations group, 2 patients in the patient-reported outcome measures-only group, and 5 patients in the nonparticipants group.

The radiographic measurements assessed by the two examiners at long-term follow-up were highly correlated (Table 2), therefore the measures of one examiner were used in the analyses of this study.

Table 2. Intraclass correlation coefficient for radiographic measurements at 12-14 years by the two raters

Radiographic measure	Intraclass correlation coefficient (95% CI)
Dorsal angulation	0.99 (0.98 to 0.99)
Ulnar variance	0.97 (0.94 to 0.98)
Radial inclination	0.97 (0.95 to 0.98)

At the long-term follow-up, malunion was present in 25 patients (40%). Radiocarpal OA was present in 38 patients (60%), of whom 37 had grade-1 OA and one had grade-2 OA. Radiocarpal OA was classified independently by the two examiners and discrepancies (12 [19%]) were resolved by discussion and consensus. Ulnar styloid nonunion was present in nine patients (14%), four of whom had a styloid base fracture. Except for one patient with a 5-mm scapholunate interval, no scapholunate dissociation was seen.

Patients with malunion (dorsal angulation of ≥10°, ulnar variance of ≥3 mm, and/or radial inclination of ≤15°) had a larger negative change in DASH scores than those without malunion; the adjusted mean difference was 11 points (95% CI, 4 to 17 points; $p = 0.002$). None of the other variables in the model (including whether the fracture was extra-articular or intra-articular) was significant. In the subgroup analysis of patients who were ≤67 years of age at the long-term follow-up, patients with malunion had a larger negative DASH score change over time than those without malunion; the adjusted mean difference was 11 points (95% CI, 3 to 18 points; $p = 0.005$).

Analyses of the continuous radiographic variables showed significant associations ($p < 0.05$) between a larger negative DASH score change over time and increased ulnar variance and decreased radial inclination, and between a higher DASH score at the time of the long-term follow-up and increased dorsal angulation, increased ulnar variance, and decreased radial inclination (Table 3).

Table 3. Association between the DASH score and the radiographic variables

Radiographic Variables[a]	Effect on Change Over Time[bc]	P Value	Effect at Final Follow-up[bd]	P Value
Dorsal angulation (deg)	0.3 (−0.1 to 0.7)	0.12	0.4 (0.02 to 0.7)	0.041
Ulnar variance (mm)	2.0 (0.3 to 3.7)	0.019	2.6 (0.8 to 4.4)	0.006
Radial inclination (deg)	−1.0 (−1.8 to −0.2)	0.016	−1.2 (−2.0 to −0.4)	0.005

[a] These were measured on radiographs at the time of follow-up 12 to 14 years after the fracture, analyzed here as continuous variables.
[b] The values are given as the mean change in DASH score (in points) per degree or millimeter change in the radiographic variable, with the 95% CI in parentheses. The DASH score range is 0 to 100 points, and a lower score is better (less activity limitations).
[c] Analysis of the change in the DASH score over time (baseline, 2 years, and 12 to 14 years): values are the mean change in score (in points) per degree of dorsal angulation, millimeters of ulnar variance, or degree of radial inclination, adjusting for age, sex, dominance of injured hand, fracture AO type, and treatment method (using a GEE).
[d] Analysis of the follow-up (12 to 14 years) DASH score; the values are the mean change in score (in points) per degree of dorsal angulation, millimeters of ulnar variance, or degree of radial inclination, adjusting for the abovementioned baseline factors (using linear regression). For example, with each 1° increase in dorsal angulation, the DASH score at the long-term follow-up increases, on average, by 0.4 point.

Malunion was associated with larger negative patient-reported outcomes recorded at the time of the long-term follow-up; the adjusted mean difference was 14 points (95% CI, 7 to 22 points) for the DASH score, 10 points (95% CI, 0 to 20 points) for the VAS pain score, and 26 points (95% CI, 11 to 41 points) for the VAS satisfaction score, but no differences were found in range of motion or grip strength (Table 4). Analyses including radiocarpal OA and ulnar styloid nonunion as covariates gave similar results. No significant association ($p > 0.05$) was found between malunion and the presence of radiocarpal OA at the long-term follow-up.

Table 4. Patient-Reported Outcomes and Physical Measures According to Fracture Malunion

Scales or Physical Measures[a]	Malunion[b] (N = 25)	No Malunion[b] (N = 38)	Adjusted Difference[c]	P Value
DASH (points)	19 (19)	6 (9)	14.4 (6.6 to 22.1)[d]	<0.001
VAS (points)				
Pain	15 (19)	7 (16)	9.9 (0.1 to 19.7)	0.049
Satisfaction	29 (35)	9 (20)	25.8 (10.7 to 40.8)	0.001
Flexion (deg)	46 (13)	52 (12)	−4.4 (−10.2 to 1.4)	0.13
Uninjured side	52 (16)	56 (15)		
Extension (deg)	71 (11)	71 (9)	0.7 (−4.02 to 5.4)	0.77
Uninjured side	68 (7)	69 (9)		
Supination (deg)	76 (11)	79 (8)	−3.6 (−7.3 to 0.2)	0.062
Uninjured side	80 (7)	80 (8)		
Pronation (deg)	70 (6)	71 (8)	−1.9 (−5.2 to 1.5)	0.27
Uninjured side	71 (7)	70 (8)		
Grip strength (kg)	28 (11)	36 (12)	0.06 (−2.7 to 2.8)	0.97
Uninjured side	27 (11)	36 (13)		

[a] The DASH and VAS for pain and satisfaction are scored from 0 points (best) to 100 points (worst).

[b] The values are given as the mean and the standard deviation.

[c] The between-group difference, given as the mean with the 95% CI in parentheses, in values at 12 to 14 years adjusted for age, sex, dominance of the study hand, fracture AO type, treatment method, and values for the uninjured side (for range of motion and grip strength).

[d] In a secondary analysis that also included the baseline DASH score as a covariate (with only data from patients with baseline scores included in the analysis; 18 with malunion and 30 without malunion), the adjusted mean difference was 10.5 points (95% CI, 2.2 to 18.8 points; p = 0.014).

