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Epidemiological and clinical studies in Malmö, with focus on fracture classifications and their utility

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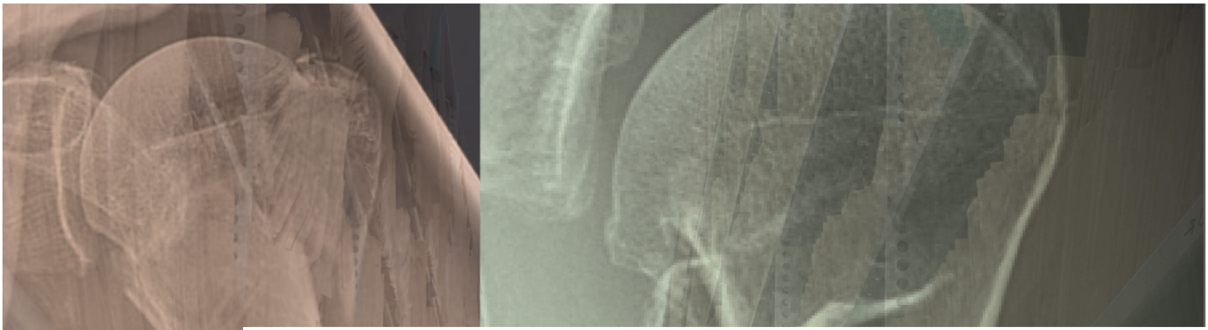

Proximal Humeral Fractures

Epidemiological and clinical studies in Malmö, with focus on fracture classifications and their utility

ANTON CEDERWALL

DEPARTMENT OF CLINICAL SCIENCES MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

Proximal Humeral Fractures

Epidemiological and clinical studies in Malmö, with focus on fracture classifications and their utility

Anton Cederwall

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 12th of December 2025 at 09.00 in Lilla Aulan, Jan Waldenströms gata 1, Malmö.

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Title and subtitle: Proximal Humeral Fractures - Epidemiological and clinical studies in Malmö, with focus on fracture classifications and their utility.

Abstract

Background: Proximal humeral fracture (PHF) is common and cause significant suffering for the affected individuals, but the long-term epidemiological data regarding PHF complexity, isolated greater tuberosity fracture (IGTF), and clinical long-term follow-up data for different fracture types treated non-operatively are insufficiently described in the present literature.

Aims: To increase the knowledge about PHF epidemiology (Paper I), PHF complexity (Paper II), IGTF epidemiology (Paper III) and the clinical long-term outcome after non-operatively treated PHF (Paper IV).

Methods: The data collection regarding Papers I-III is similar and is based on a review of radiographs over 17 sample years, between years 1944 to 2020, in the analogue- and digital archives in Malmö. PHF were classified according to the Neer- and AO-classifications. Paper IV is based on a previous follow-up of individuals regarding range of motion, pain and function 10 years after the fracture event.

Results: 3031 PHFs (73% women, mean age 69; men, mean age 59) were identified. The incidence was 52/100,000 in 1944, 120 in 1977, and 85 in 2020. A seasonal variation, with higher PHF incidence in winter months, was found 1944-1995 but not 2005-2020. No time trend in fracture complexity was observed. 614 IGTF (60% women, mean age 60; men, mean age 48) were identified. IGTF incidence was higher in men than women in the <50 age-group, but higher in women than men in the ≥50 age-group. Individuals with Neer 1 fractures had better 10-year outcome compared to Neer 3&4.

Conclusions: The age- and sex-adjusted incidence increased from 1944 to 1977, then decreased until 2020. A seasonal variation, with higher incidence in winter months, was apparent in earlier but not in recent decades. No time trend in fracture complexity was found with Neer or AO classifications from 1944 to 2020. IGTF is more common in men <50 years, and more common in women ≥50 years. Less complex PHF, according to the Neer classification, had better ROM and function compared to more complex PHF.

Key words: Proximal humeral fracture, epidemiology, incidence, classification, Neer, AO, time trends, isolated greater tuberosity fracture, clinical outcome.

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MADE IN SWEDEN

Till min familj

"Ett av symptomen på ett närliggande nervöst sammanbrott är tron att ens arbete är oerhört viktigt."

- Bertrand Russell

Table of Contents

Abstract

Background

Proximal humeral fractures (PHF) are common and cause significant suffering. Long-term epidemiological data regarding PHF complexity, isolated greater tuberosity fracture (IGTF), and clinical long-term follow-up data for different fracture types treated non-operatively are insufficiently described in the present literature.

Aims

To increase the knowledge about PHF epidemiology, PHF complexity, IGTF epidemiology and the clinical long-term outcome after non-operatively treated PHF.

Methods

The data collection for Papers I-III is similar and based on a review of radiographs from 17 sample years, between years 1944 to 2020, in the analogue- and digital archives at Skåne University Hospital, Malmö. PHFs were classified according to the Neer and AO classifications. Paper IV is based on a previous clinical follow-up of individuals regarding range of motion, pain and function 10 years after the fracture event.

Results

3031 PHFs (73% women, mean age 69; men, mean age 59) were identified in the archives. The incidence was 52/100,000 in 1944, 120 in 1977, and 85 in 2020. A seasonal variation, with higher PHF incidence in winter months, was seen 1944-1995 but not 2005-2020. No time trend in fracture complexity was observed from 1944 to 2020. 614 IGTF (60% women) were identified, the IGTF incidence was higher in men than women <50 years old, but higher in women than men ≥50 years old. Individuals with Neer 1 fractures had better 10-year outcome compared to Neer 3&4.

Conclusions

The age- and sex-adjusted incidence increased from 1944 to 1977, then decreased until 2020. A seasonal variation, with higher incidence in winter months, was apparent in earlier but not in recent decades. No time trend in fracture complexity was found with Neer or AO classifications from 1944 to 2020. IGTF is more common in men than women <50 years old, and more common in women than men ≥50 years old. Less complex PHF, according to the Neer classification, had better ROM and function compared to more complex PHF.

Populärvetenskaplig sammanfattning

Denna avhandling handlar om frakturer på den övre delen av överarmsbenet vid axeln (så kallade proximala humerusfrakturer). Trots att denna typ av fraktur är den fjärde vanligaste bland vuxna finns fortfarande många saker vi inte känner till.

Alla studier i denna avhandling handlar om vuxna personer i Malmö. Studierna försöker besvara följande frågor:

- Har förekomsten av axelfrakturer ändrats över tid, och i så fall hur? **(Studie I)**
- Finns någon skillnad i förekomsten av dessa frakturer mellan årets månader? **(Studie I)**
- Hur ser fördelningen, dvs. svårighetsgraden, ut mellan olika typer av axelfrakturer? Har svårighetsgraden ändrats över tid? Är svårighetsgraden olika för män och kvinnor samt i olika åldersgrupper? **(Studie II)**
- Hur vanlig är den typ av axelfraktur där endast en del av överarmsbenet, det s.k. tuberculum majus, är bruten, och hur ser fördelningen mellan olika typer av denna fraktur ut? **(Studie III)**
- Vilken rörlighet, smärta och funktion i axeln har personer som behandlats för sin axelfraktur utan operation 10 år efter frakturen? Är det någon skillnad vad gäller rörlighet, smärta och funktion beroende på vilken typ av axelfraktur de drabbats av? **(Studie IV)**

I Malmö finns ett röntgenarkiv där röntgenbilder från nästan alla röntgenundersökningar som gjordes på sjukhuset i Malmö sparats. För att besvara frågorna i **Studie I-III** bestämde vi oss för att granska röntgenbilder av axelområdet i detta arkiv för 17 år under perioden 1944 till 2020. När vi hittade en axelfraktur så granskade vi den utifrån de två mest använda klassifikationssystemen för denna typ av fraktur, Neer och AO. Totalt granskade vi fler än 6000 röntgenundersökningar och hittade mer än 3000 axelfrakturer.

Ungefär tre fjärdedelar av de drabbade var kvinnor och de hade en medelålder på ungefär 70 år, 10 år äldre än genomsnittsåldern för de män som drabbades. Vi kunde också se att axelfrakturer blev vanligare från 1944 fram till slutet av 1970-talet, därefter minskade förekomsten fram till vår undersökning tog slut år 2020. Under perioden 1944-1995 var axelfrakturer vanligare på vintern än på sommaren, medan förekomsten under året var mer jämnt därefter **(Studie I)**. Vad gäller svårighetsgraden av frakturerna såg vi ingen förändring från 1944-2020. Det verkar dock som att äldre personer drabbas av svårare frakturer än yngre **(Studie II)**. Den frakturtyp som bara drabbar en viss del av överarmsbenet, tuberculum majus, skiljer sig jämfört med andra axelfrakturer genom att de som drabbas är yngre och i högre grad män **(Studie III)**.

För att försöka besvara frågorna i **Studie IV** använde vi personer som hade en axelfraktur 1981, blev behandlade utan operation, och sedan följdes upp 10 år senare. De som deltog vid uppföljningen, vilket var 80% av de som fortfarande levde, undersöktes gällande rörlighet och svarade på ett formulär gällande smärta och funktion. Vi tog också fram de gamla röntgenbilderna från 1981 och klassificerade frakturerna (på samma sätt som i Studie II). Genom att jämföra rörlighet, smärta och funktion mellan olika frakturtyper kunde se att personer med mindre svåra axelfrakturer, enligt Neer klassifikationen, verkar ha bättre rörlighet och funktion 10 år efter skadan jämfört med de som drabbats av svårare frakturer. Denna koppling kunde vi inte se med AO klassifikationen, vilket gör att Neer klassifikationen verkar vara mer användbar för att förutse det kliniska långtidsresultatet.

Förändringar i förekomsten av axelfrakturer över tid kan ge värdefulla ledtrådar om kommande utmaningar för sjukvården. Genom att tydliggöra dessa kan sjukvårdsresurser fördelas dit behovet och nyttan är störst. Att hitta grupper av personer med hög frakturrisk gör det också möjligt att rikta förebyggande åtgärder dit de har störst effekt. Vidare kan information om frakturernas svårighetsgrad, tillsammans med långtidsresultatet för olika frakturtyper och tidigare data som beskriver utfall efter operation, ge vägledning kring vilka och hur många av dessa frakturer som är rimligt att operera.

Det kliniska långtidsresultatet efter behandling utan operation för olika typer av frakturer kan ha betydelse i den kliniska vardagen, till exempel när läkare och patient tillsammans ska bestämma om frakturen ska behandlas med eller utan operation. Det kan också användas som jämförelseunderlag vid utvärdering av olika, moderna behandlingsmetoder.

Sammanfattningsvis bidrar denna avhandling, och studierna som ingår i den, med svar på några viktiga frågor inom området axelfrakturer. Denna nya kunskap har också lett till att nya frågeställningar och utmaningar har identifierats som behöver undersökas i framtida studier.

List of papers

I. **Time trends in proximal humeral fractures from 1944 to 2020- A cohort study in Malmö, Sweden.**
Anton Cederwall, Magnus K Karlsson, Björn E Rosengren.
BMC *Musculoskeletal Disorders 2024; 25(1): 491.*

II. **No obvious time trend in proximal humeral fracture complexity - A cohort study from 1944-2020 in Malmö, Sweden.**
Anton Cederwall, Anders Nordqvist, Magnus K Karlsson, Björn E Rosengren.
Bone & Joint Open 2025; 6(9): 1006-1012.

III. **Epidemiology and time trends of isolated greater tuberosity fractures in Malmö, Sweden 1944-2020.**
Anton Cederwall, Björn E Rosengren, Henrik Ahlborg.
Shoulder & Elbow 2025; 17585732251344547.

IV. **The Neer classification, but not the AO classification, is associated with 10-year clinical outcome in non-operatively treated proximal humeral fractures - A cohort study in Malmö, Sweden.**
Anton Cederwall, Anders Nordqvist, Magnus K Karlsson, Björn E Rosengren.
Submitted to Journal of Shoulder and Elbow Surgery, 2025.

Description of contributions

Paper I

Study design: Anton Cederwall, Björn Rosengren and Magnus Karlsson

Data collection: Anton Cederwall

Data analysis: Anton Cederwall and Björn Rosengren

Manuscript writing: Anton Cederwall and Björn Rosengren

Manuscript revision: Anton Cederwall, Björn Rosengren and Magnus Karlsson

Paper II

Study design: Anton Cederwall, Björn Rosengren, Magnus Karlsson and Anders Nordqvist

Data collection: Anton Cederwall

Data analysis: Anton Cederwall

Manuscript writing: Anton Cederwall

Manuscript revision: Anton Cederwall, Björn Rosengren, Magnus Karlsson and Anders Nordqvist

Paper III

Study design: Anton Cederwall, Björn Rosengren and Henrik Ahlborg

Data collection: Anton Cederwall

Data analysis: Anton Cederwall

Manuscript writing: Anton Cederwall

Manuscript revision: Anton Cederwall, Björn Rosengren and Henrik Ahlborg

Paper IV

Study design: Anton Cederwall, Björn Rosengren, Magnus Karlsson and Anders Nordqvist

Data collection: Anders Nordqvist and Anton Cederwall

Data analysis: Anton Cederwall

Manuscript writing: Anton Cederwall

Manuscript revision: Anton Cederwall, Björn Rosengren, Magnus Karlsson and Anders Nordqvist

Thesis at a glance

Paper	Aims	Methods	Results	Conclusions
I	Primarily to describe time trends in the age- and sex-adjusted incidence of proximal humeral fractures (PHF) from 1944 to 2020. Secondarily to describe the monthly distribution of PHF incidence.	PHF were identified by reviewing relevant radiology examinations in adults during 17 sample years between 1944 and 2020 from the analogue and digital archives in Malmö. Joinpoint was used for time trend analyses.	3031 PHF were identified (73% women). The age- and sex-adjusted incidence was 52 per 100 000 in year 1944, 120 in 1977 and 85 in 2020. A seasonal variation in PHF incidence was apparent 1944-1995 but not in 2005-2020.	The age- and sex-adjusted incidence increased from 1944 until 1977, and thereafter decreased until 2020. A seasonal variation with higher incidence in winter months, was apparent in earlier but not in recent decades.
II	To explore possible time trends in PHF complexity and report the distribution of different types of PHF from 1944 to 2020 according to the Neer- and AO classifications.	We reviewed and classified relevant radiographic examinations in individuals ≥18 years with a PHF during 17 sample years from 1944 to 2020 in Malmö, Sweden using the Neer- and AO-classifications.	We saw no time trend in fracture complexity. Fracture complexity according to AO was higher in older than younger age-groups, which was true also with the Neer classification for women.	We found no obvious time trend in fracture complexity with the Neer or AO classifications from 1944 to 2020.
III	Describe the epidemiology and time trends of isolated greater tuberosity fractures (IGTF) in Malmö, Sweden, 1944-2020.	We identified IGTF in Malmö residents (≥18 years) by reviewing relevant radiology examinations during 17 sample years from 1944-2020. Fractures were classified according to the Mutch classification.	614 IGTF (60% women) were identified. In age-group <50 years the incidence was higher for men than for women, whereas the opposite was observed in age-group ≥50 years. No time trends in IGTF incidence were observed from 1944 to 2020.	IGTF is more common in men than women in age-group <50 years, while the opposite is found in age-group ≥50 years. No time trends were observed in IGTF incidence from 1944 to 2020 in Malmö, Sweden.
IV	To evaluate the long-term clinical outcome of non-operatively treated PHF across various fracture types using the Neer- and AO-classifications.	Individuals with a PHF were followed up regarding range of motion (ROM), pain and function 10 years after the fracture event. The PHF were classified according to the Neer- and AO-classifications for fracture type specific analyses	Individuals with Neer 1 fractures had better ROM and function compared to Neer 3&4 fractures. No association between fracture type and clinical outcome was apparent for the AO classification.	Individuals with less complex PHF according to the Neer classification had greater ROM and better function compared to those with more complex PHF 10 years after a non-operatively treated PHF.

Abbreviations

3D-CT	Three-dimensional Computed tomography
AI	Artificial intelligence
ANOVA	Analysis of variance
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	Anteroposterior
APC	Annual percent change
BMD	Bone mineral density
CI	Confidence interval
CMS	Constant-Murley Score
CT	Computed tomography
DASH	Disability of the arm, shoulder and hand
HA	Hemiarthroplasty
HSL	Hill-Sachs lesion
ICD	International classification of diseases
IGTF	Isolated greater tuberosity fracture
MCID	Minimal clinically important difference
PHF	Proximal humeral fracture
RCT	Randomized controlled trial
ROM	Range of motion
RSA	Reverse shoulder arthroplasty
SD	Standard deviation
SFR	Swedish Fracture Register
SPSS	Statistical Package for the Social Sciences
SUS	Skåne University Hospital

Introduction

History of PHF

The management of PHF has long posed challenges to medical practitioners and has been described in the earliest medical texts available. One of the earliest recorded treatments of PHF dates back to 460 BC when Hippocrates described a reduction method involving weight traction and manipulation (Figure 1). The outcome of this treatment is unknown, but based on my interpretation of the fascial expression of the individual in the image (Figure 1), it appears to have been a painful method [1, 2].

Figure 1. The Hippocratic method of PHF reduction. Reprinted from: Richter AL. *Theoretisch-praktisches Handbuch der Lehre von den Brüchen und Verrkungen der Knochen*. Berlin, Germany: Verlag von TCF Enslin; 1828).

The Hippocratic way of treating PHF was largely unchanged until the late 18th century. In the 19th century, a better understanding of the anatomy, largely due to topographic features and postmortem examinations, led to the development of new treatment methods for these fractures. Surprisingly accurate insights into different fracture patterns were made and described, even before radiographs existed [2].

In 1851, Johann Ludwig Wilhelm Thudichum in the city of Giessen, Germany, proposed a PHF classification in his doctoral thesis, freely translated to: "On the bone fractures occurring at the upper end of the humerus" [3]. This classification divides the proximal humerus into distinct anatomical regions and includes subgroups based on whether the fracture is impacted and whether a concomitant dislocation is present. Considering that roentgen rays had not been invented at the time, Thudichum´s classification is surprisingly similar to the most commonly used classification systems for PHF today [3].

A successful method of treatment with immobilization in a sling followed by physiotherapy was described by Cooper in 1839 [4]. Throughout history, a variety of methods for immobilizing the arm during the healing period have been described. Liston´s bandage, which provides valgus pressure and compression over the hand and forearm to reduce swelling, and Hamilton´s bandage, which applies a continuous traction along the longitudinal axis of the humerus, are two of many examples (Figure 2).

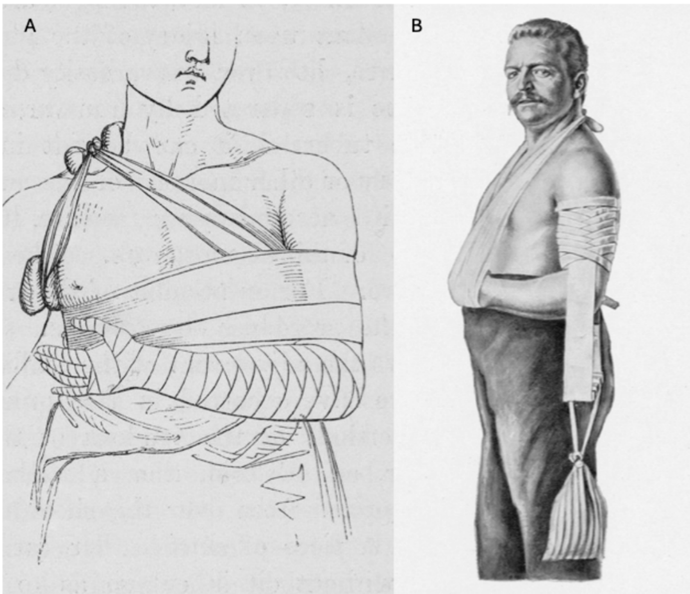


Figure 2. Historical immobilization methods. A: Liston´s bandage. Reprinted from Liston R. *Practical Surgery*. 2nd ed. London, England: John Churchill; 1838. **B**: Hamilton´s bandage. Reprinted from Hoffa A, Grashey R. *Verbandlehre* (first published 1896). 5th ed. Munich, Germany: JF Lehmans Verlag; 1914).