At the long-term follow-up the DASH score and the VAS pain and satisfaction scores had no association with the presence of radiocarpal OA (Table 5) or ulnar styloid nonunion had (Table 6). Wrist flexion was significantly lower (p = 0.006) among patients with radiocarpal OA, and forearm pronation was significantly lower (p = 0.041) among patients with ulnar styloid nonunion, but no other differences were found in range of motion or in grip strength. The results did not differ according to styloid fracture location.

Table 5. Patient-reported outcomes and physical measures according to radiocarpal osteoarthritis

Scales or Physical Measures[a]	Osteoarthritis[b] (N = 38)	No Osteoarthritis[b] (N = 25)	Adjusted Difference[c]	P Value
DASH (points)	12 (16)	10 (14)	2.9 (-4.9 to 10.8)	0.46
VAS (points)				
Pain	7 (14)	14 (22)	-6.5 (-15.7 to 2.7)	0.16
Satisfaction	18 (30)	16 (28)	2.3 (-12.9 to 17.5)	0.77
Flexion (deg)	46 (14)	54 (10)	-6.8 (-11.7 to -2.0)	0.006
Uninjured side	53 (17)	55 (13)		
Extension (deg)	70 (10)	73 (8)	-0.7 (-5.2 to 3.7)	0.74
Uninjured side	68 (9)	71 (6)		
Supination (deg)	78 (9)	78 (10)	-0.4 (-3.9 to 3.2)	0.83
Uninjured side	80 (8)	80 (8)		
Pronation (deg)	70 (7)	71 (9)	-2.2 (-5.2 to 0.8)	0.14
Uninjured side	71 (6)	70 (9)		
Grip strength (kg)	33 (13)	31 (9)	-0.3 (-2.8 to 2.2)	0.81
Uninjured side	33 (15)	31 (9)		

[a] The DASH and VAS for pain and satisfaction are scored from 0 points (best) to 100 points (worst).
[b] The values are given as the mean with the standard deviation in parentheses.
[c] The between-group difference, given as the mean with the 95% CI in parentheses, in values at 12 to 14 years adjusted for age, sex, dominance of the study hand, fracture AO type, treatment method, and values for the uninjured side (for range of motion and grip strength).

Table 6. Patient-reported outcomes and physical measures according to ulnar styloid nonunion

Scales or Physical Measures[a]	Nonunion[b] (N = 9)	No Nonunion[b] (N = 54)	Adjusted Difference[c]	P Value
DASH (points)	10 (10)	11 (16)	0.3 (-10.7 to 11.4)	0.95
VAS (points)				
Pain	9 (17)	10 (18)	1.3 (-11.8 to 14.3)	0.85
Satisfaction	13 (19)	18 (30)	-1.8 (-23 to 19.3)	0.86
Flexion (deg)	53 (10)	49 (13)	2.6 (-5 to 10.1)	0.49
Uninjured side	53 (22)	54 (14)		
Extension (deg)	71 (10)	71 (9)	-0.5 (-6.5 to 5.5)	0.87
Uninjured side	69 (8)	69 (8)		
Supination (deg)	76 (12)	78 (9)	-0.2 (-5.1 to 4.7)	0.93
Uninjured side	78 (9)	80 (8)		
Pronation (deg)	68 (4)	71 (8)	-4.2 (-8.3 to -0.2)	0.041
Uninjured side	72 (4)	70 (8)		
Grip strength (kg)	33 (14)	32 (12)	-3.3 (-6.8 to 0.1)	0.058
Uninjured side	38 (16)	31 (12)		

[a] The DASH and VAS for pain and satisfaction are scored from 0 points (best) to 100 points (worst).
[b] The values are given as the mean with the standard deviation in parentheses.
[c] The between-group difference, given as the mean with the 95% CI in parentheses, in values at 12 to 14 years adjusted for age, sex, dominance of the study hand, fracture AO type, treatment method, and values for the uninjured side (for range of motion and grip strength).

Paper III

The search yielded 7,649 records and after removal of duplicates, 5,917 records remained for title and abstract screening (Figure 11). Of these, 380 articles were read in full text and considered for inclusion. After full-text review 11 articles judged to potentially fulfil the inclusion criteria [59,62,64,89,90,100-105]. We contacted eight authors for additional data [59,62,64,90,101-104], of whom five responded [59,62,64,90,101]. One study was excluded [89], because it represented the same population as another included study [62]. Four studies judged to have high RoB on the QUIPS tool were excluded [101-104]. Thus, six studies were included in the systematic review; five cohort studies and one randomized controlled trial (Table 7).

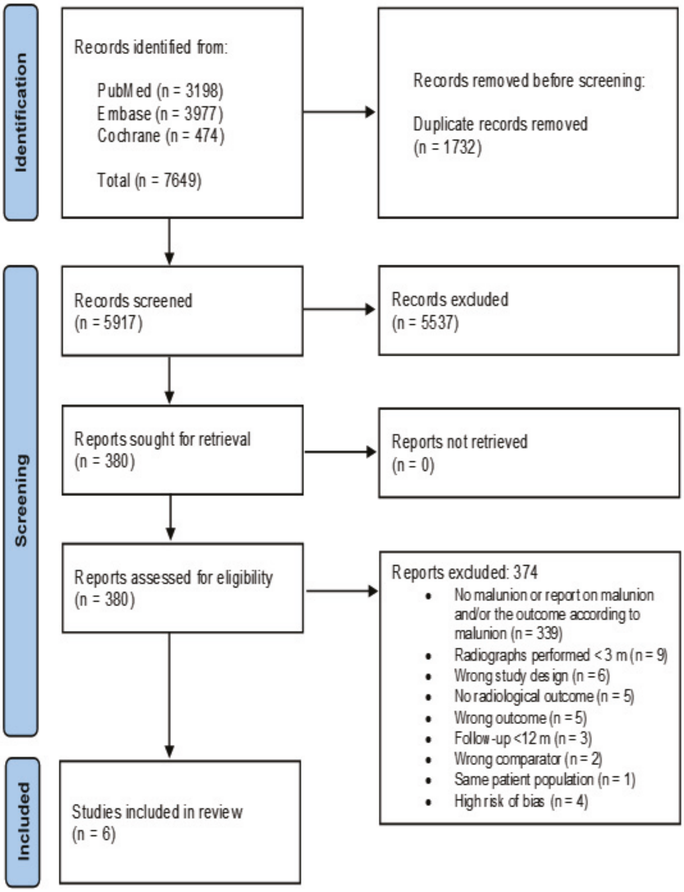


Figure 11. Flowchart of the study selection process

The six studies comprised 707 patients with a distal radius fracture (536 women [76%]). The range of the mean age was 55 to 77 years. The range of the mean follow-up time was 1.0 to 13.2 years. The type of treatment was cast or closed reduction and cast in one study [105] and cast (with or without closed reduction) or percutaneous surgical fixation in four of the included studies [59,62,90,100]. The randomized study compared closed reduction and cast with open reduction and internal fixation with volar locking plate.