In 1896 Wilhelm Conrad Röntgen announced a new technique in his paper "On a new kind of rays" [5]. The introduction and clinical use of radiographs at the turn of the 20th century enabled imaging of PHF [6]. This led to an increased understanding and knowledge of PHF.

In 1908 Buchanan et al. reported cases related to the treatment of PHF dislocations. They treated a 73-year-old man with humeral head resection. He was ready for discharge 13 days later but tragically succumbed to diarrhea one week thereafter. A "male adult" was treated with open reduction of the humeral head and then "pegging", with primary union and a "fair" result [7].

In 1934, Ernest Almory Codman presented a morphological description of PHF, dividing the proximal humerus into four anatomical parts: the humeral head, the greater- and lesser tuberosity and the humeral shaft [8]. He observed that fracture lines typically occurred between these four parts in various combinations. Codman´s four part description has similarities to Thudichum´s classification from 1851 and is the precursor to the classification systems commonly used today.

Throughout the 20th century, various treatment methods have been described, including the use of wires, screws, pins and suture materials (Figure 3). However, these approaches had high incidence of malunions, infections and other complications which dampened the enthusiasm for their use [9].

In the 1950s intramedullary nailing was developed and at the end of the 1960s the Arbeitsgemeinschaft für Osteosynthesefragen (AO) group in Switzerland developed plates for internal fixation and reported promising results. Their results were difficult to reproduce and hardware loosening in the osteoporotic bone was common. In an attempt to provide better fixation in osteoporotic bone and allowing soft tissue fixation via suture materials to small holes in the plate angular stable plates were developed at the beginning of the 21st century [9]. The clinical outcome following operative treatment do not seem superior to non-operative treatment, but concerns with operative treatment persist regarding adverse events and the need for reoperations [10].

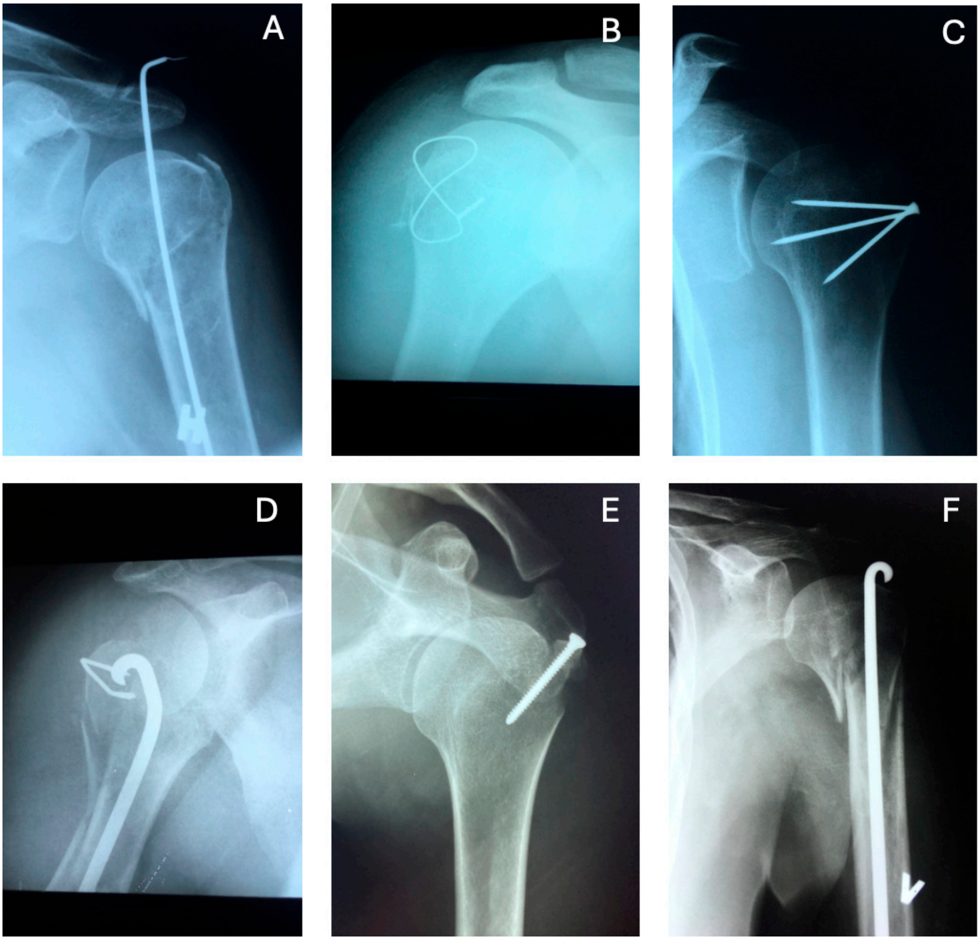


Figure 3. Treatment methods for PHF during the 20th century. A: Wire. B: Cerclage. C: Nails. D: Rushpin and bone-staple. E: Screw. F: Rushpin. All radiographs photographed by the author in the analogue radiology archive in Malmö, Sweden.

In 1970 Charles Neer reported promising results after hemi-arthroplasty (HA) in individuals with a PHF [11]. However, replicating these results has proven difficult, and recent studies indicate rather disappointing clinical outcome, particularly when the tuberosities fail to heal [12]. The reversed shoulder arthroplasty (RSA) was introduced at the end of the 20th century [13]. RSA have shown better and more reproducible clinical outcome than HA [14] and has recently gained popularity in the treatment of PHF [15].

Despite technical advancements in diagnostic imaging and treatment methods with for example plates, screws, suture materials, prostheses since Hippocrates' time, a recently published systematic review found no advantage in clinical outcome for operative- compared to non-operative treatment [10].

Despite the lack of evidence favoring operative over non-operative treatment of PHF [10, 16-22], the proportion of operatively treated individuals with a PHF increased during the first decade of the 21st century. In Finland a 4-fold increase in the incidence of operative treatment of PHF between 1987 and 2009 was seen [23] and a report from Sweden demonstrated an almost two-fold increase in the operative treatment rate between 2001-2012 [24].

During the 2010s, a change in the increasing frequency of operatively treated PHF was seen in Finland, Denmark, and the USA [25-27]. In Denmark, Brorson et al. reported a declining trend from 2008 (17%) to 2018 (11%) in the proportion of operatively treated individuals with a PHF [25]. Patel et al. also found a decrease in the same proportion in USA between 2010 (20%) and 2019 (15%) [27]. Leino et al. reported the incidence of operatively treated individuals with a PHF in Finland and found an initial increase between 1997 and 2009 (11 to 19 per 10^5 person years) followed by a decrease between 2009 and 2019 (19 to 13 per 10^5 person years) [26].

The city of Malmö

Malmö is a city in the south of Sweden (Figure 4) that had 131 718 adult inhabitants in 1944, which increased to 273 455 in 2020. The city has one emergency hospital, the Skåne University Hospital (SUS), where acute fractures were treated throughout the period covered by the papers included in this thesis.

In the mid-20th century, Malmö was one of Sweden´s wealthiest industrial cities, with hundreds of factories and high employment, exemplified by Kockums, which in 1973-1974 erected the world´s largest gantry crane. Due to global competition and oil crises, the city lost jobs and population. Since then, Malmö has transformed into a more modern, knowledge-based city [28].

The mean temperature in Sweden has increased from the 1940s until 2020 [29], as has the number of days without snow in the south of Sweden when comparing the time periods 1960-1990 and 1990-2014 [30].

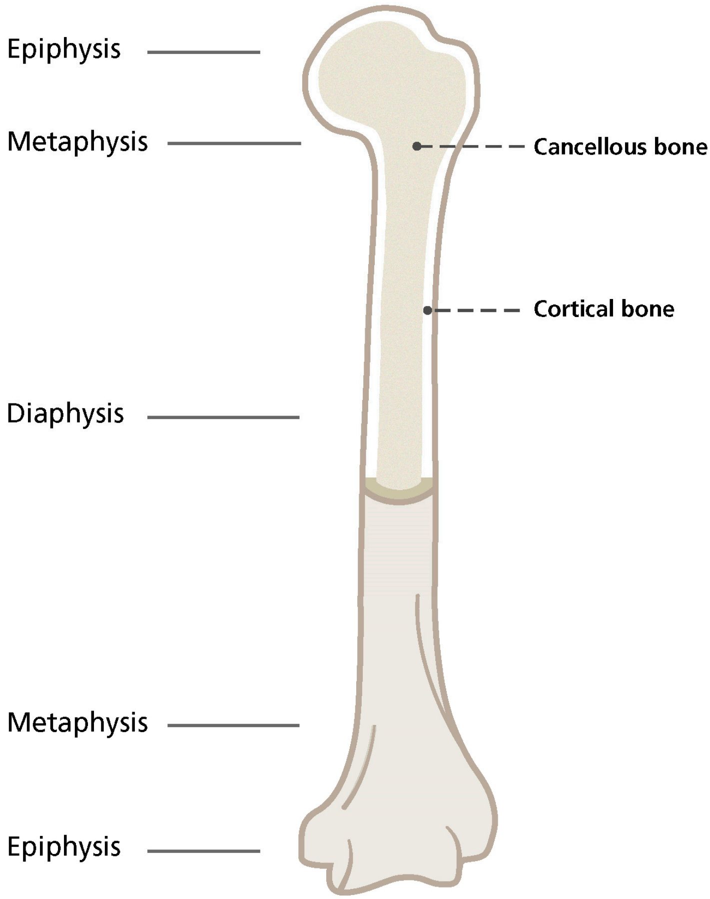
According to data from 2024, Malmö is Sweden's third-largest city and one of its fastest growing urban areas. The population is young, with nearly half of the inhabitants under the age of 35. Roughly one-third of Malmö's inhabitants were born outside of Sweden, and the city is home to people from more than 180 different countries, contributing to its present multicultural character [31]. However, Malmö has not always been this diverse; demographic changes have taken place during the period covered by this thesis. During the 1980´s immigration increased to Sweden and Malmö, especially from Iran, Chile, Lebanon, and Turkey, in the early 1990´s from former Yugoslavia [32] and in the mid 2010s also from Syria [33].

Figure 4. Photographs from Malmö, 1947 and 2021. A: Bergsgatan in Malmö 1947. In the photo, the 25-years old elephant Karnaudi is followed by admiring children as he makes his way to Mazetti´s Chocolate Factory to move a six-ton steam boilder. Note the left-hand traffic. Unknown photographer, MSA collection, Malmö City Image Archive. Reprinted with permission from Malmö City Image Archive. **B:** Bicycles and e-scooters in Malmö city center 2021. Photograph by News Øresund - Jenny Andersson. Licens: CC BY 3.0

Bone and fracture

Bone

Bone is a structure in the human body that protects organs in the body, produce red and white blood cells, store minerals, enable mobility and provide structure and support for the body. Human bone consists of 50-70% mineral, mainly hydroxyapatite, 20-40% organic matrix, mainly collagen, and 5-10% water. It is the mineral that gives the bone its rigidity and load-bearing strength and the organic matrix that provides flexibility and elasticity. The external portion of the bone, the cortical bone, is stronger and denser than the cancellous, or trabecular, bone which is the internal tissue of skeletal bone arranged in a honeycomb-like network. The cancellous bone is weaker, more flexible and more biological active than the cortical bone. The bone mass in the adult human skeleton comprises 80% cortical- and 20% cancellous bone overall. There are four main categories of bone: long, short, flat and irregular bone. Long bones, like the humerus, consist of the epiphysis, metaphysis, and diaphysis [34]. The physis, the growth zone, is located between the epi- and metaphysis. The proximal humeral physis contributes approximately 80% to the total longitudinal growth of the humerus. Physeal closure in the proximal humerus begins around age 14 in females and 16 in males, and is typically complete by 17 to 18 years of age [35]. The central part of long bones is called the diaphysis. The diaphysis is composed primarily of dense cortical bone, whereas the metaphysis and epiphysis are composed of cancellous bone surrounded by a relatively thin shell of dense cortical bone (Figure 5) [34].



Figur 5. Bone structure. Long bone structure illustrated by a humerus. Illustration by Katarina Jandér. Reproduced with permission.

Osteoporosis

Osteoporosis is a silent disease, often unknown by the affected individual, until the symptom - a fracture - occurs.

The disease is characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures [36]. The diagnosis of osteoporosis is based on measurements of bone mineral density (BMD), usually with Dual-energy X-ray absorptiometry. The definition of osteoporosis is BMD equal to or less than 2.5 standard deviations (SD) below the mean BMD of a young, healthy reference population. Individuals with osteoporosis are at greater risk of suffering from a PHF than individuals without osteoporosis [37].

Fracture

A fracture is a mechanical event that occurs when a force applied to the bone, such as during a fall from a standing height, exceeds bone strength and results in structural failure [38]. Bone strength is a multifactorial term, influenced by bone stiffness and the ability of the bone to undergo deformation and absorb energy. The BMD, used to diagnose osteoporosis, correlates with bone stiffness but is just one of many factors effecting bone strength [39]. Fractures occur through a process involving nonlinear material and structural behaviour which leads to the accumulation of sub-microscopic damage merging into a macroscopic ‘‘fatal” crack [38]. Fractures resulting from low-energy trauma, a force equivalent to a fall from a standing height or less, are usually called fragility fractures. A risk factor for fragility fracture is reduced BMD, i.e. osteoporosis or osteopenia [40]. PHF is often described as a fragility fracture, associated with osteoporosis or osteopenia [37].

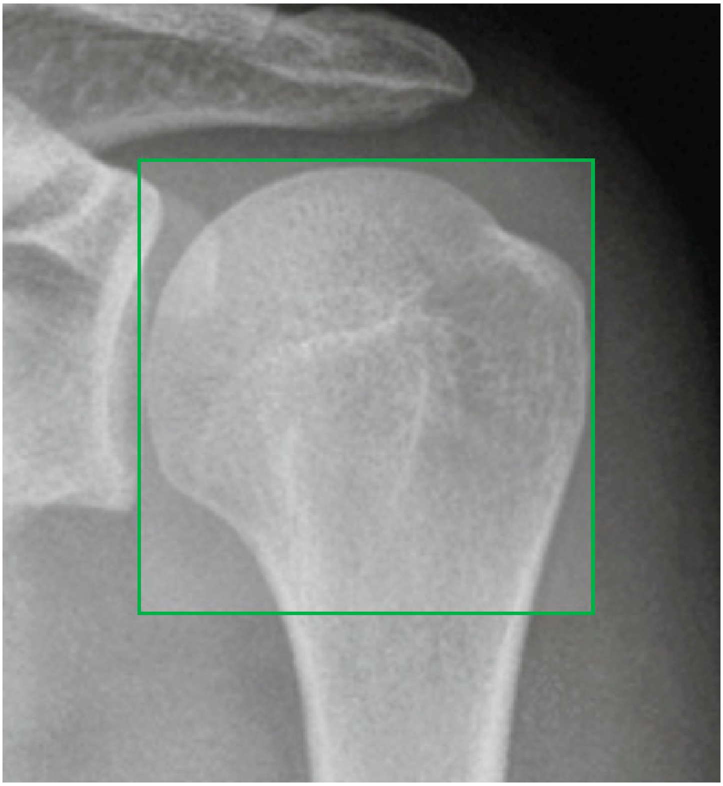


Figure 6. The proximal humeral region. Radiograph of a normal shoulder with a square with sides equal to the width of the caput humeri, i.e., the area within the square defines the proximal humeral region. Photographed and illustrated by the author.

Proximal humeral fracture

In the AO Fracture and Dislocation Classification Compendium from 2018 a PHF is defined as a fracture within the proximal humerus region (Figure 6 and 7). The proximal humerus region is defined as the area created by a square with sides equal to the caput humeri width (Figure 6) [41]. An isolated greater tuberosity fracture (IGTF) is defined as a fracture within the proximal humeral region only involving the greater tuberosity. These definitions are used throughout this thesis, and all papers included in it.

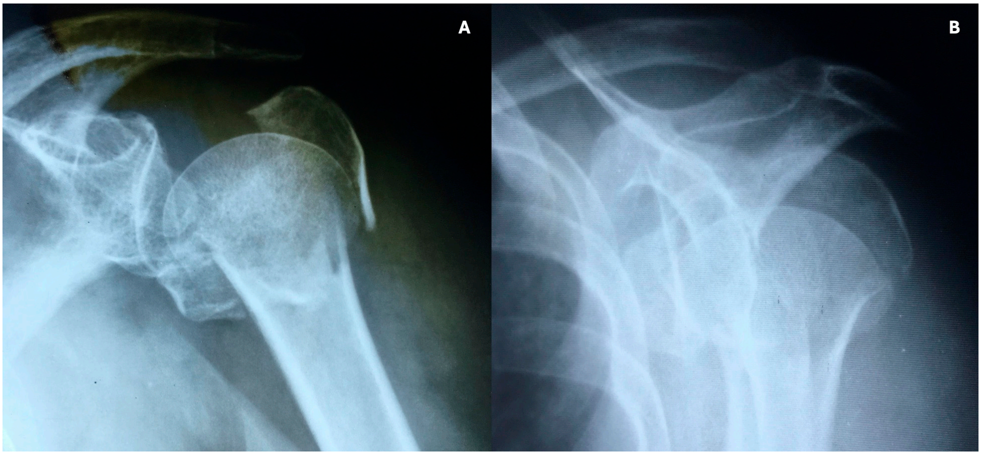


Figure 7. A Proximal Humeral Fracture. A. Anteroposterior view. B. Scapular Y-view. Photographed in the analogue archive in Malmö, Sweden, by the author.

Anatomy

The shoulder is a complex joint with a wide range of motion (ROM) and its function and stability depends on bones, joints, muscles, ligaments and the capsule to interact properly [42]. This section will focus on the proximal humerus region.

The bony parts of the proximal humeral region consist of the head, the shaft, the intertubercular groove and the greater- and lesser tuberosities (Figure 8). The anatomical neck, collum anatomicum, divides the head from the tuberosity region. The surgical neck, collum chirurgicum, divides the tuberosity region from the shaft. The lesser tuberosity is located in the anterior aspect of the proximal humerus and is the insertion site for the subscapularis tendon. Lateral to the lesser tuberosity is the intertubercular groove, where the tendon of long head of the biceps normally lies. The greater tuberosity is located further lateral and posterior to the intertubercular groove and is the insertion site for the supraspinatus, infraspinatus and teres minor tendons [42].

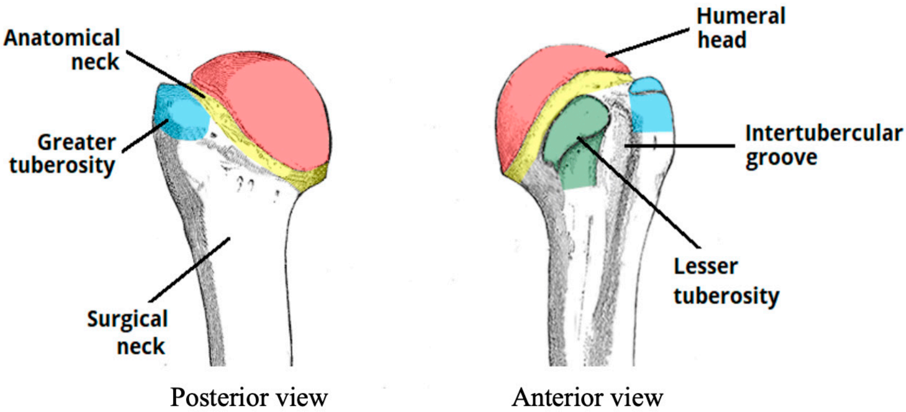


Figure 8. The bony anatomy of the proximal humeral region. From The Humerus, by Oliver Jones, 2024, https://teachmeanatomy.info/upper-limb/bones/humerus. Reprinted with permission from TeachMeSeries.

The rotator cuff and deforming forces

The rotator cuff is composed of four muscles/tendons (subscapularis, supraspinatus, infraspinatus and teres minor). The subscapularis internally rotates the humerus, the supraspinatus abducts the humerus and the infraspinatus and teres minor externally rotate the humerus [42]. When a PHF occurs the bony parts can be displaced by the tendons/muscles attached to them [43]. The displacement pattern is influenced by the location of the fracture lines and by which muscles mainly affect the fragments (Figure 9). For example, in the case of a fracture of the greater tuberosity the supraspinatus, infraspinatus and teres minor can displace the greater tuberosity posteriorly and superiorly. In the case of a three-fragment fracture with fracture lines between the head and shaft and between the head and the greater tuberosity the subscapularis can rotate the head fragment internally because the lesser tuberosity still is attached to the humeral head [43].

The deltoid muscle inserts on the deltoid tuberosity on the humeral shaft and can displace the shaft laterally and cranially. The pectoralis major muscle with insertion on the lateral, distal aspect of the intertubercular groove can displace the shaft medially [43] (Figure 9).

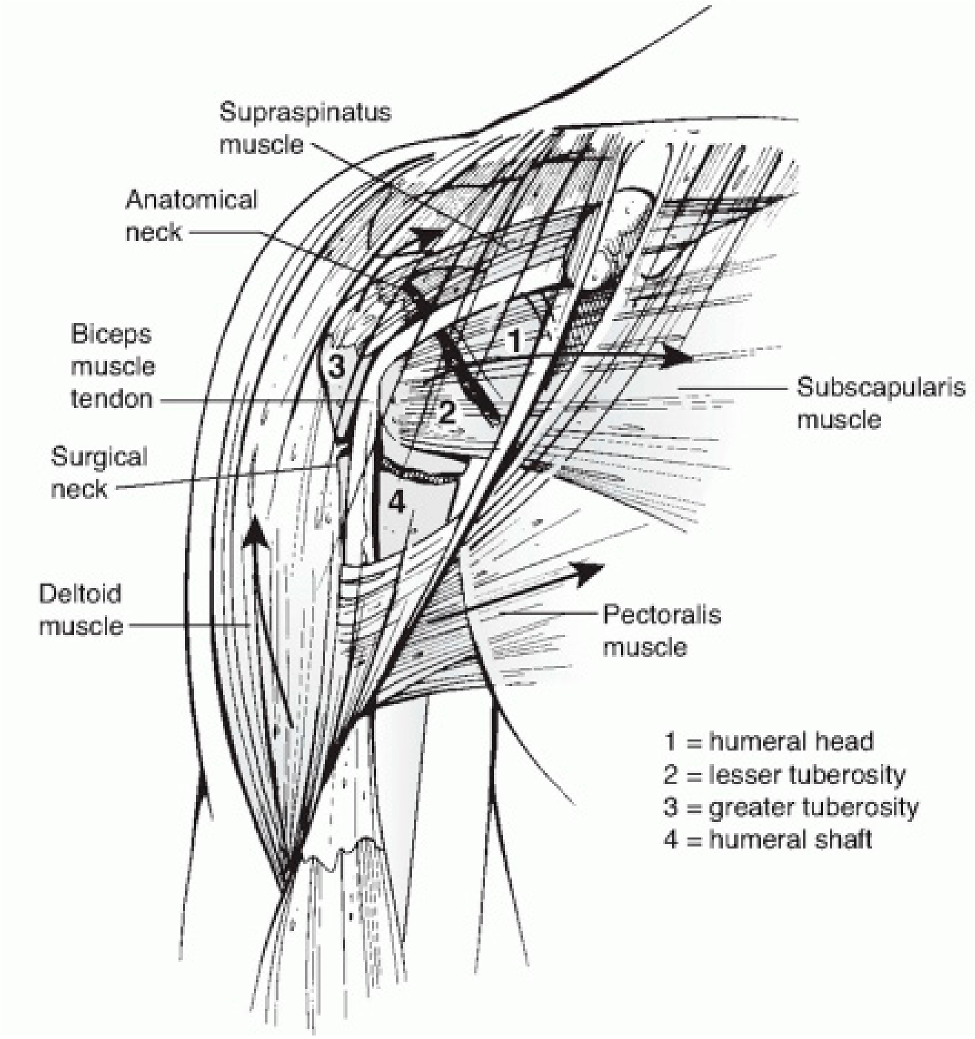


Figure 9. PHF deforming forces. From Rockwood and Greens fractures in adults, by Paul Tornetta, 9th edition. Reprinted with permission from Wolters Kluwer Health, Inc.

Vascular supply and risk of avascular necrosis

The anterior- and posterior circumflex arteries supply the proximal humerus with blood. Both arteries arise from the axillary artery. The arcuate artery is a continuation of the anterior humeral circumflex artery and penetrates the bone in the area of the intertubercular groove. The anterior circumflex artery has previously been considered the main source of blood to the proximal humerus [44] but this was questioned in 2010 when a cadaveric study reported that 64% of the blood to the proximal humerus originates from the posterior circumflex artery [45].

In 2004 Hertel et al. described three features on preoperative radiographs that may influence blood supply and the risk of avascular necrosis of the humeral head. According to the study a combination of a medial metaphyseal head extension of less than 8mm, a disrupted medial hinge (more than 2mm diastasis between head and shaft medially) and a fracture of the collum anatomicum resulted in a 97% risk of having ischemia of the humeral head [46]. Subsequent studies have however reported a poor ability of the Hertel system to predict avascular necrosis in PHF [47, 48].

Risk factors

The risk of PHF has been associated with factors such as bone strength and an increased tendency to fall. It has been reported that women afflicted solely with either osteoporosis or a high fall risk exhibit only a marginally elevated incidence of PHF in comparison to women lacking these risk factors. However, the incidence of PHF in women with both osteoporosis and a high fall risk is more than twice as high compared to women lacking these risk factors [37].

Numerous variables exert influence on the risk of falls and bone strength. The following table lists some of these factors, though it is not intended to serve as a complete description of all factors affecting the risk of falling and bone strength (Table 1) [37, 49].

Table 1. Examples of risk factors for proximal humeral fracture.

Fall risk	Bone strength
History of fall	Low BMD
Diabetes mellitus	High age
Epilepsy	Female sex
Left handedness	Maternal history of hip fracture
Visual impairment	Personal history of fracture
Impaired balance	
Lower extremity pain	
Low physical activity level	

A high body mass index has been reported as a risk factor for PHF in one study [50], whereas another study did not find this association [37].

Lee et al. found that a low BMD and a history of maternal hip fracture, which reflects family transmission of factors that influence the determination of bone mass, were associated with a higher risk of PHF [37].

Previous falls, impaired balance and pain in the lower extremity are all associated with a tendency to fall and are risk factors for a proximal humeral fracture. A high level of physical activity is generally considered to be a protective factor since it affects both bone strength and neuromuscular control positively. Conversely, Lee et al. found that women practicing one physical activity were at higher risk of humeral fracture than women who did not practice any activity at all. This finding suggests that for certain individuals with compromised physical condition, engaging in a physical activity may be more hazardous than beneficial [37].

Chu et al. identified left-handedness as a risk factor for PHF, demonstrating an odds ratio of 2.6 compared to right-handed individuals. It has been hypothesized that left-handedness may serve a marker for biologically inherent risk factors associated with falls, and that the increased fracture risk among left-handed individuals are the consequence of an environment developed mainly for right-handed people [49].

Trauma mechanism and clinical presentation

87% of PHF are caused by a fall from standing height [51]. Classically, the patient will have fallen from standing or sitting onto an outstretched hand or directly onto their side with a point of impact at the lateral aspect of the shoulder [52]. In younger individuals, the mechanism is more likely to be one of high energy trauma [51].

On presentation, the patient typically holds the injured arm in a protective posture close to the chest. On palpation, there will be tenderness at the proximal humerus. A restricted ROM, pain, swelling, ecchymosis and tenderness of the proximal portion of the humerus may also indicate the presence of a PHF. Neurological symptoms may be present, manifesting as numbness, tingling, or weakness in the arm or hand [53]. The axillary nerve is most commonly affected, with reduced sensation on the skin in the proximal humeral region as the main finding in the acute setting [54]. Vascular involvement is less common, but it is important to also examine the circulation in the injured arm since impaired circulation need immediate attention and significantly affects the timing of treatment for the fracture.

Radiology

Initial radiological investigation of a suspected PHF should include a standard shoulder trauma series with an anteroposterior- (AP), a lateral scapular Y- and an axillary-view (Figure 10). The axillary view is often unobtainable in the acute setting because of pain [55]. The AP view can be taken with the arm in a neutral position, where the contour of the greater tuberosity is visible, and/or with the arm internally rotated, where the posterior part of the proximal humerus is better visualized. These images enable fracture classification and are most often the only radiological investigation needed in the acute setting of a PHF.

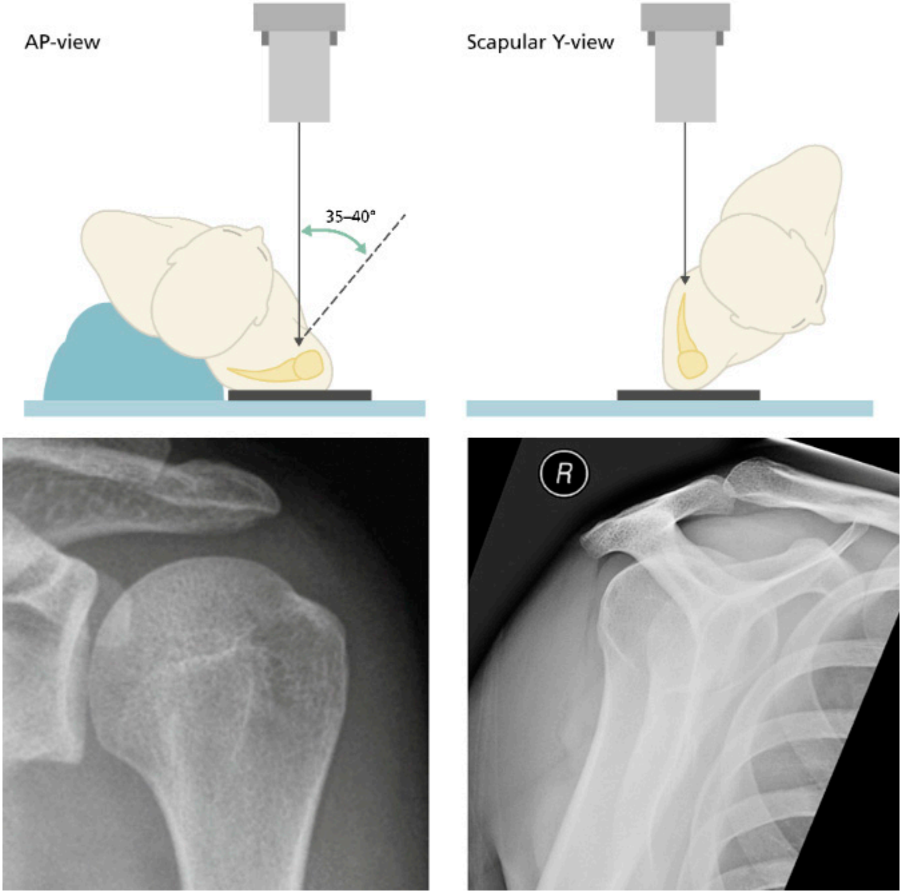


Figure 10. AP- and scapular Y-view of the shoulder. The illustrations demonstrates the patients positioning in relation to the source and the detector and the bottom pictures the actual radiographs of a normal shoulder for the AP (left)- and scapular Y-view (right). Illustrations by Katarina Jandér. Reproduced with permission. The AP radiograph photographed by the author. The scapular Y-view radiograph reproduced from radiopeadia.org, case courtesy of Dai Roberts, under CC-BY-NC-SA 3.0 license.

Papers I-III span a period that includes the transition from analogue to digital radiographs. Analog radiographs use photographic film to capture images, requiring chemical processing, which is time-consuming and less flexible for image adjustments. Digital radiographs, however, use digital sensors, providing immediate image availability and easier manipulation. They offer higher image quality, lower radiation exposure, and faster processing times. Despite these advantages, digital radiographs come with higher initial costs [56].

Some degree of magnification is always present in conventional radiographs. The magnification is affected by multiple factors, including the distance between the source and object, the distance between the source and detector, as well as the position and orientation of the object [57]. The average magnification factor of the glenohumeral joint has been reported as 12% [58]. To the best of our knowledge, and based on personal communication with the radiology department at the Skåne University Hospital in Malmö, the method for radiographic examination of the shoulder did not changed during the period covered by the papers included in this thesis [59].

Computer tomography (CT) is nowadays readily available in Sweden and has a role in PHF diagnostics. A CT is warranted if inadequate images are acquired by conventional radiographs (often due to pain limiting patient positioning), if there is uncertainty about the amount of displacement of the humeral head/tuberosity fragments, number of fragments or if the glenoid needs detailed investigation. CT can further give information on comminution, evaluation of articular surface involvement, glenoid version and bone quality. Three-dimensional computed tomography (3D-CT) reconstruction is also available and probably finds its greatest role in preoperative planning. All radiology examinations that form the basis of the papers in this thesis are conventional radiology examinations, i.e., no CT examinations have been reviewed.

Magnetic resonance imaging (MRI) rarely has value in the acute setting of PHF but may be used to further image the soft tissues if required. No MRI examinations have been reviewed or used in the work on the papers in this thesis.

Classification systems

A fracture classification system stratifies fractures into subgroups/types. Ideally it should be synoptic and user friendly in the everyday clinical setting, guide treatment, predict outcome and risk of complications whilst demonstrating intra- and interobserver reliability on an acceptable level. A fracture classification should further serve as a tool for reporting both in the scientific literature and in the clinical setting, assist documentation in clinical databases and enable pooling of data across studies.

Multiple classification systems regarding PHF exist today, but none fully meets these criteria. In this thesis, we primarily employ the following, commonly utilized, classification systems, which are delineated as follows.

The Neer classification

The Neer classification, devised by Charles S. Neer II in 1970, is the most well-known and widely used classification system for PHF. This classification is based on the four part theory of the proximal humerus, described by Codman in 1934 [8] and divides the proximal humerus into four principal components: the humeral head, the greater and lesser tuberosities and the humeral shaft. What distinguishes the Neer classification from other classification systems for PHF is the definition for what constitutes a displaced fracture. According to the Neer classification, a fracture is considered displaced if any fragment is displaced more than 1 cm or angulated more than 45°. All fractures, regardless of the number of fracture lines or fragments, in which no fragment is displaced more than 1.0 cm or is angulated more than 45°, are considered as minimally displaced and classified as Neer 1. If one or both displacement criteria are met, the fracture is considered displaced and classified into one of the other categories [60] (Figure 11).

The original Neer classification and its illustration have since 1970 been updated. The roman numerals have been removed, as this subdivision was considered unclear and inadequate in terms of categorizing fractures by complexity and prognosis [61].

The categories can further be stratified into four overarching subgroups:

Neer 1 (non/minimally displaced 2-4-part fracture).

Neer 2 (displaced 2-part fracture).

Neer 3 (displaced 3-part fracture).

Neer 4 (displaced 4-part fracture or a fracture affecting the articular surface) [60] (Figure 11).

In the papers concerning the Neer classification in this thesis, an illustration of the Neer classification which also includes a category for head-split fractures has been used, resulting in a total of 17 possible categories [62]. This 17th, head-split, category belongs to the Neer 4 subgroup.

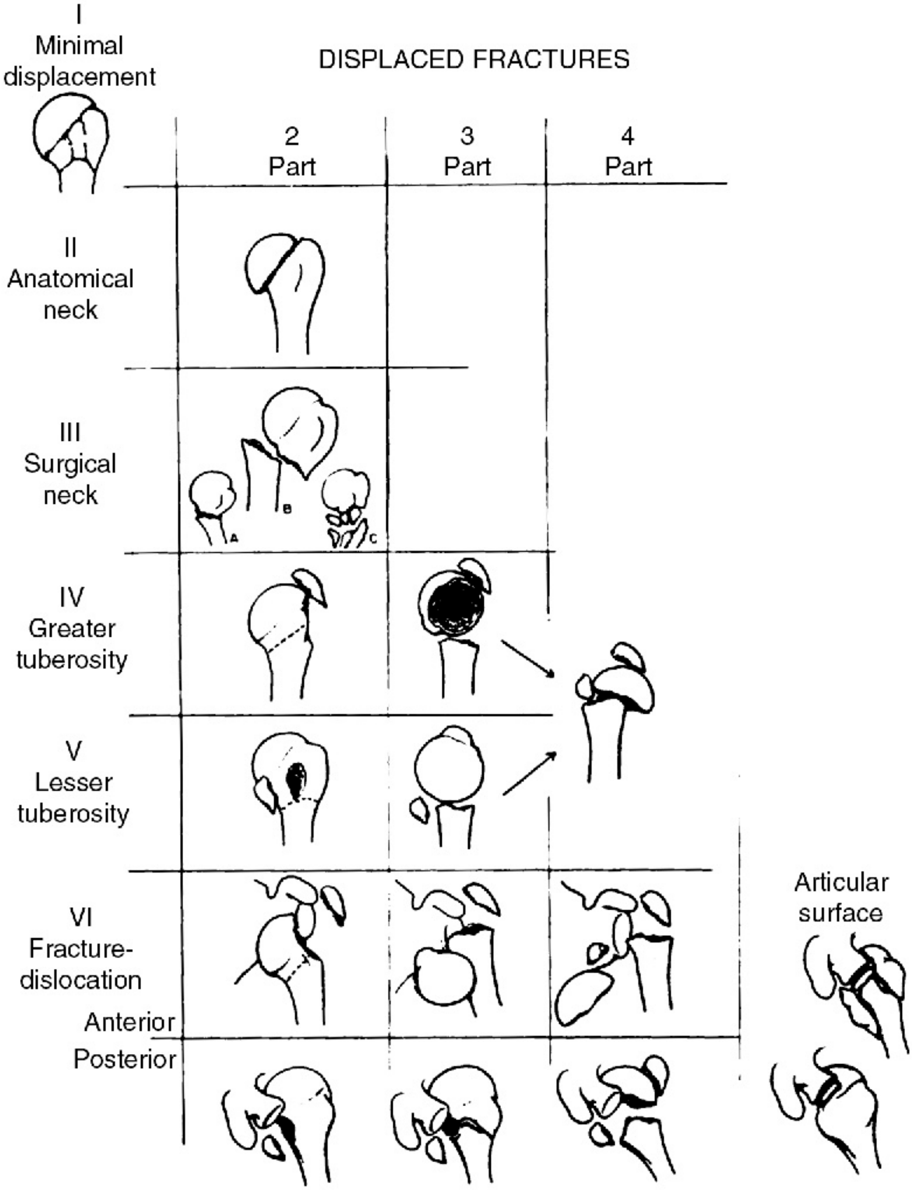


Figure 11. The Neer classification. Reprinted with permission from Journal of Bone & Joint Surgery.

Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification

The AO classification (Figure 12) is another commonly used classification of PHF. It was initially published in 1987 and most recently revised and updated in 2018. The system classifies the fractures into three types, each with their separate subgroups:

Type A: Extra-articular, unifocal, 2-part fractures.

Type B: Extra-articular, bifocal, 3-part fractures.

Type C: Articular or 4-part fractures [41].

Figure 12. The AO Classification. Published in Archives of orthopeadic and trauma surgery [63]. Copyright by AO foundation, Switzerland. Source: AO Surgery Reference, https://surgeryreference.aofoundation.org.

Observer agreement for PHF classifications

To assess a classification systems consistency and reproducibility between observers and over time, observer agreement can be evaluated. Intraobserver agreement refers to the level of agreement when an observer classifies the same fractures at two separate occasions. Interobserver agreement, on the other hand, refers the level of agreement between different observers classifying the same fractures. Cohen´s kappa statistics (κ) [64] is commonly used to evaluate observer agreement for categorical data involving two observers, for example in the assessment of fracture classification systems. The kappa coefficient ranges from 1 (perfect agreement), to 0 (agreement by chance) to -1 (perfect disagreement). If two observers classify a fracture into two different categories, they cannot both be correct. However, if two observers classify a fracture into the same category, they might be correct, but they may also be incorrect. Therefore, substantial observer agreement does not necessarily mean correct classification.

The intra- and interobserver agreement regarding both the Neer- and AO-classifications in the literature are generally low but vary ranging from fair to almost perfect [65-70]. Attempts to improve the intra- and interobserver agreement with simplified versions of the systems and adding CT and 3D-CT have been tried without improvement in results [65, 69, 71, 72]. In 2023, Magneli et al. published a study in which they reported high classification accuracy of a convolutional neural network (a type of artificial intelligence) classifier for PHF using the AO system [73], but the clinical use is currently limited.

In 2002, Brorson et al. randomized 14 orthopaedic surgeons to either receive two training sessions in the Neer classification or no training. They found both clinically and statistically significant improvements in interobserver agreement. This improvement was particularly pronounced among specialists, with the mean kappa increasing from 0.30 to 0.79 with training [66].

Mutch classification

In 2014, Mutch et al. pointed out limitations in the Neer and AO classifications for IGTF. They described and presented a new classification system, specifically designed for IGTF and based on morphology (Figure 13).

- Avulsion (39%). Small fragment with horizontal fracture line.
- Split (41%). Larger fragment with vertical fracture line.
- Depression (20%). Inferiorly displaced. The inferior glenoid edge impacts the humeral head when it is displaced inferiorly or impacted by the inferior surface of the acromion in extreme abduction [74].

Both intra- and interobserver agreement have been reported as substantial [74, 75].

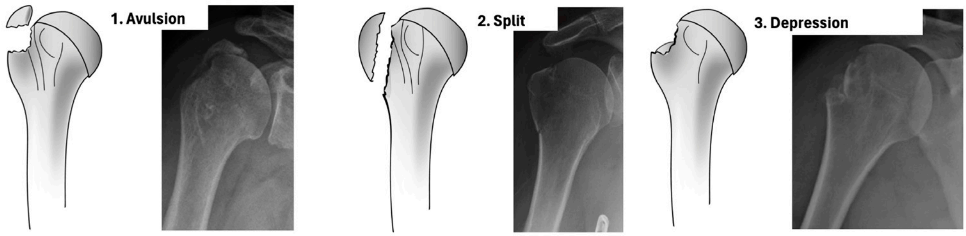


Figure 13. The Mutch classification. Radiological and drawn presentation of the three cathergories in the Mutch classification. Reprinted with permission by the original author Jennifer Mutch [74].

Epidemiology

Epidemiology is the study of the distribution and determinants of health-related states or events, for example fractures, in specified populations and the application of this study to the control of diseases and other health problems [76].

Proximal humeral fracture epidemiology

PHF have been reported as the 4th most common non-spinal fracture in adults accounting for up to 10% of all non-spinal fracture with a mean age of 69 years and a male:female ratio of 3:7 [77]. PHF is a potentially devastating fracture in the elderly, associated with mortality and health care costs higher than from distal radial fractures [78]. Suffering from a PHF effects life quality in a similar manner, but to a lesser extent, as suffering from a hip fracture [79] and is associated with two times higher mortality one year after fracture compared to the general population [80].

The overall incidence of PHF in Sweden year 2012 was 120 per 100 000 person-years [24]. The incidence of PHF increases with age [15, 81]. In age-groups <50-year men and women display a similar incidence, but in age-groups >50-year the incidence in women is higher than in men [15, 82] (Figure 14).

Studies from Sweden and Finland have reported increasing incidences of PHF from the 1950´s until the 1990´s [83, 84]. A previous study from southern Sweden (including the city of Malmö) indicated increasing PHF incidence between 1999-2010 [82] while the incidence in Denmark between 1996-2018 [25] and the US between 1999-2005 [85] seemed stable.

Neer proposed in his original article from 1970 that 85% of proximal humeral fractures are minimally displaced, i.e., Neer 1 fractures [60]. Several subsequent epidemiological studies [86-88] have not been able to confirm the high prevalence of Neer 1 fractures reported by Neer [60], and Neers 85% dogma have recently been questioned [89]. Among others, Court-Brown et al. reported 49% Neer 1 fractures in 2001 [51]. Regarding the AO classification, Bergdahl et al. used a variant of the

AO-system to describe PHF epidemiology, and in 2016 reported approximately 45% type A, 45% type B and 10% type C fractures [81].

A seasonal variation in PHF incidence, with higher rates during winter months, has previously been reported in Sweden [81], Finland [90] and the United Kingdom [91]. One possible, but unexplored, explanation to this seasonal variation is the colder climate, which leads to icier and more slippery conditions during winter months. However, data on the monthly distribution of PHF in other regions of the world with different climate remain scarce.

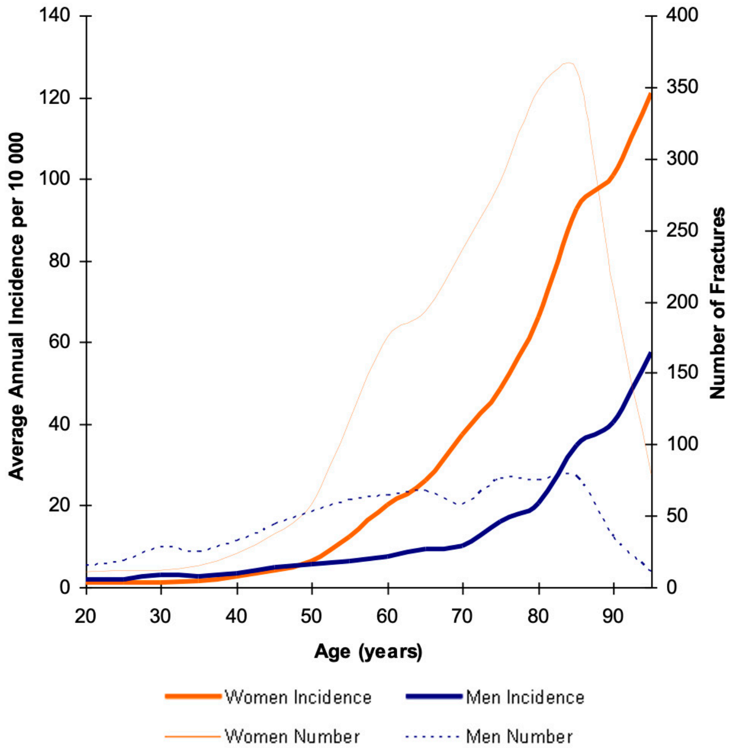


Figure 14. Proximal humeral incidence in relation to age. Estimated incidence (per 10 000 person-years) and total number of proximal humerus fractures per gender and age in adults (≥ 20 years of age) in the Skåne County, Sweden year 1999-2010. Incidence is presented on the primary y-axis in bold lines and number of fractures in interrupted lines on the secondary y-axis. Supplemental data to Rosengren et al. [82]. Reprinted with permission from the author.

Isolated greater tuberosity fracture epidemiology

Among PHF subgroups, IGTF represent a noteworthy subset, accounting for approximately 16% to 25% of all PHF cases [51, 81, 92]. IGTF are often included in studies on PHF, but studies specifically addressing their epidemiology and treatment remains relatively scarce. Previous studies have reported a mean age of

51 to 58 years in individuals with IGTF, while the proportion of women affected ranges from 42% to 60% [74, 93]. A previous study from Korea found that the incidence of IGTF increased up to the age of 50, after which a decrease was apparent. The study also found that individuals who suffered from an IGTF were younger and that the proportion of men was higher compared to individuals with other types of PHF [94].

Treatment of PHF

Neer stated that 85% of proximal humeral fractures are minimally displaced and can be treated non-operatively with a satisfactory outcome [60]. As previously mentioned, this statement has recently been questioned, as subsequent studies have reported a lower percent of minimally displaced fractures [89]. The clinical outcome after a conservative treated PHF has been reported as inferior to the uninjured shoulder [95, 96]. In 2008, Edelson et al. reported 72% forward flexion and 53% external rotation of the injured shoulder compared to the uninjured [95]. Despite this inferior function compared to the contralateral side a systematic review including randomized controlled trials (RCTs) has not been able to demonstrate any advantage with operative treatment compared to non-operative treatment [10, 18]. In summary, shoulder function following a PHF rarely returns to its pre-injury level, and current operative methods appear to have limited, or no, ability to improve this outcome.

Brorson et al. discussed the "optimal surgery rate" and reasoned that according to current evidence 12% of all PHF should be considered for surgery [25]. A systematic review, updated in 2022, reports high- or moderate-certainty evidence that, compared with non-operative treatment, surgery does not result in a better outcome at one and two years after injury for people with displaced proximal humeral fractures. The evidence is insufficient regarding individuals under 60 years, high-energy trauma, two-part tuberosity fractures or less common fractures, such as fracture dislocations and articular surface fractures [10].

When the treatment decision is made, ideally through shared decision-making with the patient, multiple factors need to be taken into consideration. These include age, activity level, expectations, handedness, medication use, physical and mental health status, as well as the fracture pattern.

Non-operative treatment

Current evidence suggests that most PHF can be treated non-operatively [10, 25]. Several different approaches to non-operative treatment exist today. The scientifical evidence guiding these approaches between benefits and harms is however currently limited. At present, the optimal duration of immobilization [97, 98], and whether rehabilitation is more effective performed under the supervision of a physiotherapist than independently [99] is unclear. At our unit, at Skåne University Hospital in Malmö, we currently use the following approach: For stable fractures where the shaft and head have good contact and move together as a unit, the arm is placed in a sling, and gentle pendulum movements are started. These fractures are then monitored by physiotherapists in primary care. For more displaced fractures, involving the greater tuberosity, or where secondary displacement may occur, the arm is placed in a shoulder immobilizer. Movements in the hand, wrist, and elbow are initiated immediately, but the glenohumeral joint is kept immobilized. A follow-up with radiographs is performed at our outpatient clinic approximately 1-2 weeks after the injury. If the decision is made to continue non-operative treatment, the patient is referred to physiotherapist in primary care. The shoulder immobilizer treatment is discontinued during the day after 4 weeks and then also at night after 6 weeks. Four weeks after the fracture, gentle movement training is started, which is then gradually increased as the pain decreases, and mobility improves.

Non-operative treatment is generally safe avoiding risks associated with surgery such as anaesthesia, infection, hardware failure and iatrogenic intraoperative damage.

Previous studies have evaluated the clinical outcome of different physiotherapeutic approaches [98, 100]. A systematic review from 2021 noted that early mobilization after a PHF may have a beneficial effect on function. However, the effect was small, less than the minimal clinically important difference, and based on low-quality evidence [98]. A later systematic review from 2025 found that early mobilization within one week of injury for non-surgically treated PHF is safe and may provide short-term benefits compared to delayed mobilization. Furthermore, they found similar pain, secondary fracture displacement, and total complications between patients with early and delayed mobilization [100].

The clinical outcome after a non-operatively treated PHF has been the subject of numerous scientific reports. In general, non-operative treatment of PHF produces considerable variation in clinical outcome and seems to be mainly influenced by preexisting patient-related psychosocial factors and only to a smaller extent fracture related factors such as displacement, nonunion, and tuberosity displacement [10, 16-19, 22, 25, 96, 101-115].

The classification subgroup-specific clinical outcome following non-operative treatment of PHF has to some extent been previously explored [104, 106, 108, 111, 114]. Kristiansen reported on 188 PHF between 1976 and 1982 with a mean follow-up time at 4 years (range 2-7) and found better clinical outcome in minimally displaced than displaced PHF, as well as better clinical outcome in Neer 2 than Neer 3- and 4-fractures. However, 20% were treated with closed reduction and 23% with open reduction and the results therefore do not really represent the natural course of different PHF subgroups [104]. Soler-Peiro et al. reported better clinical outcome in Neer 3- than Neer 4- fractures, treated non-operatively, in a systemic review, based on 6 studies (133 patients and mean follow-up time 32 months) [106]. Koval et al. described the clinical outcome for non-operatively treated Neer 1 in 104 individuals and found 77% good or excellent results and a ROM of 88% compared to the uninjured shoulder at a mean follow-up time of 41 months [114]. Dettmer et al. observed impaired clinical outcome in more complex PHF according to Neer classification approximately one year after non-operatively treated PHF among 743 patients [111].

Operative treatment

If the surgeon, taking the patient's preferences into account and after evaluating relevant individual- and fracture-specific factors, considers surgery to be beneficial, the next question to address is whether the fracture can be adequately reduced and subsequently stabilized in a position that maintains adequate alignment during the healing period. If this is deemed possible, open reduction and internal fixation may be considered. If the fracture is deemed irreducible or if stable fixation cannot be achieved, replacement of the humeral head with a prosthesis may be indicated.

Several factors warrant careful consideration. These include bone quality, age, level of physical activity, specific fracture pattern, overall physical and mental health as well as Hertel criteria for humeral head blood supply.

Open reduction internal fixation

If the fracture is deemed repairable, the surgeon must choose an appropriate method of fixation. A brief overview of the methods most utilized in our practice is presented (Figure 15).

Locking plate

Around the turn of the millennium, the use of locking plates gained popularity as a surgical option for the treatment of PHF [23, 24, 116]. Between 2004 and 2012, this was the predominant surgical technique for treating PHF in Sweden [24]. Screws placed in the humeral head is locked to the plate in attempt to compensate for the poor bone stock in the humeral head. The clinical outcome following this procedure do not appear to demonstrate superiority over non-operative treatment. Nevertheless, concerns regarding plating persist due to potential adverse events and the need for reoperations. [10, 17].

Nail

An intramedullary nail is placed through the humeral head down into the humeral shaft and then fixed with screws on each side of the fracture. In our practice, this method is mostly used for pathological humeral fractures and occasionally 2-part PHF with displacement between the head and shaft.

Sutures and screws

In our practice this method is mostly used for IGTF. Sutures are placed in the rotator cuff tendons and then passed through drilled holes in the humeral shaft to fix the fracture. If the fracture is a split type and the fragment is in one piece the sutures are sometimes combined with a screw through the greater tuberosity into the humeral head.

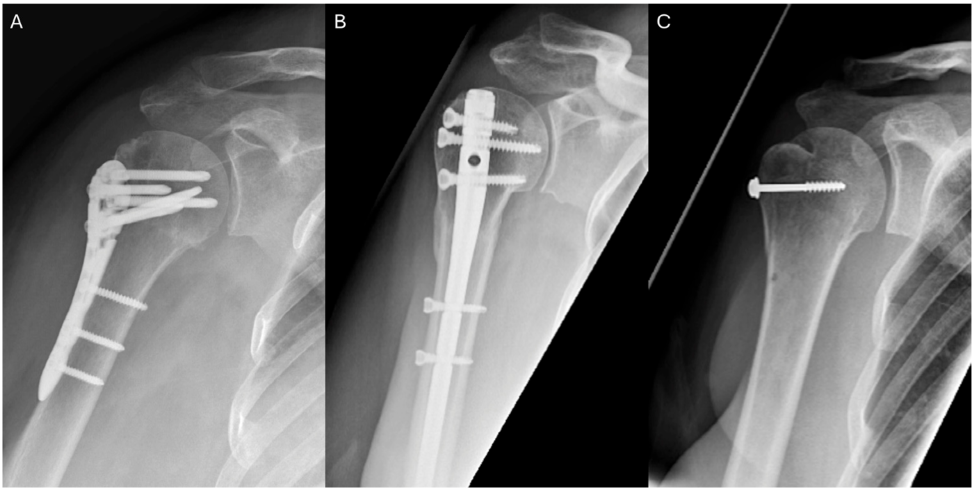


Figure 15. Open reduction internal fixation. Three alternatives to open reduction internal fixation for proximal humeral fractures. **A**: Locking plate. **B**: Intramedullary nail. **C**: Screw fixation combined with sutures (the sutures are not visible on the radiograph; however a hole in the humeral shaft, used for suture fixation, is identifiable). Radiographs photographed by the author.

Prosthesis

In cases where the fracture is deemed irreparable, the humeral head is replaced with a prosthesis. Numerous different prostheses for PHF are available from various manufacturers, but they mainly fall into two categories, briefly described below (Figure 16).

Hemi-arthroplasty (HA)

The humeral head is replaced with a prosthesis with a stem into the humeral shaft. The prosthesis is typically fixed in the humeral shaft with bone cement, but non-cemented options are available. The prosthesis articulates to the native glenoid. A prerequisite for a HA to function is that the rotator cuff is intact and functional, and that the tuberosities heal properly to the prosthesis and the humeral shaft [117]. Due to these prerequisites, we currently use HA for younger individuals with a PHF.

Reversed shoulder arthroplasty (RSA)

The humeral head is removed. A metal head is affixed onto the glenoid and a prosthesis with a stem and socket is cemented into the humeral shaft. The term "reverse" originates from the interchange of the head and socket, medializing the center of rotation of the glenohumeral joint and repositioning the attachment of the deltoid muscle to a more distal location. This change in mechanical dynamics enhances the strength and importance of the deltoid muscle, reducing the reliance on tuberosity healing. RSA has demonstrated superior clinical outcome compared to HA following a PHF in individuals aged 70 or older [103]. Consequently, in our practice, we use RSA for elderly in whom the prospects of tuberosity healing are uncertain.