The definition of malunion differed among the studies (Table 7). For dorsal angulation, a cut-off value of 10° was used in five studies [62,64,90,100,105], and 15° in one study [59]. The cut-off value for ulnar variance was 3 mm in three studies [62,90,100], and 2 mm in three studies [59,64,105]. For radial inclination, the cut-off value was 15° in two studies [90,100], and 10° in two studies [59,105], while two studies did not use radial inclination as part of the definition of malunion [62,64]. Only two studies used articular incongruity (step-off ≥2 mm) as part of malunion definition, with one reporting that no patient had incongruity [64], and the other did not report the number of patients with articular incongruity [105].

Table 7. Characteristics of the six included studies

Author/ publication year	Study design	No. of patients [women (%)]	Mean age (range) yrs	Type of fracture	Type of treatment	PROM	Mean follow-up time (range) yrs	Definition of malunion
Ali et al. 2018	Cohort	63 [47 (74)]	66 (36 to 79)	AO type A, B and C	C, CRC, CRPF	DASH	13.2 (12.1 to 14.0)	DA ≥10°, UV ≥3 mm, and/or RI ≤15°
Arora et al. 2011	RCT	73 [55 (75)]	76.7 (65 to 89)	AO type A and C	CRC, ORIF	DASH, PWRE	1	DA >10°, UV >2 mm, and articular incongruity ≥2 mm
Brogren et al. 2013[a]	Cohort	102 [78 (76)]	63 (19 to 88)	Extra- and intra-articular fractures	CRC, CRPF	DASH	2	DA ≥10° and/or UV ≤3 mm
Grewal et al. 2007	Cohort	222 [168 (78)]	55.2 (18 to 89)	Extra-articular fractures	C, CRC, CRPF	DASH, PRWE	1	DA >10°, UV ≥3 mm or RI <15°
Wadsten et al. 2018	Cohort	175 [135 (77)]	56 (15 to 74)	AO type A, B and C	C, CRC	QuickDASH	1	DA ≥10°, UV ≥2 mm, RI ≤10° and/or articular incongruity ≥2 mm
Wilcke et al. 2007[a]	Cohort	72 [53 (74)]	59 (22 to 95)	Extra- and intra-articular fractures	CRC, EF	DASH	1.8 (1 to 2.6)	DA >15°, RS ≥2 mm and/or RI <10°

[a] Data provided by authors.

Abbreviations: C, cast; CRC, closed reduction and cast; CRPF, closed reduction and percutaneous fixation; EF, external fixation; ORIF, open reduction and internal fixation; DASH, Disabilities of the Arm, Shoulder and Hand; PRWE, Patient-Rated Wrist Evaluation; DA, dorsal angulation; UV, ulnar variance; RI, radial inclination; RS, radial shortening.

The RoB assessment is shown in Table 8. One study was judged to have low RoB in all domains [100]. Five studies had low RoB in all domains except one; study attrition, which was judged to have moderate RoB because of inadequate description of participants lost to follow-up or inadequate description of attempts to collect information on participants who had dropped out. However, these five studies had an adequate response rate for study participants, with low rate of drop-out and loss to follow-up [59,62,64,90,105].

Table 8. Risk of bias assessment of the six included studies[a]

Author/ publication year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Ali et al. 2018	Low	Low	Low	Low	Low	Low	Low
Arora et al. 2011	Low	Moderate	Low	Low	Low	Low	Low
Brogren et al. 2013	Low	Moderate	Low	Low	Low	Low	Low
Grewal et al. 2007	Low	Moderate	Low	Low	Low	Low	Low
Wadsten et al. 2018	Low	Moderate	Low	Low	Low	Low	Low
Wilcke et al. 2007	Low	Moderate	Low	Low	Low	Low	Low

[a] For each domain the risk of bias (RoB) can be classified as low, moderate, or high: a study with low RoB in all six domains, or low RoB in five and moderate in one domain is classified as having low RoB; a study with high RoB in at least one domain or moderate RoB in three or more domains is classified as high RoB; all other combinations are classified as moderate RoB.

Four studies judged to have high RoB and were excluded from the systematic review and meta-analysis (Table 9) [101-104]. All the four excluded studies had high RoB in the domain "study participation" due to inadequate participation in the study by eligible persons, and three of them also had moderate RoB in one of the other domains.

Table 9. Risk of bias assessment of the four excluded studiesa

Author/ publication year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Finsen et al. 2013	High[a]	Moderate[b]	Low	Low	Low	Low	High
Kodama et al. 2014	High[a]	Low	Low	Low	Moderate[c]	Low	High
Larouche et al. 2014	High[a]	Low	Low	Low	Low	Low	High
Quadlbauer et al. 2020	High[a]	Low	Low	Low	Low	moderate[d]	High

[a] Inadequate participation in the study by eligible persons.
[b] Inadequate description of participants lost to follow-up and inadequate description of attempts to collect information on participants who dropped out.
[c] Confounders were not accounted for in the analysis.
[d] Insufficient presentation of data to assess the adequacy of the analytic strategy.

Scores for the DASH or QuickDASH were reported in all six studies and two studies also reported PRWE scores. Four of the studies showed significantly worse patient-reported outcome in patients with malunion compared to patients without malunion [59,62,90,100], whereas two studies found no statistically significant difference in patient-reported outcome between the two groups [64,105].

Data about PROMs in patients with malunion compared to patients without malunion could be retrieved from all the six studies that were then included in the meta-analysis. The randomized study included only patients aged 65 years or older [64], while the other five studies included adults of all ages. Therefore, a meta-analysis with these five studies was first performed and then a secondary meta-analysis including all six studies was performed. The results of the primary meta-analysis (856 observations) showed that patients with malunion had a significantly worse patient-reported outcome compared to patients without malunion, with an SMD of 0.58 (95% CI, 0.39 to 0.77; p<0.001) as shown in the forest plot (Figure 12). The Q test had a p-value of 0.13 and the I^2 was 38%, indicating no significant heterogeneity. The funnel plot showed no visual asymmetry, the p-value for the Egger test was 0.17 and for the Begg test was 0.26, indicating no publication bias.

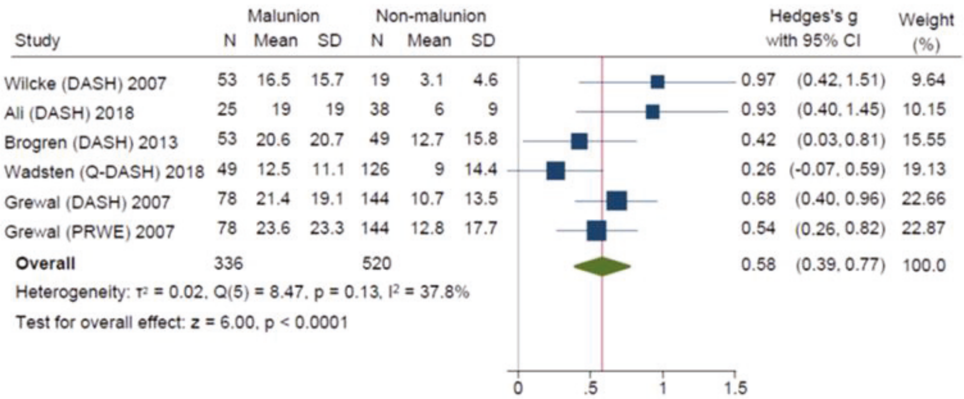


Figure 12. The effect of malunion on patient-reported outcome measures

The results of the secondary meta-analysis with all six studies included (1002 observations) also showed that patients with distal radius fracture malunion had a significantly worse patient-reported outcome compared to patients without malunion with an SMD of 0.50 (95% CI, 0.30 to 0.69; $p<0.001$). However, the Q test showed a p-value of 0.05 and the I^2 was 49%, indicating a moderate but significant heterogeneity.

Paper IV

Before training the software, sensitivity was 76% (95% CI 59 to 88), specificity was 25% (95% CI 10 to 47), and AUC was 0.50 (95% CI 0.35 to 0.65), indicating that the computer software had poor ability to discriminate between radiocarpal OA and no OA. After training, sensitivity was 46% (95% CI 29 to 63), specificity was 70% (95% CI 47 to 87), and AUC was 0.58 (95% 0.43 to 0.73), implying low ability to improve the performance through training with a labelled data set. Using only the 51 radiographs of the original 63 patients, in which the two surgeons made identical first-time assessment regarding the presence of radiocarpal OA gave similar results.

Discussion

The changing incidence: where are we now?

Studies reporting the incidence of distal radius fracture show different incidence rates from different countries, and that the incidence is changing even in the same country or region when estimated during different periods in time (Table 10).

Table 10. Reported incidence rates of distal radius fracture from different countries

At risk population	Year	Age (years)	Incidence per 10,000 person-years
Rochester, Minnesota, USA [17]	1945-1954	≥ 35	25
Rochester, Minnesota, USA [17]	1955-1964	≥ 35	23
Rochester, Minnesota, USA [17]	1965-1974	≥ 35	29
Rochester, Minnesota, USA [17]	1975-1984	≥ 35	30
Rochester, Minnesota, USA [17]	1985-1994	≥ 35	29
Zaragoza, Spain [106]	1998-1999	> 15	31
Skåne, Sweden [19]	1999-2010	≥ 17	28
Taiwan [22]	2000-2007	≥ 20	15
Northeast Skåne, Sweden [30]	2001	> 18	26
Reykjavik, Iceland [24]	2004	≥ 16	27
Stockholm, Sweden [12]	2004-2010	≥ 18	25
Leicester, UK [29]	2007-2014	≥ 18	13
Oulu, Finland [20]	2008	≥ 16	26
Almere and Hoofddorp, Netherlands [107]	2009	≥ 18	20
Oslo, Norway [21]	2010-2011	≥ 16	20
Edinburgh, Scotland, UK [2]	2010-2011	≥ 35	30
Denmark [108]	2013-2017	> 10[a]	20
Northeast Skåne, Sweden [109]	2016	> 18	22

[a] Only patients with closed epiphysial plates included.

In this thesis the incidence rate was compared over time in the same geographical region with wrist radiographs used to identify and verify the fracture cases. In the adult general population of Northeast Skåne in southern Sweden, the overall incidence of distal radius fracture, adjusted for age, sex and at-risk population decreased in 2016 compared with 2001 by 24%. The incidence during 2016 was 22 (95% CI 20 to 25) per 10,000 person-years. Similar incidence rates have recently been reported from Denmark and Norway [21,108]. In a population-based epidemiological study using radiographs to identify fracture cases in the North Denmark Region, the overall incidence of distal radius fracture in adults during the period 2013 to 2017 was 20 per 10,000 person-years [108]. In a cohort with prospectively collected and radiologically verified cases of distal radius fracture, the overall annual incidence among individuals aged 16 or older in one hospital's catchment area in Oslo, Norway during the years 2010 to 2011 was 20 (95% CI 19 to 21) per 10,000 person-years [21]. That incidence was lower than the incidence reported in two earlier Norwegian studies from Oslo (1-year study period in 1998 to 1999) [110] and from Bergen (1988) [23].

The decreased incidence shown in *Paper I* stands in contrast to the results of a register-based study from Skåne region in Sweden [19] that reported a significant increase in the incidence of distal forearm fracture from 1999 to 2010, in both men and women 17 years or older. The results of *Paper I* are also in contrast to a study from Taiwan that reported an annual increase in the incidence of distal radius fracture between years 2000 and 2007 in adults aged 20 or older [22]. These two studies were however based on register data only, which requires caution when interpreting the results as registers might not have high reliability and validity and the diagnosis of wrist fractures by emergency physicians may lack adequate accuracy [111,112]. Another possible explanation to the contrasting results is the different time periods during which the incidence estimates were made. The studies showing an increase in the incidence rate were conducted about a decade earlier than *Paper I* that showed a decrease in incidence.