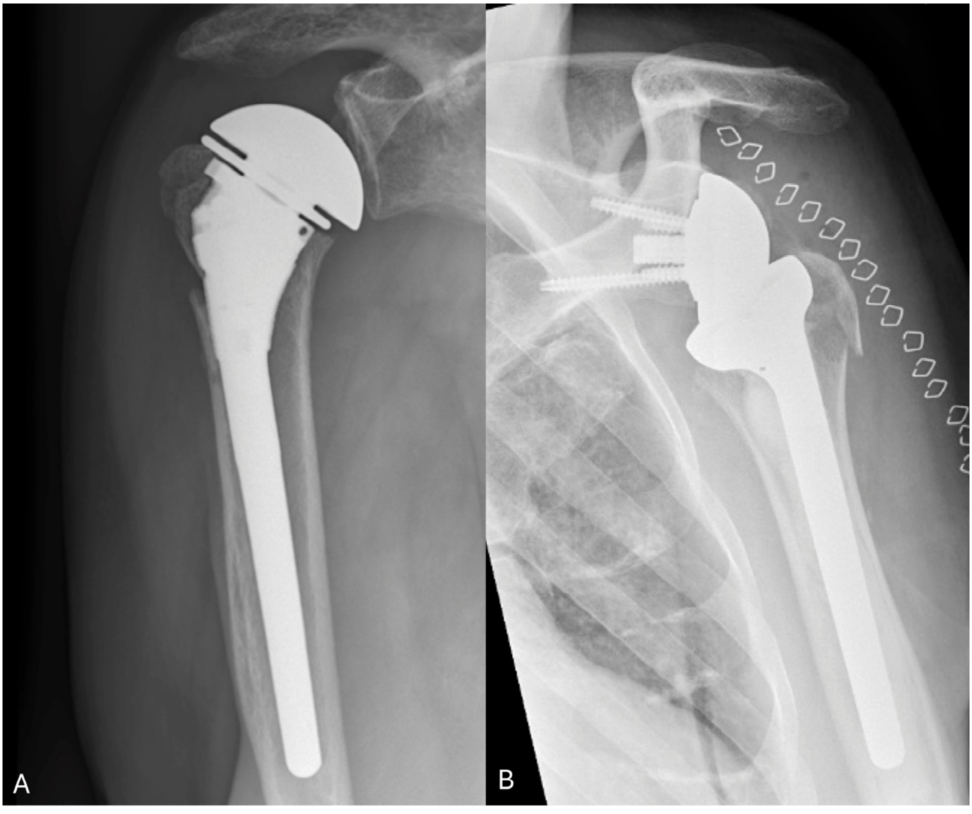


Figure 16. Shoulder prostheses. Two alternatives for shoulder prostheses following a proximal humeral fracture. **A**: Hemi-arthroplasty, non cemented. **B**: Reversed shoulder arthroplasty, cemented stem. Skin staples are still present, and visible, on this early postoperative radiograph. Radiographs photographed by the author.

Clinical outcome

In a clinical setting, individuals are monitored regarding ROM (forward elevation, abduction, internal and external rotation) and their experience of pain. In a scientific setting, one or more of the many available outcome measure instruments are often used. Today, there is no consensus on which of these should be used and comparisons between different studies are therefore often challenging [118]. The minimal clinically important difference (MCID) for PHF indicates the smallest difference in an outcome measure associated with a clinically important difference for the individual affected by the fracture [119]. Below is a brief description of the most used outcome measure instruments for PHF. In **paper IV,** which evaluates clinical outcome, we do not use any outcome measure instruments but rather ROM as well as patient-reported pain and function.

Constant-Murley Score (CMS)

The CMS, introduced in 1987, is the most used outcome measure instrument for PHF [118]. It is designed to evaluate overall shoulder function, regardless of diagnosis. The CMS scale assesses four components related to shoulder pathology: two subjective (pain and activities of daily living) and two objective (ROM and strength). The subjective components can receive up to 35 points, and the objective 65 points, resulting in a possible maximum total score of 100 points (best function). Pain and activities of daily living are reported by the patient, whereas ROM and strength are assessed by a physician or a physiotherapist [120]. The MCID for CMS in PHF has been reported as 5.4 to 11.6 [119].

Disability of the arm, shoulder and hand (DASH)

The DASH score is a self-report questionnaire designed to measure physical function and symptoms in individuals with any or several musculoskeletal disorders of the upper limb. The rationale behind the use of one outcome measure for different upper extremity disorders is that the upper extremity is a functional unit. The main part of the DASH is a 30-item disability/symptom scale concerning the individual's health status during the preceding week. The scores for all items are used to calculate a scale score ranging from 0 (no disability) to 100 (most severe disability) [121]. The MCID for DASH in PHF has been reported as 8.1 to 13.0 [119].

Demographic changes and future challenges

Demography is the study of human populations. It involves analysing factors such as birth rates, deaths, age, sex, migration, and age pyramids [122]. Since the risk of sustaining a PHF is higher in older than younger age-groups, and greater among women than men [15], changes in these demographic factors will influence the number of PHF cases in a population, and consequently the burden on the healthcare system both in terms of resources and costs.

In 2009 Christensen et al. reported that life expectancy is expected to increase and birth rates to decline over the coming decades [123]. Oden et al. proposed that the number of individuals over the age of 50, who are at higher risk of osteoporosis-related fractures like PHF, will double between 2010 and 2040 [124].

After these predictions were presented, the world was struck by the COVID-19 pandemic. The effects of the pandemic include a further decline in birth rates, a reduction in migration, and increased mortality rates among the oldest part of the population [125]. The long-term impact of the pandemic on the risk of PHF is, to the best of our knowledge, still unclear. However, a conclusion drawn from the demographic predictions described above, is that the proportion of older individuals, with higher fracture risk, that no longer contribute to the tax system, will increase meanwhile the proportion of younger, working individuals who support the healthcare system will decrease.

Based on these predictions, it seems more important than ever to identify individuals at particularly high risk of PHF to target preventive interventions where they will have the greatest impact and to provide treatments that offers true value to those suffering from the fracture. To plan resource allocation within the healthcare system, direct preventive strategies appropriately, and ensure the best available treatment for individuals with PHF, epidemiological studies and research on treatment outcome, effectiveness, and risks are essential.

Aims

Overall aims

The overall aim of this thesis project was to increase the knowledge of PHF epidemiology, PHF complexity, IGTF epidemiology and the clinical long-term outcome after non-operatively treated PHF through investigations of epidemiology, fracture complexity, time trends and clinical outcome in the city of Malmö, Sweden.

Specific aims

Paper I. The primary aim was to identify and describe time trends in the age- and sex-adjusted incidence of PHF, from 1944 until 2020 in adults (≥18 years). The secondary aims were to describe the variation in incidence according to age and the monthly distribution.

Paper II. The primary aim was to explore possible time trends in PHF complexity between 1944 and 2020 using the Neer and AO classifications. Secondly, we aimed to describe PHF complexity in relation to age and sex.

Paper III. The primary aim was to provide a comprehensive description of IGTF patient characteristics and assess how the incidence varied according to age. The secondary aims were to examine time trends in the sex- and age-adjusted incidences from 1944-2020 and to describe the distribution and characteristics of IGTF by the Mutch classification.

Paper IV. The aim was to describe the long-term clinical outcome following non-operatively treated PHF across different fracture types according to the Neer and AO classifications.

Materials and methods

Papers I-III share a similar methodological approach, described in a dedicated section. In contrast, **Paper IV** was conducted with a different methodology, presented separately. To commence, a discussion of general methods is provided.

General methods

Adult individuals, ≥18 years, residing in Malmö, Sweden, with a PHF treated either in the in- or outpatient setting were included. All PHF in this thesis were verified through a manual review of the radiology examinations conducted by the author (A.C). A PHF was defined as a fracture within the proximal humerus region. The proximal humerus region was defined as the area created by a square with sides equal to the caput humeri width, a definition in agreement with the AO Fracture and Dislocation Classification Compendium from 2018 [41].

The city of Malmö, located in the southern region of Sweden, had an adult population of 131,718 in 1944, which subsequently increased to 273,455 by the year 2020. Malmö is served by a single hospital, SUS in Malmö, which is responsible for the treatment of acute fractures.

Only conventional radiographs were reviewed. In the situation where a CT was available this examination was not reviewed. In cases where radiographs from both the time of injury and follow-up were available, only the radiographs from the time of injury were reviewed. Malmö residents that suffered a PHF at locations other than Malmö and attended a follow-up visit at SUS were included. In this scenario, the classification was determined based on the follow-up radiology examination. Individuals who underwent operative treatment at other hospitals, for whom no pre-operative radiology examination were available were excluded.

We did not consistently record the radiological views available for each case during the reviewing process. To gain insight into the types of radiological views typically available, a review of 100 randomly selected examinations of IGTF was conducted, covering all study years in **papers I-III**. This review showed that a frontal view was present in 99% of cases, a scapular Y-view in 73%, and an axillary view in 1%. Additionally, a frontal view with the arm in neutral rotation was present in 96% of cases, while a frontal view with the arm in internally rotation was present in 45%.

The text in this thesis has, in part, been produced with the assistance of the generative artificial intelligence (AI) models ChatGPT and Microsoft Copilot. I, Anton Cederwall, have processed the generated text and take full responsibility for the content.

Radiology archives in Malmö

The papers in this thesis span the period from 1944 to 2020, during which two different radiological archives were used at Skåne University Hospital in Malmö: initially an analogue archive, followed by a digital archive.

From 1944 to the turn of the millennium, both in- and outpatient radiographic examinations performed at the University Hospital in Malmö were archived in an analogue archive (Figure 17). This archive is organized so that all examinations of an anatomical region with a fracture are filed together and assigned the same code, for example "S.F 1" where S is the region (shoulder), F indicates that the examination displays a fracture, and the number is unique for every person.

The first author reviewed all radiographs labeled with the codes S.F and Brach.F (i.e., a fracture in the shoulder- and brachialis region) during the years 1944-1946, 1952, 1957, 1962, 1967, 1972, 1977, 1981, 1987, 1994 and 1995. Aside from PHF the radiographs with the above referenced codes also included fractures in adjacent regions, for example scapula, clavicle and humerus diaphysis.

From 2004 and thereafter, radiology examinations were archived in a new, digital archive. Regarding the years 2005, 2010, 2015 and 2020 we searched the hospital records, both in- and outpatient, for the International Classification of Diseases 10 (ICD 10) code S42.20, i.e., fracture of the upper end of the humerus. Radiographs of identified persons were retrieved by use of the unique personal identity number and then classified by the first author using Sectra IDS7, version 24.1 (Sectra AB, Teknikringen 20 SE-58330 Linköping, Sweden). Case-finding of fractures by ICD-codes has previously been validated in our setting with a misclassification rate of 3% [82, 126].

Figure 17. The analogue radiology archive in Malmö. One of many shelves with radiographs in the analogue radiology archive in Malmö, Sweden. Photographed by the author.

Population data

Official information on the population at risk was retrieved from Statistics Sweden. For 1944-1967, sex-specific population counts in 1-year age classes were available every fifth year starting at 1945 (except 1955). For sample years without available population details, we used linear regression of the two nearest available years (taking date of collection into account). From 1968 annual sex-specific population figures in 1-year classes were available. The mid-year population regarding the years examined for fracture occurrence was calculated using these population data.

Inter- and intraobserver agreement

The first author (A.C) is an orthopaedic consultant with a subspeciality in shoulder surgery since 2018 and regularly treats individuals with PHF. Before study start, he was trained by a senior shoulder surgeon/researcher (A.N) in the Neer classification. The first author classified the radiographs of 40 consecutive PHFs from 2010 using the Neer- and AO-classifications. The number of cases was determined based on recommendations and previous studies that employed similar sample sizes for observer agreement calculations [66, 127, 128]. The distribution of fractures across subgroups, according to both the Neer and AO classifications, was similar between the fractures included in the observer agreement analysis and those in the overall cohort. The senior surgeon/researcher (A.N) classified the same fractures using the same classification systems, permitting calculation of interobserver agreement. A.C repeated the classification with the same fractures six weeks later, permitting calculation of intraobserver agreement.

Both the percental agreement and Cohens kappa coefficient (κ) were calculated in the observer agreement analyses. We interpreted κ to indicate the following agreement: slight agreement (κ 0.0 to 0.20); fair agreement (κ 0.21 to 0.40); moderate agreement (κ 0.41 to 0.60); substantial agreement (κ 0.60 to 0.80); and almost perfect agreement (κ 0.81 to 1) [129].

Interobserver agreement was 90% (κ=0.76) for Neer and 85% (κ=0.77) for AO. Intraobserver agreement was 93% (κ=0.81) for Neer and 93% (κ=0.89) for AO.

To examine the intraobserver agreement of the Mutch classification, the first author re-classified the 40 most recent IGTF in the digital dataset about one year after first classifying them. We found a substantial intraobserver agreement for the Mutch classification, 85% and κ=0.71.

Papers I-III

The data utilized in **Papers I-III** originate from a retrospective review of radiology examinations during 17 sample years, ranging from 1944 to 2020. The author personally reviewed all radiology examinations. Demographic information, including age and gender, as well as fracture-related data such as the date and side of fracture, were registered. In **paper II**, the fractures were classified utilizing two commonly used classification systems relevant to PHF; The Neer- and AO-classifications. Additionally, in **paper III**, IGTFs were classified according to the Mutch morphological classification. The Mutch classification was chosen as it is specifically designed for IGTF cases, unlike the Neer and AO classifications. Parameters such as the dislocation distance and direction, the presence or absence of humeral head dislocation, and measurements of the greater tuberosity-ratio were also recorded for IGTFs.

The time period from 1944 to 2020, covered in **papers I-III,** spans the period during which two different radiological archives at the Skåne University Hospital in Malmö was used: the analogue (Figure 17) and the digital. The sample years were selected as follows: the earliest and latest years available in both archives at study start were reviewed, 1944 to 1995 for the analogue archive, and 2005 to 2020 for the digital archive. Additional years in the intervening period were selected for even distribution. Radiographs from 1996-2000 were unavailable due to flood damage.

In subgroup analyses, individuals were stratified by age into two groups: <50 and ≥50 years. This cut-off was chosen due to the well-established epidemiological differences in both PHF and IGTF between these age-groups [15, 94] and to enable comparison to other studies.

In **paper II**, we used established overarching types for each classification system to permit a more synoptic presentation: Neer 1(non/minimally displaced), Neer 2 (displaced 2-part fracture), Neer 3 (displaced 3-part fracture) and Neer 4 (displaced 4-part fracture or a fracture affecting the articular surface) [60] and AO type A (extraarticular, unifocal, 2-part fracture), type B (extraarticular, bifocal, 3-part fracture) and type C (articular or 4-part fracture) [41]. Fractures classified as Neer 1 in the Neer classification, and as type A in the AO classification were considered the least complex. Fractures classified as Neer 4 in the Neer classification and as AO type C in the AO classification was considered the most complex. We used the term higher fracture complexity to describe a higher proportion of fractures classified as Neer 3 or 4 and/or AO types B or C.

Statistical methodology and data management

The age- and sex-adjusted incidences were calculated using direct standardization with the mean mid-year population during the investigated period, i.e., 1944-2020, as standard population.

In **paper I and III**, we used joinpoint regression analysis (Joinpoint Regression Program, Version 4.9.1.0 - April 2022; National Cancer Institute) for analysis of time trends and results are presented as annual percent changes (APC) with 95% confidence intervals (CI). The Joinpoint Regression software is a statistical tool developed by the National Cancer Institute, that enables examination of temporal trends. In trend data, such as cancer or fracture rates, the program is able to identify points where the trend changes, i.e., joinpoints, dividing the data into segments each with its own linear trend. Additionally, the software offers information regarding the statistical significance associated with the various trend segments.

For analyses on monthly distribution in **paper I**, we used analysis of variance (ANOVA) to assess the variance between months. We tested differences between pairs of months by Tukey's test.

For analysis of temporal trends in fracture complexity in **paper II**, we used descriptive statistics and trends were evaluated by visual inspection. This method was chosen due to the long-term study design and the relatively low number of fractures, especially the more uncommon fracture types, during each timepoint.

P-values <0.05 were considered statistically significant.

We used SPSS v28.0 (IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp) and Microsoft Excel v16.67 (Microsoft Corp., Redmond, WA, USA) for statistical analysis and database management.

Paper IV

In 1989, a senior shoulder surgeon (A.N) reviewed shoulder region fractures in the radiology archive and included adult individuals with a PHF sustained from January 1 to December 31, 1981. These individuals constitute the cohort in **paper IV**.

Patient and treatment data from the fracture event were collected from the chart by one of the authors (A.N). Approximately 10 years after the fracture event, all surviving individuals were invited to a follow-up. Operatively treated individuals were excluded. Operative treatment was defined as either open reduction with or without implant(s) or closed reduction with implants, i.e., closed reduction without implant(s) was accounted as non-operative treatment. All individuals who attended the follow-up was examined by the same physician (A.N) in terms of active ROM (flexion, abduction, internal- and external-rotation) with the aid of a goniometer. Flexion and abduction were measured in relation to the horizontal plane. Internal- and external rotation were measured in relation to neutral rotation of the arm (i.e., the forearm pointing anteriorly when the elbow is flexed at 90 degrees). The individuals also reported pain and functional levels via a non-validated questionnaire administered by the same author (A.N). An additional 23 of the included individuals, who either did not want to or were unable to attend the follow-up, also responded to the questionnaire through telephone interviews conducted by one of the authors (A.N). The inclusion, exclusion, missing data and follow-up status of the cohort is presented in Figure 18.

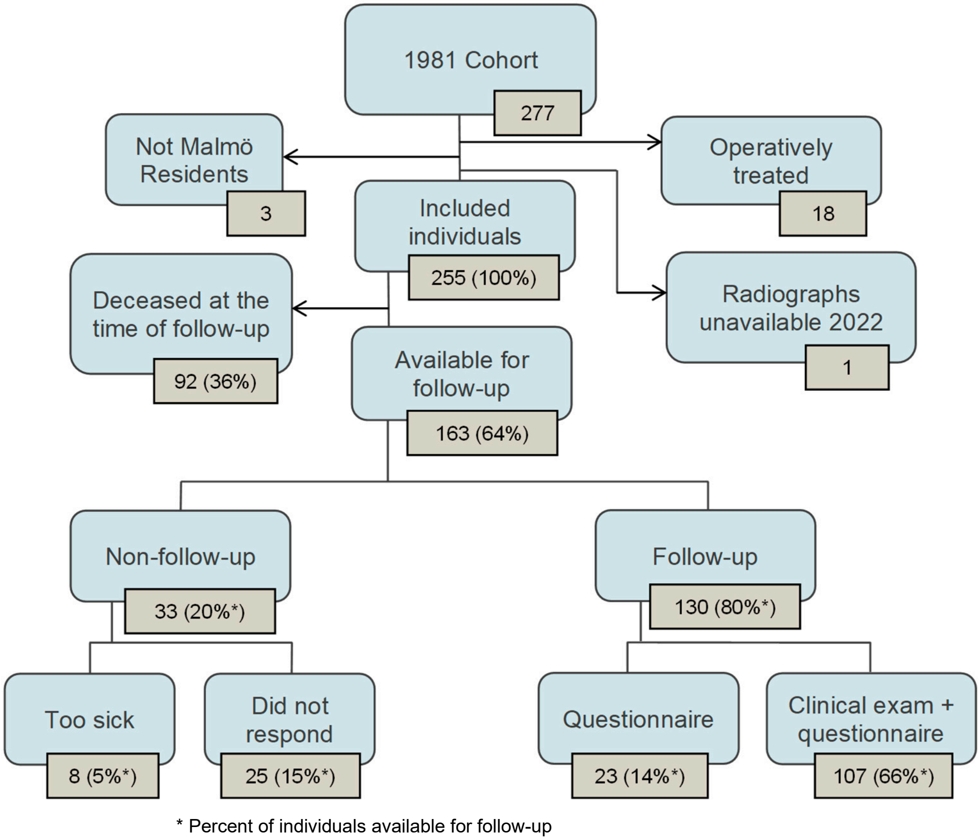


Figure 18. Flowchart of individuals included in Paper IV, i.e., adult individuals with a PHF in Malmö, Sweden 1981, depicting inclusion, exclusion, missing data, follow-up and non-follow-up.