The decrease in the overall fracture incidence in 2016 compared to 2001 was mainly due to a decrease in the incidence among patients aged 50 or older, while the incidence among patients below 50 years of age remained almost unchanged. Similar trends have previously been observed in Norway, where the incidence of distal radius fracture among women aged 50 to 59 in Oslo during a 1-year period (1998 to 1999) had fallen markedly compared to the incidence in 1979 [110]. In Iceland the incidence among women aged 50 to 70 was considerably lower in 2004 than in 1985 [24]. In Stockholm, Sweden, lower incidence among women aged 50 to 79 was found during the period 2004 to 2010 compared to earlier investigations from 1988 and 1992 [12]. However, *Paper I* have now shown that this decrease in incidence involves all individuals above the age of 50. These findings are important and might indicate the effect of an improved osteoporosis treatment even at old age. Data about prescription of osteoporosis medication (oral bisphosphonates) in Skåne County in southern Sweden showed that the number of Defined Daily Dose (DDD), which is the average daily maintenance dose for a drug used for its main indication in adults [113], had more than doubled among women from 4.9 DDD/1000 women during 2000-2002 to 11.1 DDD/1000 women during 2014-2016, and almost quadrupled among men, from 0.66 DDD/1000 men to 2.32 DDD/1000 men [114]. However, this alone would not explain the decrease in incidence, as the total number of individuals with osteoporosis treatment still is low and compliance to osteoporosis medications has been shown to be suboptimal [115]. Another explanation for the decrease in incidence could be that many elderly individuals remain physically active, leading to a better neuromuscular coordination and improved bone mineral density, which may reduce fracture risk. Besides, changes in demography might also explain the decrease in incidence; however, the composition of at-risk population in the study region remained unchanged (Table 11) [88].

Table 11. Population at risk according to sex and age group for 2001 and 2016

Sex	Age group (years)	At-risk population			
		2001	**Percentage[a]**	**2016**	**Percentage[b]**
Women	19-49	31547	24	33165	23
	50-79	28132	22	31536	22
	80-	6288	5	6584	5
Men	19-49	32767	25	34819	25
	50-79	26828	21	31729	22
	80-	3532	3	4381	3
Total		129094		142214	

[a] Percentage of total at-risk population 2001.
[b] Percentage of total at-risk population 2016.

One possible limitation of the study could be that eligible individuals may have sustained a minor fracture while staying outside the study region and that this injury was deemed, at the treating hospital, to not require further follow-up at the study region's orthopaedic department. This would probably involve only few cases and would only have minor influence on the incidence estimates. Besides, it would have had similarly affected the incidence rates in 2001 and 2016 and would likely not explain the change in incidence. The incidence of distal radius fracture may be influenced by weather conditions, as lower temperatures increase risk of falls and fractures [29]. However, data about the daily temperatures during 2001 and 2016 in the study region showed that the mean temperature for days when fractures occurred did not differ substantially between the two study years [116]. Another limitation is that part of the methodology of identifying fracture cases was not exactly the same in the current study compared to the previous study estimating the incidence in 2001 [30]. The ICD-10 codes and the search strategy using the department's patient register for distal radius fractures were the same in both 2001 and 2016. In 2001, the radiographs (non-digital) of all identified cases were examined to verify the fractures and in addition all ICD-10 codes for forearm fracture and wrist sprain were searched and the radiographs examined to find any distal radius fracture that might have been incorrectly coded. Since digital radiographs were not available in 2001, the strategy with examining all wrist radiographs at the two hospitals in 2016 was not possible in 2001. However, this would rather imply a possible underestimation of the incidence in 2001 and that the decrease in incidence shown in 2016 may even be larger.

Although extra-articular fracture (AO type A) was the most common type (52% of the distal radius fracture fractures) in the study region during 2016, this was substantially lower than in 2001 when type-A fracture accounted for 79% of the fractures. The proportion of type-C fracture increased from 16% in 2001 to 39% in 2016. A similar observation has recently been made in Germany where the proportion of type-A fractures was lower and of type-C fractures was higher than previously reported in the literature [117]. The proportion of type-C fracture and the lower proportion of type-A fracture compared to 2001 was seen in all age groups, not only the elderly. Thus, the higher proportion of intra-articular fractures cannot be explained by increased life expectancy and the fact that many elderly individuals are more active with higher risk of more severe wrist injury. One possible explanation of the higher proportion of type-C fractures could be the higher resolution of the modern, digital radiographs leading to more accurate classification. This theory is supported by the fact that the proportion of displaced fractures remained almost unchanged in 2016 as compared to 2001.

Regarding the long-term results, does it matter if a distal radius fracture heals with malunion?

In 1814, Abraham Colles (1773-1843) described in detail the fracture of the distal radius in his classic article, proposed a treatment and made a prediction about the outcome of the malunited distal radius fracture;

"One consolation only remains, that the limb will at some remote period again enjoy perfect freedom in all its motions, and be completely exempt from pain: the deformity, however, will remain undiminished through life" [118]

Colles predicted that even with a malunited distal radius, in the long term, the patient would regain full range of motion and be completely free from pain despite persistent deformity. While some more recent studies have shown an association between malunion and worse functional outcomes and symptoms [91,102,119,120] other studies have found conflicting results or no association between unacceptable radiological parameters and patient outcomes following distal radius fracture, especially among elderly patients [103,121,122]. Controversy still exists regarding whether distal radius fracture malunion is associated with greater disability and poor functional outcomes. This issue is important because it may impact the choice of treatment, since treatment methods may differ in their ability to restore anatomy.

Paper II showed that, at a long-term follow-up (12 to 14 years), adults with malunion of the distal radius fracture defined as dorsal angulation of ≥10°, ulnar variance of ≥3 mm, and/or radial inclination of ≤15° had greater activity limitations as reported on the DASH questionnaire, worse pain, and lower satisfaction than those whose healed fracture did not meet the criteria for malunion. The effect of malunion did not differ with age at the time of fracture. However, although the difference in DASH score over time between the cohort with malunion and the cohort without malunion was significant and larger than the MCID, it was close to the MCID (i.e., 10 points in accordance with previous research [92,123]).

The MCID represents the smallest improvement in a score to reflect a change that is clinically meaningful for the patient. The concept has been developed to overcome the shortcomings of the statistically significant difference which might not necessarily reflect a meaningful difference of clinical relevance to the patient. However, there are different methods to determine the MCID which yield different values for the MCID [124]. For the DASH score, various MCID values have been reported ranging from 6.5 to 14.5, while for the QuickDASH the reported MCID values have ranged from 7.9 to 17.2 points [46]. None of these previous estimates of the MCID was developed specifically for patients recovering from a malunited distal radius fracture.

In addition to finding a statistically significant and clinically important difference in long-term patient-reported outcomes between patients with malunion and those without malunion, the analyses of the relationship between the DASH scores and the radiographic variables of dorsal tilt, ulnar variance, and radial inclination (analysed as continuous variables without cut-offs) showed significant associations in the same direction as in the binary malunion definition.

These results could be interpreted as that with increased deformity there is an increased risk of greater long-term disability and pain. Knowledge about long-term outcomes of distal radius fracture malunion can influence decisions about treatment of acute fractures as well as whether and when to perform a corrective osteotomy.

The development of radiocarpal OA following intra-articular distal radius fractures that had healed with substantial articular incongruity is well-known [125,126]. However, little has been known about the extent to which radiocarpal OA affects long-term functional and patient-reported outcomes. A previous study found mild radiocarpal OA in 20 of 153 patients at 9 to 13 years after the distal radius fracture, with no relation to clinical outcome [127]. Another retrospective study found that seven years after the distal radius fracture, 16 of 21 patients had radiocarpal OA on both radiographs and computed tomography (CT), but without correlation to patient-rated- or functional outcomes [125]. A subsequent re-evaluation at 15 years after the fracture showed that radiocarpal OA had worsened, but the patients had maintained good function [126]. A retrospective study of 106 adults who sustained a distal radius fracture when they were younger than 40 years found that, at 38 years after the fracture, 53% had radiographic OA that was mild in the majority and had no relationship with functional outcome except for loss in wrist flexion [128]. However, a study of 54 patients, all with AO type-C fractures treated with volar locking plate reported, based on a simple correlation analysis, that radiocarpal OA correlated with patients' subjective results but not with objective results six years after the fracture [129]. The results of *Paper II* show that at 12 to 14 years after the fracture, 60% of the patients had radiocarpal OA (mostly mild) but with no association with DASH, pain or satisfaction scores. Mild (grade 1) OA may not be enough to affect patient-reported outcomes.

Distal radius fracture is frequently associated with ulnar styloid fracture and there have been concerns that ulnar styloid nonunion may be an indicator of associated soft-tissue injuries with increased risk of disability [83-85]. However, several studies and a recent meta-analysis have concluded that ulnar styloid nonunion does not influence the short-term outcome [83-85]. The long-term results in *Paper II* support the conclusion that ulnar styloid nonunion in patients with distal radius fracture has little effect on patient-reported disability, pain, and satisfaction.

Paper II had strengths and limitations. There have been no other studies that involved long-term outcomes of distal radius fractures in relation to fracture malunion using a validated PROM with baseline values. One limitation was the incomplete patient participation; of the 85 living patients eligible for the study (without subsequent fracture), 63 (74%) provided PROMs and underwent physical and radiographic examination. However, the additional 14 patients (16%) who provided patient-reported outcomes without attending examinations did not differ substantially from those who underwent examinations and the eight nonparticipants had better 2-years DASH scores. Baseline DASH scores were missing in 15 of the 63 patients, but the GEE analysis accounts for missing data and utilizes all available data from all patients. The VAS pain and satisfaction scores were only measured at the time of follow-up and the satisfaction scores, although generally consistent with the other scores, showed larger variability among those with malunion. Another limitation was the lack of radiographic examination of the non-injured wrist, which would have provided useful information but would have involved ethical issues of asking asymptomatic individuals to undergo bilateral wrist radiography. Determining radiocarpal OA on radiographs may be an imprecise technique and CT could have been more accurate. The study did not address possible associated ligament injuries. However, scapholunate dissociation was rare, and there is no suggestion that clinically important ligament injuries are more common in fractures that healed with malunion.

The question still exists: does it matter for the patient if a distal radius facture heals with malunion?

In the cohort with long-term follow-up of patients with previous distal radius fracture (*Paper II*), patients with malunion were more likely to have worse long-term outcomes including activity limitations and pain. However, other authors found no association between radiological outcomes and patient-reported outcomes [122,130,131]. Discrepancy between the results from various studies existed and the evidence remained unclear. One striking observation was the large variation in the quality of the different studies. Thus, it was deemed important to perform a systematic review and meta-analysis of high or moderate quality studies to address the question.

The systematic review and meta-analysis in *Paper III* showed a statistically significant association between distal radius fracture malunion and greater patient-reported disability as measured with the DASH, QuickDASH or PRWE, with a moderate effect size in terms of clinical importance. The analysis excluded studies with high risk of bias on the QUIPS tool. This approach, previously recommended by other authors [132,133], would yield results that more accurately reflect the effect of malunion on patient-reported outcomes.

The results are in the same direction as those of a previous meta-analysis by Mulders et al. (search until October 31, 2016; 582 observations), showing that an "unacceptable" radiological reduction of distal radius fracture in adults was associated with worse patient-reported outcomes measured with DASH, QuickDASH or PRWE [134]. The difference in patient-reported outcomes found in the meta-analysis by Mulders et al. was however considered by the authors to be small and unlikely of clinical importance. One of the six studies in the meta-analysis by Mulders et al. included patients above 55 years of age with less than 12 months of follow-up [122], another included patients with radiographs performed less than three months after the fracture [130], and one study included only patients above 60 years of age with unclear malunion definition and possible high risk of bias regarding study participation rate [121]. Besides, the study by Mulders et al. showed significant heterogeneity among the included studies. The above-mentioned limitations of the study of Mulders et al. may explain the small difference found in patient-reported outcomes between patients with and without malunion. In the meta-analysis (*Paper III*) the effect size was moderate indicating clinical importance.

Paper III has some strengths and limitations. The search strategy, constructed with the help of a clinical librarian, was comprehensive and the search criteria aimed to include any study that potentially reported on distal radius fractures and presented radiological outcome measures to identify malunion (Appendix1). Another strength was the stringent eligibility criteria applied to include a study in this review and meta-analysis. These criteria demanded that the patient-reported outcome measure had been collected not earlier than one year after the fracture and that the radiographs had been performed not earlier than three months after the fracture. Studies with less than one year of follow-up may not reflect the long-term effect of malunion on the patient-reported outcomes. Besides, relying on radiographs performed earlier in the follow-up period may underestimate the extent of malunion.