Several categorical options for the variables pain (4 options) and function (3 options) were used in the questionnaire. Due to the low number of included individuals, grouping into dichotomized variables (pain/no pain and full function/impaired function) was done. We were thereby still able to identify pain-free and fully functional individuals.

In 2022, the first author (A.C) re-evaluated and classified the initial radiographs of the individuals in the cohort according to the Neer and AO classifications, to allow for classification subtype analyses. The fractures were classified and subgrouped according to the same criteria as in **paper II**, described above.

Statistical analysis was performed using SPSS and Microsoft Excel, and $p<0.05$ were considered statistically significant. Due to the low number of fractures in Neer 3 and 4, these types were aggregated for statistical analysis and referred to as Neer 3&4. To describe uncertainty for the continuous variables we estimated 95% confidence intervals by bootstrapping with 10,000 iterations. We used the Welch ANOVA and the Games-Howell post-hoc test to assess differences between fracture types as our continuous variables (flexion, abduction, internal- and external rotation) demonstrated unequal variances. For categorical variables (pain and function) we used Fisher's exact test to assess differences between fracture types since the expected values in some groups were low. Adjustment for multiple testing was performed using the Benjamini-Hochberg procedure.

Ethics

For **papers I-III**, where radiographs from 1944 to 2020 were reviewed, this concerns individuals with a certain fracture. My assessment is that this does not make the group particularly exposed, vulnerable, or in need of special protection. The data collected were age, gender, fractured side, fracture date and several parameters based on the appearance of the fracture. This information should not be considered as sensitive as other health-related information such as, for example, details about mental health or substance abuse and the individuals were anonymized in the dataset. Ethical approval for **papers I-III** was obtained prior to study start from the regional ethical review board of Lund University (LU 2012-394). In addition to this approval, we also received ethical approval to review and handle data and radiographs stored at the hospital from the local data and ethics committee in Skåne, KVB (2019 250-19).

Regarding **paper IV**, information about pain, function, treatment, etc. were retrieved, making the information in this paper more sensitive and subject to ethical considerations. The individuals were also invited to a follow-up, which may have been painful and/or troublesome. Moreover, some individuals may have experienced a degree of dependency on my senior colleague, who in some cases was also the treating physician. This relationship could have influenced their decision to participate in the follow-up, even though participation was entirely voluntary. There is a risk of so-called therapeutic misunderstanding, as the participants may very well have believed that their participation in the study could affect their clinical treatment. Ethical approval for **paper IV** was obtained prior to start of data management from the Swedish Ethical Review Authority (2024-01365-01). We published an advertisement in Sydsvenskan, the largest daily newspaper in the region, informing about the planned study and providing information on where individuals who believe they may be included in the material but did not wish to participate could contact us to be excluded. At the time of writing, no individual has contacted us with a request to be excluded.

Funding

Funding was received from ALF (2022/0286), FoUU (2022/1539), the Skåne University Hospital Foundations (2022 and 2024), Herman Järnhardt Foundation, and Stiftelsen Guldbyxan (2025). Funders had no influence on study design, data collection, data analysis, interpretation of data, writing of the papers or decision on where to submit the papers.

Main results

General results papers I-III

We reviewed 6 064 radiology examinations and identified 3 031 PHF in adult residents of Malmö during the 17 sample years (3 231 161 person years), ranging from 42 PHF in 1944 to 232 PHF in 2020. The overall incidence was 94 per 100 000 person years (130 in women and 53 in men) and 73% of all fractures affected women. The overall mean age at the fracture event was 67 (SD 16) years, 69 (SD 14) in women and 59 (SD 17) in men. 52.5% of all fractures affected the left side (53.1% in women, 50.9% in men).

Paper I

Time trends in PHF incidence

The age- and sex-adjusted incidence, for women and men combined, increased from the 1940`s until 1977 (APC +2.6% [95% CI +1.5 to +3.8]) followed by a decrease until 2020 (APC -0.7% [95% CI -1.4 to -0.0]). Similar time trends were observed in the subgroup analysis of individuals aged ≥50 years, whereas no such time trends were evident among individuals aged 18-49 (Figure 19).

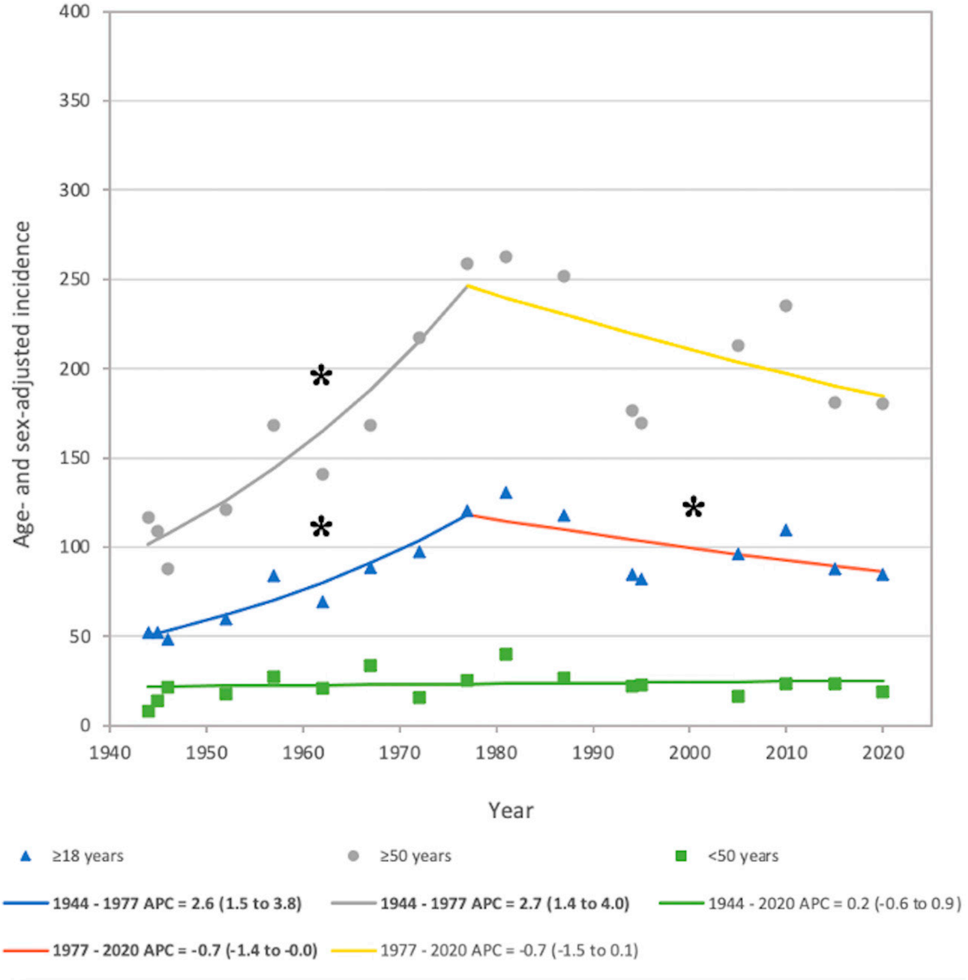


Figure 19. Age-group-specific time trends in the age- and sex-adjusted incidence of proximal humeral fracture in Malmö, Sweden, 1944-2020 presented as annual percent change (APC) with 95% confidence interval (95% CI). For clarity, statistically significant changes are marked by * and bolded legend.

PHF incidence variation in relation to age and sex

In age-groups 18-49 years we found similar incidence of PHF in men and women. In age-groups ≥50 years the PHF incidence was higher in women than men (Figure 20).

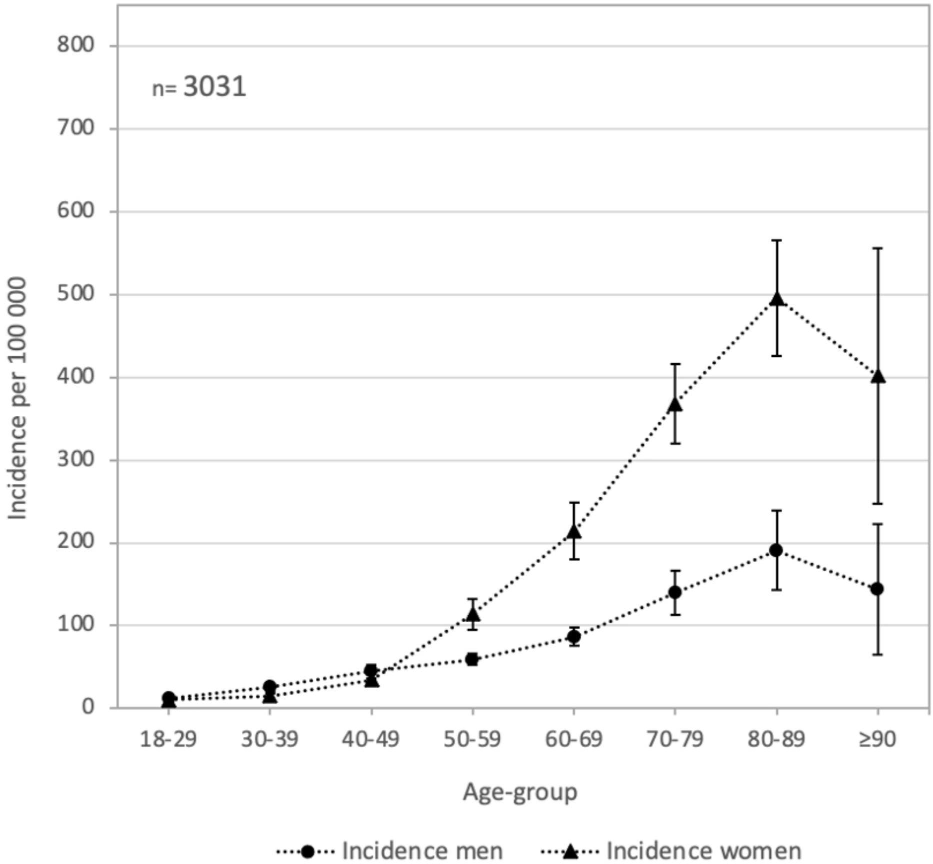
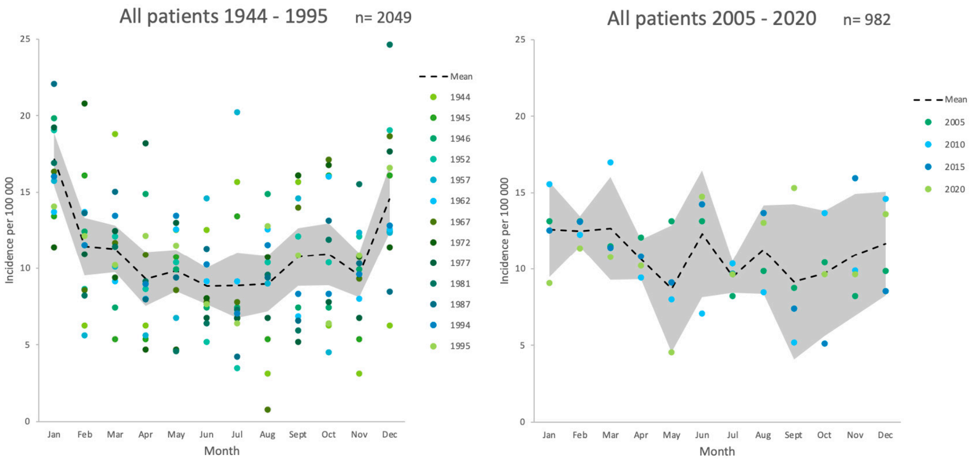


Figure 20. Sex-specific incidence of proximal humeral fractures in 10-year age-groups. Sex-specific sample year average incidence per 100 000 of proximal humeral fractures in 10-year age-groups in Malmö, Sweden 1944-2020. Error bars represent 95% confidence intervals.

Seasonal variation

A seasonal variation was apparent, with higher incidence in the colder winter months, in distant but not in recent decades (Figure 21).



ANOVA

p <0.001 p = 0.228

Figure 21. Monthly distribution of proximal humeral fractures. Year-weighted sex-, age- and year-group-specific monthly distribution of proximal humeral fracture incidence in Malmö, Sweden 1944-2020. Shaded areas represent 95% confidence intervals and colored dots individual year data.

Paper II

PHF complexity

We saw no obvious time trend in fracture complexity overall (Figure 22), nor when stratified by sex or age, in either the Neer- or AO-classification.

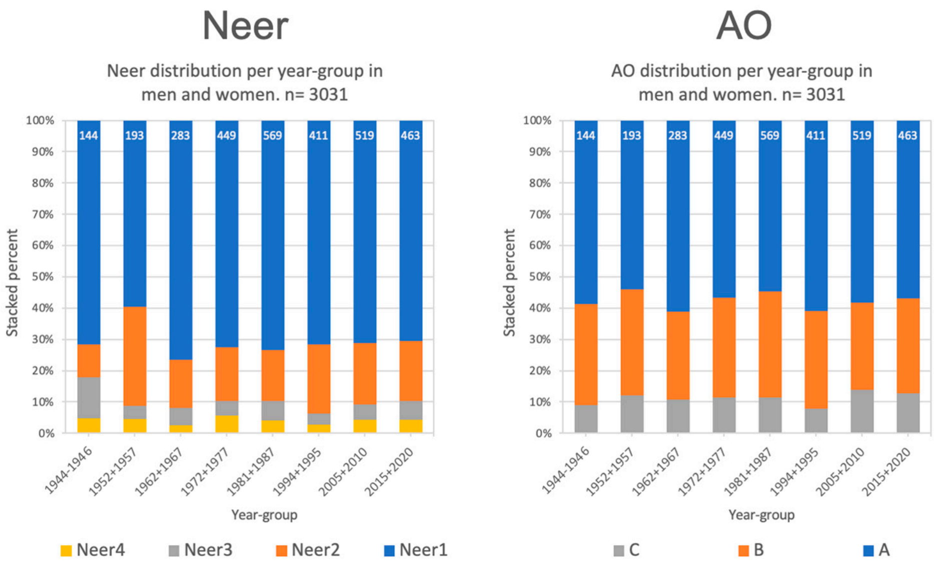


Figure 22. Proximal humeral fracture complexity in relation to time. Fracture distribution per period for proximal humeral fractures in Malmö residents aged ≥18 years during 17 sample years from 1944 to 2020 based on sex- and age-adjusted incidence, presented as stacked percent (%) and categorized by fracture subgroup for the Neer- and AO-classifications. Data labels represent fracture numbers.

We observed that fracture complexity according to AO was higher in older than younger age-groups. This trend was also observed in the Neer classification for women. For men according to the Neer classification however, we saw a higher fracture complexity in younger than older age-groups (Figure 23).

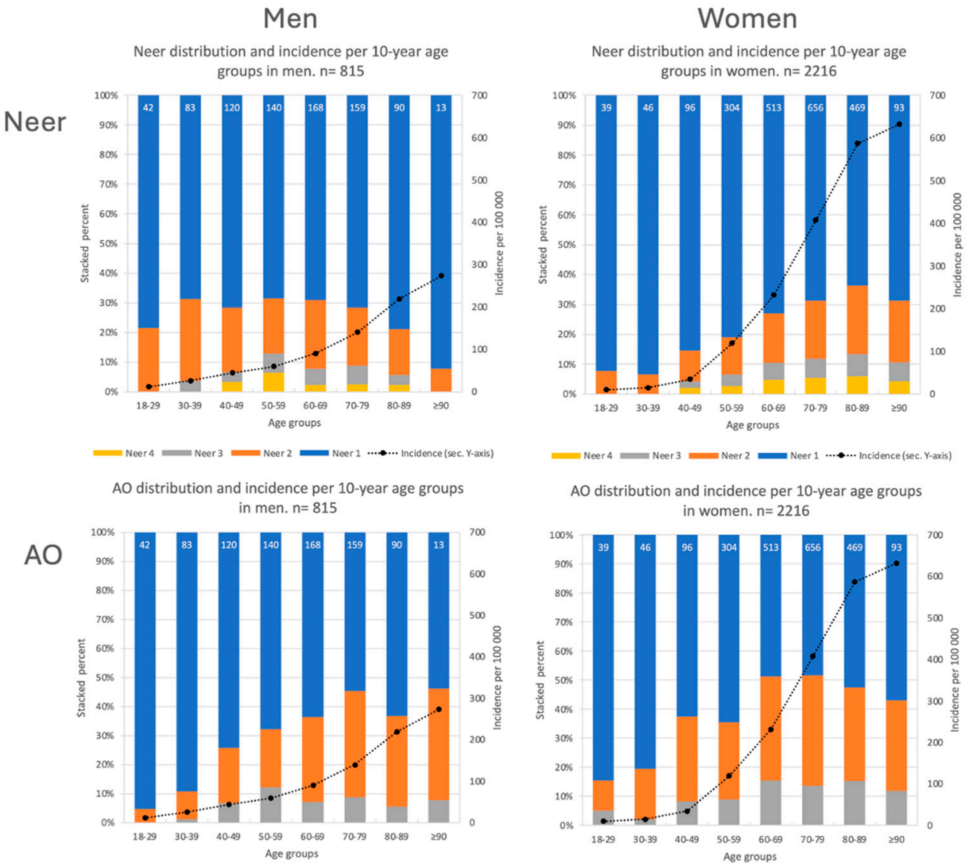


Figure 23. Proximal humeral complexity in relation to age. Sex-specific fracture distribution and incidence per age-group for proximal humeral fractures in Malmö residents aged ≥18 years during 17 sample years from 1944 to 2020. On the primary y-axis fracture distribution based on age-adjusted incidence is presented as stacked percent (%) per classification subgroup while incidence per 100 000 person years are presented on the secondary y-axis. Data labels represent fracture numbers.

Paper III

IGTF epidemiology

We found 614 IGTF in adults during 17 sample years from 1944 to 2020 in Malmö, Sweden. The overall incidence was 19 per 10^5 person years. 366 individuals were women (60%) and 248 (40%) men. The overall mean age was 55 years (SD 17); women 60 years (SD 16) and men 48 years (SD 16). 19% of all IGTF were accompanied by a concomitant shoulder dislocation, 46% were displaced superiorly and 23% were displaced ≥5 mm. We identified 45% avulsion-, 44% split- and 11% depression-fractures.

The incidence of IGTF was higher in men than in women in the <50-year age-group, but conversely higher in women than in men in the ≥50-year age-group. For women, but not men, the incidence of IGTF was higher in ages ≥50 years compared to <50 years (Figure 24). We found no time trend in the sex- and age-adjusted incidence of IGTF between 1944-2020.