One limitation was that the included studies had some differences in the definition of malunion, reflecting current lack of consensus regarding which radiological criteria should be used to define malunion. However, the definitions used by the included studies did not show large discrepancy. In fact, five of six included studies used a cut-off value of >10° of dorsal angulation as part of the definition of malunion. As cut-off for ulnar variance three studies used 3 mm and the other three used 2 mm. Although it is unknown to what extent the patients in these studies had knowledge about their radiological outcomes, which could potentially have affected self-reported disability scores, it is highly unlikely that patients were informed about the exact radiological values before being asked to complete the scales. Another possible limitation was the different fracture types and treatment methods in the included studies.

Although the secondary meta-analysis (six studies included) also showed that patients with distal radius fracture malunion had significantly worse patient-reported outcomes compared to patients without malunion with a moderate effect size, this analysis showed significant heterogeneity. In addition to the studies included in the primary analysis, the secondary meta-analysis included a study involving only patients above the age of 65 years [64]. That study did not find a statistically significant association between malunion and patient-reported outcome measures. This might indicate that malunion is more tolerable by elderly patients compared to younger individuals, depending on the individual level of activity and functional demands. However, further studies are needed to investigate whether age (or other characteristic) influences the association between malunion and disability.

Is artificial intelligence ready to help us in diagnosing radiocarpal osteoarthritis?

In contrast to prior successful results of AI trained computerized textural analysis of knee joint OA, the results could not be reproduced for radiocarpal OA in patients with a previous distal radius fracture. The computer software had poor ability to discriminate between radiocarpal OA and no OA. There are several possible explanations to the poor performance of the software in this cohort. First, the computer software was developed for the knee joint, and in *Paper IV* the radiocarpal joint was assessed. The mechanical and anatomical differences between the complex wrist joint and the weight-bearing knee joint may have importance in the development of OA [76]. In cross-sectional and longitudinal studies of hand and knee OA, Buckland-Wright et al. have shown that although changes were similar in early OA, with progression of the disease, cortical plate thickness in hand OA increased in 60% of the patients but did not change in knee OA patients until severe narrowing of the joint space occurred [76]. Additionally, in bone texture analyses, when the methods developed for detection of knee OA were directly applied to the finger joints, the results were considered encouraging, but not as reliable as the results shown for knee OA. This was due to the fact that the selected ROIs on hand radiographs were considerably smaller than those on knee radiographs not rendering enough data for analysis [77]. Altogether, those findings may suggest some differences in OA pathology in the hand compared to the knee that may affect texture analyses.

A second possible explanation is that patients with fracture might have altered microstructure of the subchondral bone. Rozental et al. showed worse trabecular bone microarchitecture at the distal radius manifested by reduced trabecular plate volume, number, thickness, and connectivity three months after a distal radius fracture in 40 premenopausal women compared to 80 non-fracture controls [135]. In fact, altered microstructure of the subchondral bone has been shown long time after a fracture. Stein et al. found a deterioration of the trabecular microarchitecture at the distal radius in 68 postmenopausal women at a mean (SD) of 5.5 (5.6) years after a variety of central and peripheral fragility fracture, including distal radius fracture, compared to 101 postmenopausal women without history of a fragility fracture [136]. Furthermore, Sornay-Rendu et al. found similar architectural alterations of the trabecular and cortical bone in 101 postmenopausal women 13 years after a fragility fracture, compared to 101 matched controls who never had a fracture [137]. It is possible that longstanding alterations of the trabecular bone after fragility fractures affect the computer software ability to differentiate cases with OA from those without OA.

The results showed that the sensitivity worsened after training the computer software while the specificity improved substantially, however, without improvement in the overall performance as the AUC was essentially unchanged. The reason for this shift in sensitivity and specificity is unknown. The person who operated the software was blinded to the labelling of the original 63 radiographs throughout the study, both before and after the software training.

The study has limitations. The labelled radiographs used to train the computer to recognize radiocarpal OA comprised patients with mixed OA cause, including distal radius fracture, scaphoid non-union, scapholunate ligament injury and Kienböcks disease. Different pathogenesis to the OA in this group could have affected the computer software's ability to train and the results may have been different if the software were trained with only cases of radiocarpal OA secondary to distal radius fracture. Another limitation was the used of the Kellgren-Lawrence scale as golden standard for defining OA. The scale is based on the presence of osteophytes and thus joint space narrowing, subchondral sclerosis and deformity are considered insufficient changes unless seen in conjunction with osteophytes [11]. Since the computer software is designed to recognize alterations in the subchondral bone rather than recognizing osteophytes, this could have affected the results. However, it is the most common classification system, and the radiographs were examined independently by two surgeons and the grading was the same for the majority.

Nine of the 63 study patients were treated using pins in the subchondral bone area of the distal radius which might have affected OA analysis. However, these pins were routinely extracted 4-6 weeks after surgery and the assessment of OA was done 12-14 years after the fracture and therefore, it is unlikely that initial treatment with pins would affect the results. Another limitation is that the sample size is relatively small. However, given the results, it is uncertain whether a larger sample size can substantially improve the performance of the software.

Conclusions

- The incidence of distal radius fracture has decreased during the last two decades, driven by lower incidence in individuals 50 years or older. This is an important development.
- Patients who sustain a distal radius fracture and develop malunion are more likely to have worse long-term outcomes including activity limitations and pain. Mild osteoarthritis of the radiocarpal joint is common 12 to 14 years after a distal radius fracture but does not seem to have clinical impact.
- There is evidence that malunion of distal radius fracture has a moderate negative effect on patient-reported outcomes. Treatment of distal radius fracture should aim to achieve fracture union with the best possible alignment.
- The software for computerized texture analysis of the subchondral bone developed for detection of early knee osteoarthritis could not detect osteoarthritis of the radiocarpal joint.

Future perspectives

The incidence of distal radius fracture is changing. In this thesis, I have shown that in a general population in southern Sweden the incidence of distal radius fracture has decreased during the past two decades. How the incidence rate will change in the future depends on several factors, including demographical, lifestyle and climate changes as well as fracture prevention and treatment programs. A new study estimating the incidence of distal radius fracture in the same region using similar methodology about 10-15 years from now would be important to monitor the change in incidence and to assess the effectiveness of fracture prevention programs.