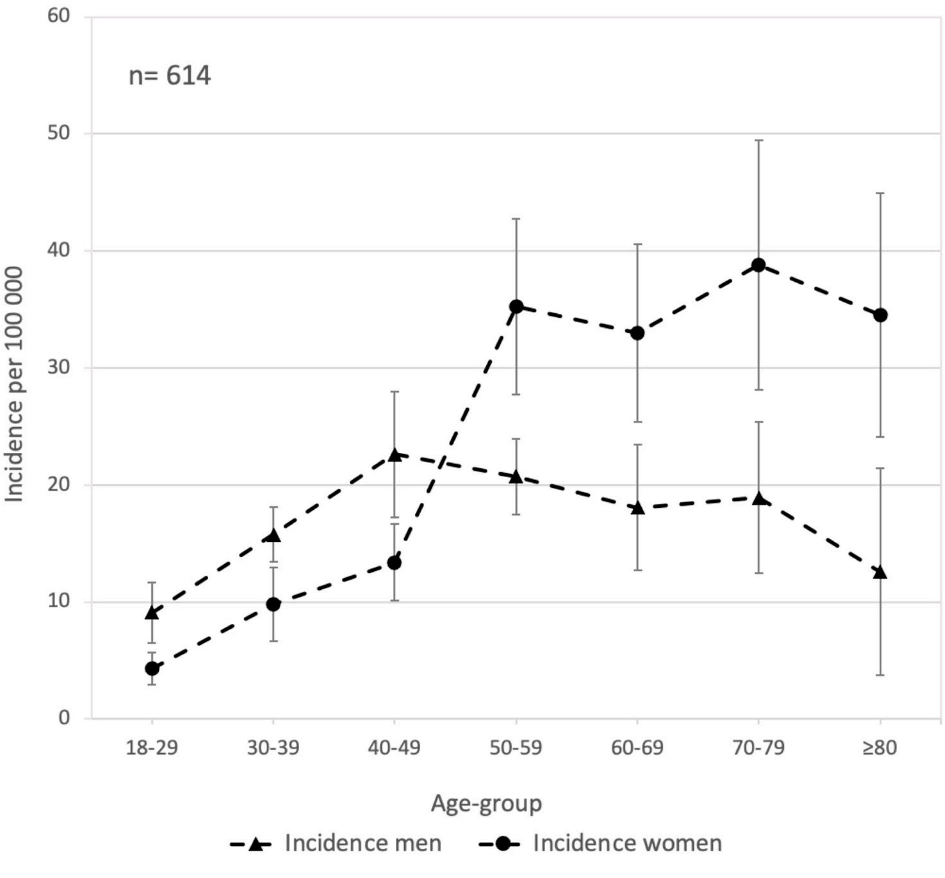


Figure 24. Sex- and age-specific incidence of isolated greater tuberosity fractures. Average sample year incidence of isolated greater tuberosity fractures per 100,000 adults, categorized by sex and 10-year age-groups, from 1944 to 2020 in Malmö, Sweden. Bars represent 95% confidence intervals.

Paper IV

Long-term clinical outcome

255 adult individuals with a non-operatively treated PHF were included. Mean age at fracture was 65 (SD 14) years. 130 individuals (80% of those available) participated in the follow-up, with a mean follow-up time of 10.4 (SD 0.4) years. 92 (36%) individuals were deceased at the time of follow-up. At follow-up, 78% reported no pain, and 79% reported full function.

The mean flexion, abduction, internal rotation, and external rotation with 95% confidence intervals at follow-up stratified by Neer- and AO-types are presented in Table 2.

The proportion of individuals with pain and impaired function at follow up stratified by Neer- and AO-types are presented in Table 3.

Patients with Neer 1 fractures exhibited greater external rotation at follow-up compared to those with Neer 3&4 (mean degree difference (95% CI) and p-value) (26° (7 to 44) p=0.043), as well as borderline statistically significant greater flexion (45° (14 to 77) p=0.054), abduction (42° (10 to 77) p=0.051), and better function (p=0.036). No association between fracture types and clinical outcome was apparent for the AO classification (Table 4).

Table 2. Distribution of mean range of motion in degrees approximately 10 years post fracture for flexion, abduction, internal rotation, external rotation, with 95% confidence intervals stratified by Neer- and AO-types, among 107 adult individuals with a non-operatively treated proximal humeral fracture sustained in Malmö, Sweden, 1981.

	All n=107	**Neer 1[a]** n=82	**Neer 2[a]** n=15	**Neer 3 & 4[a]** n=10	**AO type A[b]** n=64	**AO type B[b]** n=27	**AO type C[b]** n=16
Flexion [c]	151 (145 to 156)	156 (152 to 161)	145 (133 to 155)	112 (80 to 143)	157 (152 to 161)	148 (138 to 158)	131 (106 to 153)
Abduction [c]	155 (149 to 161)	160 (154 to 166)	152 (137 to 165)	118 (84 to 149)	162 (156 to 168)	147 (133 to 160)	139 (113 to 162)
Int. Rotation [c]	87 (85 to 89)	89 (88 to 90)	85 (81 to 88)	77 (57 to 88)	88 (87 to 89)	88 (86 to 90)	81 (68 to 88)
Ext. Rotation [c]	57 (52 to 61)	61 (56 to 65)	48 (40 to 56)	35 (17 to 54)	61 (56 to 65)	55 (46 to 63)	43 (28 to 56)

[a] Neer 1: Minimally displaced. Neer 2: displaced 2-part. Neer 3: displaced 3-part. Neer 4: displaced 4-part or articular surface [60]

[b] Type A: Extraarticular, unifocal, 2-part. Type B: Extraarticular, bifocal, 3-part. Type C: Articular or 4-part [41]

[c] Mean degrees with bootstrapped 95% cinfidence intervals

Table 3. Proportion of pain and function approximately 10 years post fracture stratified by Neer- and AO-types, among 130 individuals with a non-operatively treated proximal humeral fracture sustained in Malmö, Sweden, 1981.

	All n=130	Neer 1 [a] n=102	Neer 2 [a] n=16	Neer 3&4 [a] n=12	AO Type A [b] n=77	AO Type B [b] n=37	AO Type C [b] n=16
Pain, n (%)							
No pain	101 (78%)	85 (83%)	10 (62%)	6 (50%)	62 (81%)	30 (81%)	9 (56%)
Pain	29 (22%)	17 (17%)	6 (38%)	6 (50%)	15 (19%)	7 (19%)	7 (44%)
Function, n (%)							
Full function	103 (79%)	85 (83%)	14 (87%)	4 (33%)	63 (82%)	31 (84%)	9 (56%)
Impaired function	27 (21%)	17 (17%)	2 (13%)	8 (67%)	14 (18%)	6 (16%)	7 (44%)

[a] Neer 1: Minimally displaced. Neer 2: displaced 2-part. Neer 3: displaced 3-part. Neer 4: displaced 4-part or articular surface [60]
[b] Type A: Extraarticular, unifocal, 2-part. Type B: Extraarticular, bifocal, 3-part. Type C: Articular or 4-part [41]

Tabel 4. Distribution of mean degree differences for flexion, abduction, internal- and external rotation, with bootstrapped 95% confidence intervals and pain- and function group p-values comparing Neer- and AO-types among adult individuals with a proximal humeral fracture in Malmö, Sweden 1981, approximately 10 years post fracture. For clarity statistically significant differences are bolded.

	Neer 1 vs Neer 2 [a]	p	Neer 1 vs Neer 3 & 4 [a]	p	Neer 2 vs Neer 3 & 4 [a]	p	AO Type A vs AO Type B [b]	p	AO Type A vs AO Type C [b]	p	AO Type B vs AO Type C [b]	p
Flexion [c]	11 (0 to 24)	0.113	45 (14 to 77)	0.054	33 (0 to 68)	0.123	8 (-3 to 20)	0.195	26 (4 to 51)	0.261	17 (-7 to 44)	0.235
Abduction [c]	8 (-7 to 24)	0.300	42 (10 to 77)	0.051	34 (-1 to 71)	0.114	15 (1 to 30)	0.133	24 (-0 to 50)	0.117	9 (-18 to 38)	0.383
Int. rotation [c]	4 (0 to 8)	0.124	12 (1 to 33)	0.124	9 (-4 to 29)	0.202	0 (-2 to 3)	1.000	7 (-0 to 20)	0.121	7 (-1 to 20)	0.164
Ext. rotation [c]	13 (3 to 22)	0.072	**26 (7 to 44)**	**0.043**	13 (-7 to 33)	0.240	6 (-4 to 16)	0.244	18 (4 to 33)	0.072	12 (-4 to 29)	0.188
Pain [d]	0.4 (0.2 to 1.2)	0.149	0.3 (0.1 to 0.9)	0.068	0.8 (0.2 to 2.5)	0.790	1.0 (0.4 to 2.7)	1.000	0.4 (0.2 to 1.2)	0.112	0.4 (0.1 to 1.3)	0.154
Function [d]	1.3 (0.4 to 8.5)	1.000	**0.3 (0.1 to 0.6)**	**0.036**	0.2 (0.0 to 0.8)	0.051	1.1 (0.4 to 3.2)	1.000	0.4 (0.2 to 1.1)	0.113	0.4 (0.1 to 1.1)	0.119

[a] Neer 1: Minimally displaced. Neer 2: displaced 2-part. Neer 3: displaced 3-part. Neer 4: displaced 4-part or articular surface [60]
[b] Type A: Extraarticular, unifocal, 2-part. Type B: Extraarticular, bifocal, 3-part. Type C: Articular or 4-part [41]
[c] Mean degrees of difference with 95% confidence intervals
[d] Rate-ratios (% with pain/impaired function in the first group / % with pain/impaired function in the second group), 95% confidence intervals calculated by the Mid-P exact method and P-values calculated by the Exact Fishers test and adjusted by Benjamini-Hochberg

Discussion

General discussion

Although PHFs are common, have been described in medical literature since before the supposed birth of Christ, and are extensively studied, many questions remain unanswered. Efforts to answer these questions are complicated by inconsistent or absent definitions, both regarding what constitutes a PHF and how different types of PHF are labeled and subgrouped.

Firstly, few studies provide a clear definition of what constitutes a PHF. When different definitions are used across studies, it becomes difficult to compare results. Secondly, the scientific literature on PHF employs a wide range of terminology, often without clear explanations. Terms such as part, segment, fragment, type, group, subgroup, class, and category are frequently used, not always clearly defined.

This lack of terminological clarity can lead to confusion and uncertainty regarding which fracture types are actually being examined and discussed, thereby complicating both the interpretation of findings and the comparison of results across studies.

It is therefore important that future research on PHF is exceptionally explicit about which fracture types are being studied and how they are categorized. In **Papers II-IV**, where we classified fractures, we have made an effort to be as clear as possible in describing the fracture types and the subgrouping methodology used. Nonetheless, we acknowledge the possibility that what seems self-evident within our research context may be interpreted differently by external readers.

Sweden is, in many respects, a pioneer in population registration and demographic data collection, with efforts dating back to the establishment of Tabellverket in 1749 [130]. Nevertheless, challenges remain in describing the size and composition of the population when conducting studies, such as **paper I-III** in this thesis, that span long time periods. For **papers I-III** in this thesis, official population data used for incidence calculations were obtained from Statistics Sweden. The data was obtained from two different sources within Statistics Sweden, with some differences. Between the 1940s and 1967, data were only available for selected years. To estimate the population for specific years during which fracture data were collected but population data were missing, we extrapolated values from the available years. From 1968 onwards, annual population data were consistently available. The definition of Malmö varied slightly between the two time periods during which population data were collected. "Malmö and its suburbs" regarding the first time period, and later as "Malmö municipality". To the best of our knowledge, these two definitions largely overlap and are considered comparable for the purposes of these papers.

Fracture data for **paper I-III** was also obtained from two different sources, the analogue and the digital radiology archives, which also differ in some respects. In the analogue archive, we were unable to confirm that all individuals were residents of Malmö. We are therefore unable to rule out that some individuals living outside Malmö, who for some reason sought healthcare at the hospital in Malmö, were included. Malmö residents who sustained a PHF outside of Malmö were likely included, as follow-up examinations typically are performed at the individuals home hospital. In 1981, when more detailed data were available, we found that only 3 out of 288 individuals with PHF were non-Malmö residents. Assuming a similar distribution across the other years examined, the overall impact of this appears very limited, yet a small overestimation of the incidence during the years from the analogue archive is possible. Regarding the digital archive, data on the residence of the included individuals were available, and only Malmö residents were included. The analogue archive is to our knowledge not validated, as no obvious gold standard comparator is available. However, we observed examinations in the analogue archive from the beginning of January until the end of December in every examined year, as well as consecutive label numbers with no, or very few missing. The case finding strategy in the digital archive has previously been validated in our setting [126], with a misclassification rate of about 3%, leading to a possible small underestimation of the true incidence.

In summary, a slight overestimation of incidence during the years covered by the analogue archive, and a slight underestimation during the years covered by the digital archive, cannot be ruled out. This unlikely affected the increasing incidence trend found in **paper I** between 1944 and 1977, as the time period for this trend only contains data from the analogue archive. The decreasing incidence trend found between 1977 and 2020 may have been somewhat less pronounced, as the time period for this trend contains data from both the analogue and the digital archives. We consider that the overall impact of these challenges in our case finding strategy does not compromise our main findings or conclusions.

In **papers II-IV**, fractures were classified according to three different classification systems: The Neer and AO classifications in **papers II and IV**, and the Mutch classification in **paper III**. Fracture classification systems are used in a scientific context to, for example, describe the fracture panorama, facilitate comparison across studies and to analyse outcomes based on fracture type. Ideally, they should be synoptic, user-friendly, guide treatment, predict outcome, while demonstrating good levels of intra- and interobserver agreement. Observer agreements for the Neer and the AO classifications have generally been reported as low, though varying from fair to almost perfect [65-70]. We assessed inter- and intraobserver agreements in our setting before study start and used the percental agreement and Cohens kappa coefficient (κ) to present the results. The interobserver agreement was then 90% (κ=0.76, substantial) for Neer and 85% (κ=0.77, substantial) for AO and the intraobserver agreement was 93% (κ=0.81, almost perfect) for Neer and 93% (κ=0.89, almost perfect) for AO. Our observer agreements are higher than most previous studies [65, 70, 131], however Sidor et al. reported an intraobserver agreement for the Neer classification by a shoulder specialist similar to ours [70]. Brorson et al. demonstrated that mean kappa for shoulder specialists increased from 0.3 to 0.79 after training [66]. One explanation to our high observer agreements may be that the first author (A.C) was trained in PHF classification before study start by a senior expert (A.N).

Comparing kappa values across studies presents challenges, as a similar distribution of fracture types is required for a reliable comparison. For example, if one category is common, such as for example 85% classified as Neer a, kappa tends to be low even when percental agreement is high, since the calculation assumes that many of these agreements occurred by chance. This phenomenon is called the *kappa paradox* [132]. Conversely, kappa may be relatively high despite low actual agreement if the fracture types are evenly distributed. For this reason, it is advisable to report percental agreement alongside kappa, allowing reader to better understand the true level of agreement. There are statistical methods to adjust for the kappa paradox, such as Gwet´s AC1 [133]. We did not apply any of these, partly due to lack of awareness of them at the time of analysis, and partly because no other study on the subject uses them, making comparisons with previous studies difficult. The Mutch classification, used in **paper III**, is discussed in the section addressing IGTF epidemiology.

In all papers included in this thesis, only conventional radiographs were used, even in cases where, for example, CT imaging was available. This decision was made because the classification systems employed are based on conventional radiography, and most other studies involving classified PHFs also used conventional radiographs.

Time trends in PHF incidence

In line with a previous study [83], we observed, in **paper I**, an increase in PHF incidence from the 1940s until 1977. Suggested explanations to this is a more fragile skeleton, partly mediated through lower level of physical activity or a shift towards activities with a higher risk of trauma. Additional possible explanations include improved access to healthcare and radiographic examinations, as well as changes in patient healthcare-seeking behaviour. From 1977 until 2020, we found a decrease in incidence, whereas a study from Finland found a stabilized trend between 1995 and 2015 [134]. A possible explanation to the decreasing trend seen in **paper I** is immigration. During the 1980s, there was an increasing immigration to Sweden and Malmö, specially from Iran, Chile, Lebanon and Turkey, in the early 1990s from former Yugoslavia [32], and in the mid 2010s also from Syria [33]. Fracture incidence in these countries is generally lower than in Sweden [135], which may have contributed to the decreasing incidence in **paper I**.

PHF incidence variation in relation to sex and age

In **paper I** we found that PHF incidence was similar between men and women in age-groups 18-49. In age-groups ≥50 years however, the incidence was higher in women than men. This corresponds well with previous reports from Germany 2007-2016 [15] and Sweden 2011-2013 [81] and suggests that the PHF population can be considered as two different entities, i.e., younger and older individuals, most often in the groups 18-49 years old and ≥50 years old. In individuals ≥50 years old the incidence is higher, with a female dominance, probably attributed to risk factors mainly affecting women, e.g., menopause, changes in oestrogen levels and a more fragile skeleton.

Seasonal variation

We found a seasonal variation, with higher incidence during the colder winter months in the overall analysis. This is in line with previous studies from Sweden [81], Finland [90] and the United Kingdom [91]. It has been hypothesised that this may be attributed to an increased risk of outdoor falls on slippery snow and ice, which more frequently results in fractures of the upper limb. In contrast, lower limb fractures appear to be more common in summer [91].

The seasonal variation found in **paper I** was apparent in women and individuals aged ≥50 years during the time period 1944-2020, and among all individuals during distant decades (1944-1995). However, no seasonal variation was found among individuals aged 18-49 years during the time period 1944-2020, nor among individuals during more recent decades (2005-2020). These observations have, to our knowledge, not previously been described and need to be verified in future studies. The observed change regarding seasonal variation between distant and recent decades is probably influenced by multiple factors, and due to the design of **paper I** we can only speculate on them. By visually inspecting Figure 21, it becomes evident that the difference between distant and recent decades lies in a lower incidence during winter months in more recent decades. The mean temperature in Sweden has increased from the 1940s until 2020 [29], as has the number of days without snow in the south of Sweden when comparing the time periods 1960-1990 and 1990-2014 [30]. This may have resulted in less icy, slippery weather conditions and thus lower PHF risk in recent decades. More effectively cleared or salted walkways/roads may also have contributed as may better and more widely used spiked shoes.

PHF complexity

Our finding, in **paper II,** of a similar PHF complexity from the 1940s to 2020 has, to our knowledge, not previously been reported. Due to the long-term study design and the relatively low number of fractures during each timepoint, we used descriptive statistics and evaluated trends by visual inspection. This decision was discussed within the research group, including a statistician, and affirmed during the review process. A post-hoc proposal, not presented in **paper II**, for inferential statistical analysis regarding time trends in PHF complexity is presented in the appendix (Supplemental Table 1). This analysis also showed a similar PHF complexity from the 1940s to 2020. While this analysis uses lower resolution, given that both the time period and fracture types have been stratified into fewer groups, it nonetheless supports the conclusion, drawn from descriptive statistics in **paper II**, that PHF complexity does not appear to have changed from the 1940s to 2020.

The proportion of PHFs treated operatively increased after the turn of the millennium [23, 24, 116]. Given that PHF complexity seems stable over time, other factors, such as changes in indications and introduction of new treatment methods (locking plates, RSA), may explain this increase. It is thus possible that new treatment methods may have become available and adopted before being thoroughly evaluated. This raises further questions regarding the introduction and implementation of new treatment methods in healthcare. How should new treatment methods be introduced into clinical practice, and to what extend should they be evaluated before implementation? Strategies for this exist [136], but in this case it is unclear whether they have been applied.