The effect of malunion on patient-rated outcomes in adults recovering from a distal radius fracture has been debatable, especially in elderly patients. In this thesis, I have shown that malunion after distal radius fracture is associated with greater patient-reported disability. Whether age or other characteristics affect the association between malunion and disability is still an unanswered question. As many elderly individuals remain physically active and have higher functional demands, I believe that in future research, it is more relevant to assess whether the patient's level of activity rather than age affects the association between malunion and patient-reported outcomes and function.

Although the literature about distal radius fracture is massive, few studies have evaluated the clinical effect of malunion. To increase the knowledge about the outcomes in patients with a malunited distal radius fracture, it would be of great value if future studies on distal radius fracture report outcomes according to malunion, even if it is not the study's primary research question.

Even if systematic reviews present data about the risk of bias of the included studies, the results of such reviews are influenced by the included biased studies which would yield inaccurate estimates that may not reflect the true evidence. Therefore, I would encourage authors of systematic reviews to exclude studies with high risk of bias.

The use of AI based computer programs as diagnostic tools in the medical field is interesting, and future AI based programs, developed specifically for the wrist joint, might enable physicians and researchers to improve the quality and effectiveness in diagnosing radiocarpal OA.

Summary in Swedish

Brott på strålbenet på handledsnivå (handledsbrott) är den vanligaste frakturen som drabbar människan. Både män och kvinnor i alla åldrar, från barn till de äldre kan drabbas. Hos yngre individer sker handledsbrottet oftast i samband med högenergitrauma såsom trafikolyckor och fall från hög höjd, eller som ett resultat av olyckor under idrottsutövning eller på fritiden. Hos individer i medelåldern och hos de äldre är lågenergitrauma såsom fall i samma plan den vanligaste orsaken till brott på handleden. Handledsbrott drabbar framför allt kvinnor från 50 år och uppåt på grund av en stark koppling till benskörhet.

Det finns olika metoder för att behandla en handledsfraktur, både kirurgiska och icke-kirurgiska. Valet av behandlingsalternativ beror på olika faktorer. Målet med behandlingen är att läka frakturen så att patienten kan återfå sin handledsfunktion utan smärta.

Under de senaste två decennierna har sjukvården implementerat vårdprogram för att upptäcka och behandla benskörhet (som är en stark riskfaktor för benbrott) vilket kan ha påverkat förekomsten av handledsfrakturer. Två kända följder till en handledsfraktur är att frakturen läker med felställning eller att man får artros i handleden efter sitt handledsbrott. Vi har fortfarande inte tillräcklig kunskap om hur en felställning påverkar patientens egna upplevelser av handfunktion och smärta på lång sikt. Sådan kunskap är viktig eftersom den påverkar val av behandling.

Att ställa diagnosen handledsartros kräver att en läkare granskar röntgenbilderna, vilket både är en tidskrävande uppgift och inbegriper viss osäkerhet, då bedömningen av artrosens utbredning och svårighetsgrad är subjektiv.

I min avhandling har jag jämfört förekomsten av handledsbrott i Nordöstra Skåne i södra Sverige under 2016 med skadans förekomst under 2001. Jag har undersökt hur felställning av en handledsfraktur kan påverka patienternas handledsfunktion och symptom på lång sikt (12 till 14 år efter skadan). Jag har också undersökt kunskapsläget när det gäller frågan om hur felställning i frakturen kan påverka patienternas symptom. Jag har jämfört ett datorprograms förmågan i att upptäcka artros i handleden med standardmetoden (granskning av röntgenbilder av en läkare).

Jag har funnit att förekomsten av handledsbrott i Nordöstra Skåne under 2016 hade sjunkit med 24% jämfört med 2001. Patienter som får ett handledsbrott som läker med felställning löper större risk att på lång sikt ha sämre utfall, med mer smärta

och aktivitetsbegränsning jämfört med patienterna där frakturen läker utan felställning. Efter en omfattande litteratursökning fann jag evidens för att felställning efter en handledsfraktur har måttlig negativ påverkan på patientens handledsfunktion och symptom. Det AI baserade datorprogrammet för att upptäcka artros var inte redo för att upptäcka artros i handleden.

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Appendices

Appendix I. Search strategy

PubMed

("distal radius fracture" OR "distal radius fractures" OR "distal radial fracture" OR "distal radial fractures" OR "wrist fracture" OR "wrist fractures" OR "wrist-fracture" OR "wrist-fractures" OR "forearm fracture" OR "forearm fractures" OR "forearm-fracture" OR "forearm-fractures") AND (malunion OR mal-union OR malunited OR mal-united OR displaced OR dislocated OR dislocation OR dislocations OR radiological OR radiologic OR radiographic OR radiographical)

Embase

('distal radius fracture'/exp OR 'distal radius fracture' OR 'distal radius fractures' OR 'distal radial fracture'/exp OR 'distal radial fracture' OR 'distal radial fractures' OR 'wrist fracture'/exp OR 'wrist fracture' OR 'wrist fractures' OR 'wrist-fracture'/exp OR 'wrist-fracture' OR 'wrist-fractures' OR 'forearm fracture'/exp OR 'forearm fracture' OR 'forearm fractures' OR 'forearm-fracture'/exp OR 'forearm-fracture' OR 'forearm-fractures') AND ('malunion'/exp OR malunion OR 'mal union' OR malunited OR 'mal united' OR displaced OR dislocated OR 'dislocation'/exp OR dislocation OR 'dislocations'/exp OR dislocations OR radiological OR radiologic OR radiographic OR radiographical) NOT scaphoid NOT metacarpal NOT ('elbow'/exp OR elbow) NOT ('child'/exp OR child)

Cochrane

("distal radius fracture" OR "distal radius fractures" OR "distal radial fracture" OR "distal radial fractures" OR "wrist fracture" OR "wrist fractures" OR "wrist-fracture" OR "wrist-fractures" OR "forearm fracture" OR "forearm fractures" OR "forearm-fracture" OR "forearm-fractures") AND (malunion OR mal-union OR malunited OR mal-united OR displaced OR dislocated OR dislocation OR dislocations OR radiological OR radiologic OR radiographic OR radiographical)

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