Higher age seemed associated with higher fracture complexity in both men and women according to the AO classification, as well as for women according to the Neer classification. This is in line with previous studies [86, 88, 137]. Possible explanations include a more fragile skeleton and an inferior ability to parry a fall at higher than younger age, resulting in more complex fractures. Interestingly, for men according to the Neer classification younger age seemed associated with higher fracture complexity, aligning with data from Germany [137]. This seems partly driven by Neer VI in the full resolution of the Neer classification, i.e., isolated greater tuberosity fractures with concomitant shoulder dislocation, which were notably more prevalent in men <50 years (11%) upon closer examination of the data in **paper II**, compared to 4% of all individuals with a PHF. Passaretti et al. reported on the PHF trauma mechanism in Rome, Italy, 2013-2016 (in 711 PHF) and found a male dominance in sports- and high energy-trauma and a female dominance in low-energy trauma [92]. Based on this, we speculate that younger men tend to suffer more complex fractures, especially Neer VI, possibly due to high energy trauma while older women may rather suffer more complex fractures largely related to low energy trauma. A possible explanation for why older women sustain more complex fractures is a more fragile skeleton, i.e., osteoporosis, which is more common in older than younger women [138].

The distribution of fracture types according to the Neer and the AO classifications in previous studies in relation to the findings in **Paper II** is presented in Supplemental Table 2. Compared to these studies, PHF complexity in **paper II** was, generally lower according to the Neer classification and of similar complexity according to the AO classification. Possible explanations to the found differences are the uncertainty in reliability of the Neer and the AO classifications describes previously, as well as differences in year of data collection, population of examination, and geographical area. Brorson et al. have shown that inexperienced raters tend to use more complex categories when classifying PHF by the Neer classification. They found that the proportion of four-part fractures decreased from 10% to 2% after training, while the proportion of Neer 1 increased [139]. This may partly explain that our fracture distribution showed a lower proportion of Neer 4 fractures, and a higher proportion of Neer 1 fractures, compared to other studies [51, 86-88, 140]. Regarding the AO classification, a recent study reported only fair observer agreement for the version of the AO classification used in the Swedish Fracture Register (SFR) [141], which is the version that is used in the study from Sweden [81] included in Supplemental Table II.

A previous study has shown that our perceptions and assumptions about which fracture types are common may influence how we classify PHFs. If a particular fracture type is believed to be frequently occurring, there is a tendency to assign that fracture type more often [142]. We cannot rule out that this may have influenced the results in **paper II-IV** as well as in other studies involving classified PHFs, given that Neer´s statement, that 85% of all PHFs are Neer 1, is widely known, despite being questioned recently [89]. However, considering the expertise of the assessors we employed, we believe the risk is considerably lower than in studies involving less experienced assessors.

IGTF epidemiology

Osteoporosis is a well-known risk factor for PHF [37], but the relationship between osteoporosis and risk of IGTF is, to our knowledge, no as well established. Our finding, in **paper III**, indicating a higher incidence of IGTF among women with advancing age, may however imply such an association. The age-specific pattern found, with a four-fold increase in incidence among women after age 50 is similar to what previously have been shown for distal radial fractures [143].

The observed tendency towards an increase in IGTF incidence between 1944 and 1981, followed by a subsequent decrease until 2020, although not statistically significant, has, to our knowledge, not been reported previously. Future studies, preferably with larger cohorts, are needed to examine whether this trend becomes more evident or if no true trend exists.

We found a substantial intraobserver agreement for the Mutch classification, 85% percental agreement and κ=0.71. This is similar to κ-values from previous studies, Mutch et al. κ=0.78 [74] and Razaeian et al. κ=0.72 [75], suggesting that the Mutch classification may offer greater reliability in terms of intraobserver agreement compared to the Neer and AO classifications.

We found a similar distribution of IGTF according to the Mutch classification (45% avulsion, 44% split and 11% depression) as previous studies [74, 75]. This suggests that the true distribution of IGTF is likely similar.

As discussed above, we have only reviewed conventional radiographs. Specifically regarding IGTF, the degree and direction of displacement may be difficult to fully assess and quantify using conventional radiographs alone. In future studies on IGTF, it would therefore be valuable to include CT, particularly since posterior displacement can be challenging to identify and measure using conventional radiographs.

We found that individuals with an IGTF tend to be younger and to a greater extent male compared to individuals with other PHFs. This is similar to a previous study from South Korea that demonstrated that individuals with an IGTF had a mean age of 43 years and that 32% were women, whereas individuals with other PHFs had a mean age of 54 years, with 68% being women [94]. At present, it is unclear which degree of displacement can be managed non-operatively and which IGTF require operative treatment [144]. The thresholds for operative treatment currently used are based on a limited number of studies, many of which suffer from methodological limitations [144-146]. Despite the questionable scientific support, generally less displacement is accepted for IGTF compared to other PHFs before operative treatment is considered. The differences in demographics and treatment between PHF and IGTF suggest that a clearer distinction, in a clinical as well as in a scientifical setting, should be made. By studying these fracture types separately, it will be easier to identify the most appropriate management and treatment strategies for each fracture type.

Long-term clinical outcome

In similarity with our results in **Paper IV**, previous studies have reported an association between radiological appearance at the time of injury and clinical outcome [101, 111, 147], although preexisting patient-related psychosocial factors seems to be stronger determinants [101].

The clinical outcome following non-operatively treated PHF for different classifications and their subgroups have partially been described in the literature [104, 106, 108, 111, 114], with mean follow-up times ranging from 1 to 5 years. In summary, the results of these studies suggest that fracture complexity according to the Neer classification is associated with clinical outcome, in such a way that less complex PHF tend to have better outcome than more complex ones [104, 106, 111]. The few existing studies on the AO classification have not found an association between fracture complexity and clinical outcome [108]. These findings are consistent with our results, which show that fracture complexity according to the Neer classification is associated with the clinical long-term outcome in non-operatively treated PHF.

The data for **paper IV** was collected around the 1990s, a time when power calculations were not routinely performed. We acknowledge that **paper IV** is underpowered, particularly regarding the more complex, and less common fracture types. This creates a risk of so-called Type-II error, meaning that differences between fracture types may exist but go undetected. Considering this, we believe that the differences between fracture types that we do observe, as well as the tendencies toward differences (i.e., borderline significant p-values) should carry some weight. Borderline p-values refer to statistical results that are close to the threshold for significance, typically around 0.05. While all p-values and especially borderline p-values should be interpreted with caution, we believe that they may indicate differences in this paper, where the risk of failing to detect actual differences (Type II error) is greater than the risk of identifying statistically significant differences that do not truly exist (Type I error). The results should, of course, be verified through future studies, preferably with larger cohorts.

The follow-up visits, and the data collected at that time, were conducted more than 30 years ago, which introduces a degree of uncertainty. The fact that a long time has passed since the follow-up visits, the accuracy in which certain methodological details can be recalled may be affected. Patient expectations, treatments for other diseases affecting quality of life and life expectancy, pain management strategies, and treatment protocols, including physiotherapy and immobilization duration, used over 30 years ago may differ from current practices, making the results not fully generalizability to present-day.

The data collected in the 1990s is the material we have had at hand, and we were unable to influence the selection of variables or the methods by which they were collected. Today, one or more outcome measure instruments, such as the CMS or DASH, are commonly used. Had these outcome measures been available in our dataset, comparisons with more recent studies would have been facilitated.

The follow-up procedures could also have been improved. Instead of having a single physician, who in some cases was also the treating physician, conduct the assessments, it would have been preferable to involve another examiner blinded to both the patient identity and fracture type to reduce the risk of assessor bias. Additionally, if the follow-ups were done today, the questionnaires could have been completed digitally by the patients themselves to reduce the risk of interviewer bias, with mandatory responses to ensure data completeness.

It would also have been valuable to include additional follow-up assessments at intermediate time points, such as at 6 months, 1- and 5-years, in order to potentially identify when the final functional outcome is achieved. Radiological examinations at follow-up would also be of interest, in order to explore potential associations between the radiological outcome and the long-term clinical outcome.

Strengths and Limitations

The case-finding strategies and population data used in **papers I-III**, and their limitations, have already been discussed in the General discussion section and will therefore not be further addressed here.

The results from Malmö presented in this thesis are likely not directly generalizable to substantially different settings, such as developing countries and other regions with different age distribution and life expectancy. However, Sweden´s notably high fracture incidence [148], together with well-validated official records may enable detection of emerging trends. Some fracture types in our data are rare, which introduces uncertainty regarding the generalizability of our findings for these specific types, both in terms of epidemiology and clinical outcome.

All papers included in this thesis focus on the fracture appearance at the time of injury. In a study from 2020, Frank et al. [149] found that approximately 25% of all PHFs displayed signs of secondary displacement at follow-up. Secondary displacement was defined as a translation of 10mm or more. If a fracture becomes further displaced after the initial injury, it may, according to the Neer classification, be classified as a different fracture type than it was based on the initial radiographs. The fact that we did not assess or analyse secondary displacement may be considered a limitation, although most other studies classifying PHFs also rely on radiographs taken at the time of injury.

It would have been beneficial to record exactly which radiographic projections were available för each examination. Unfortunately, this was not done, and the issue was raised after the review of all radiographs had been completed. To gain an impression of the types of radiological projections present in our dataset, we re-reviewed 100 examinations. An AP-view was available in 99% of cases. In 96% of cases, the AP-view was taken with the arm in neutral position, and 45% of cases included an AP-view with the arm internally rotated. A scapular Y-view was present in 73% of cases, while an axial view was available in only 1%.

An AP-view with the arm in neutral position is needed to differentiate between a depression fracture and a Hill-Sachs lesion (HSL). This projection was missing in approximately 4% of cases. Assuming that the distribution of fracture types among these cases was similar to that of the entire cohort, this results in three cases in which uncertainty regarding classification is present due to the absence of the appropriate projection. Had the projection been available, we cannot rule out that some of these three cases would have been excluded from the dataset, as they might have been regarded as a HSL rather than a depression fracture.

Similarly, a scapular Y-view is needed to reliably differentiate between avulsion and depression fractures. Without this projection, there is a risk that a fracture may appear as a depression fracture on the AP-view, while a dorsal fragment, unseen on the AP-view, may still be present. In 27% of cases, a scapular Y-view was not available. Among these cases, assuming a similar distribution of fracture types as in the entire cohort, approximately 18 cases were classified as depression fracture, but there is a risk that a dorsal fragment may have been missed. Had all projections been available for all examinations, the likely effect is probably a slightly lower number of depression fractures and possibly a higher number of avulsion fractures.

The absence of certain radiological projections should be considered a limitation, particularly in relation to **paper III**, where the Mutch classification may be affected, as previously outlined. However, we consider the combined effect of missing projections in some examinations to be limited with only a small effect on the main results and conclusions of **paper III**, although a slight overestimation of depression fractures is possible.

Another limitation, regarding **paper IV**, is the potential for selection bias. Some patients passed away during the 10-year follow-up period, a small number was either unable or unwilling to attend the follow-up assessment, and 18 patients were excluded due to having undergone operative treatment.

The long time span, approximately 80 years, covered by **papers I-III** provides an opportunity to observe how incidence and fracture types have changed over time, but it also presents challenges that may be considered limitations. Are there differences in how patients sought healthcare in the past compared today? Has the healthcare system´s threshold for performing radiological examinations of a shoulder injury changed during this period? We can only speculate on changes in these and other such factors, and how they may have influenced our results. Furthermore, patients' perception of what constitutes a fully functional, pain free shoulder may also have shifted since the early 1990s, when the data for **paper IV** were collected. This introduces uncertainty whether the results regarding pain and function from **paper IV** are directly generalizable to present day.

The analogue radiology archive in Malmö, which enables epidemiological research all the way back to the 1940s, should be considered a strength. Furthermore, the official systems in Sweden from which we obtained population data are generally reliable and well-organized.

Another strength is that we reviewed all radiographs ourselves and confirmed that each case represented a PHF. In epidemiological research, it is common to rely on registry data, which requires trust in the accuracy of the individual who entered the diagnosis, and in cases involving classified fractures also that the fracture was correctly classified. A recent study has highlighted a challenge associated with registry-based epidemiological research on classified PHF, reporting only fair observer agreement within the SFR [141]. Nevertheless, registry studies offer certain advantages, particularly the ability to identify large numbers of fractures, which increases the power of the study.

The high observer agreements found across all three classification systems used in this thesis should also be considered a strength.

A strength in **paper IV** is the long follow-up period of approximately 10 years. Another strength is the inclusion of only non-operated individuals, including also more complex fractures. Conducting a similar study today would be challenging, as patients with complex fractures often are treated operatively. The fracture type specific clinical outcome, presented in **paper IV**, may serve as a benchmark in shared treatment decision-making in clinical practice. An additional strength is the high follow-up rate: 80% of individuals who were still alive 10 years after the fracture event participated in the follow-up assessment.

Conclusions

In Malmö, Sweden:

- The age- and sex-adjusted incidence of PHF increased from the 1940´s until year 1977 and thereafter decreased until 2020.
- The PHF incidence increases with advancing age and is similar in men and women in the <50 age-group, but higher in women than men in the ≥50 age-group.
- A seasonal variation, with more PHFs during winter months, was apparent earlier (1944-1995) but not in recent decades (2005-2020).
- We saw no time trend in PHF complexity, neither overall nor when the data was stratified by gender or age-groups, with the Neer or with the AO classification between 1944-2020.
- PHF complexity seems higher in older than younger age-groups for both women and men according to the AO classification, as well as for women according to the Neer classification. However, for men according to the Neer classification, PHF complexity seems higher in younger than older age-groups.
- The IGTF incidence increases with advancing age among women. IGTF is more common in men than women in the <50 age-group, while the opposite was seen in the ≥50 age-group.
- We found no statistically significant time trend in the sex- and age-adjusted incidence of IGTF between 1944 and 2020.
- In IGTF, we found 45% avulsion-, 44% split-, and 11% depression-fractures according to the Mutch classification.
- 10 years after a non-operatively treated PHF, 78% of patients reported no pain and 79% full function. Fracture complexity according to the Neer classification is associated with clinical outcome, with less complex PHF showing better ROM and function compared to more complex ones. No such associations were apparent for the AO classification.

Future perspectives

I believe it is very important to improve the reliability of the classification systems for PHF. We need to reach consensus and consistency not only in the definition of what constitutes a PHF, but also in determining which subgroup and type a fracture belongs to. As long as the reliability of the classification systems is low, there is an inherent uncertainty in all studies that include classified PHFs. One way to improve the reliability could be to use an AI model that classifies PHF with good reliability. If future studies then would use the same AI model, we could at least diminish the uncertainty regarding if we are studying the same fracture types.

Today, subgroups of PHF are treated more based on clinical experience and expert opinion than on scientific evidence. RCTs comparing operative and non-operative treatment in PHF subgroups can help identify fracture subgroups and individuals that would benefit from operative treatment. Examples of interesting fracture subgroups and individuals to study include IGTF, 2-part fractures between the humeral head and the shaft with no bony contact, fracture dislocations in the very elderly, head-split fractures, and displaced fractures in younger individuals. Conducting RCTs in subgroups of PHF is time- and resource consuming as many of these fracture types are uncommon. Multi-center studies, where hospitals in different cities and countries collaborate, might be a methodology that would facilitate these types of studies.

I believe that IGTF could be considered a distinct fracture type, and not a PHF subtype, since IGTF demonstrates different demographics and treatment recommendations compared to other PHF. Most studies on PHF include IGTF but some previous studies have examined IGTF separately. Studying IGTF and other PHFs separately could potentially lead to a better understanding of both and may support a more appropriate approach to their treatment than if they are considered as the same fracture type.

Most studies on clinical outcome following a PHF, including **paper IV** in this thesis, focus on pain, function, ROM, and radiological appearance. However, only a few studies have explored the individuals' experiences of sustaining a PHF, how it affects them, and what matters from their perspective [150, 151]. Are we measuring the outcomes that matter to the individual suffering from the fracture? I believe that qualitative studies on PHF, exploring how individuals with a PHF experience the injury, the rehabilitation period, and what is important to them, is essential for ensuring that we focus on what truly matters to the individuals we treat.

Most studies on the treatment of PHF focus on clinical outcome following different operative methods. However, the vast majority of PHF are treated non-operatively. A few studies have tried to explore the benefits and harms of different non-operative treatment strategies, but no clear difference in immobilization time [97, 98] nor whether the rehabilitation was supervised or not [99] was found. More studies on non-operative treatment are needed to understand the benefits and harms with different rehabilitation strategies.

Previous studies have shown that patient-related psychosocial factors influence the clinical outcome to a greater extent than fracture morphology [101, 114, 152]. Identifying which of these factors carry the greatest weight, to recognize these individuals and provide them with the best possible care suitable for them, would be of interest. A possible initial approach may be to analyse the individuals within a cohort with the poorest outcome and investigate whether any common factors can be identified among them.

An interesting future study would be how the treatment decision is made and the impact on the outcome. Either the patient is informed about which treatment they will receive, as was more common in the past, or the patient is informed about their injury, the available options, the pros and cons of each option, and then a shared decision is made between the patient and the surgeon.

The impact of healthcare on the climate and environment has in recent times gained increasing attention and has become a growing topic of discussion. Future clinical studies evaluating different treatment methods for PHF should take the environmental impact of each method into account. In a situation where the clinical outcome of two treatment methods are similar but their climate footprints differ, the method that best supports planetary health and the well-being of future generations should be chosen [153, 154].

A national registry for PHF, with classified fractures, patient reported outcome measures, patient characteristics and treatments, would be a powerful tool for future studies. The SFR exists today, but the classification used there, a variant of the AO classification, makes it difficult to compare classified PHF with other studies that use the full AO, or other AO variants. In 2025, concerns have been raised regarding the reliability of PHF classification within the SFR, making the register uncertain as a source regarding classified PHF [141]. Including the Neer classification in the SFR could provide additional information. However, given the large number of assessors involved in classification within the SFR, and their limited experience in fracture classification, training in both the Neer and AO classifications may be necessary to achieve acceptable levels of reliability.

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Appendix

Supplemental Table 1. Percental change in proportion of fracture subgroup between distant and recent decades.

	Percental change[a] (95% CI)
Neer 1[b]	2.5 (-1.6 to 6.2)
AO-A[c]	2.1 (-2.8 to 7.1)
AO-B[d]	1.5 (-2.7 to 5.0)
AO-C[e]	2.2 (-2.8 to 7.1)

a Percental change between distant (1944-1995) and recent (2005-2020) decades.

b Proportion Neer 1 in relation to Neer 2-4 fractures.

c Proportion AO-A in relation to AO-B and AO-C-fractures.

d Proportion AO-B in relation to AO-A and AO-C-fractures.

e Proportion AO-C in relation to AO-A and AO-B-fractures.

Supplemental Table 2. Proximal humeral fracture distribution according to overarching types for the Neer and AO classifications in different settings. Studies are presented in chronological order.

Study setting			Neer				AO		
Location	Period of examination	Population of examination	1	2	3	4	A	B	C
Malmö, Sweden[a]	1944-2020	≥18 years. n=3031	72%	18.5%	5.4%	4.2%	57.7%	30.8%	11.5%
Edinburgh, Scotland [51]	1992-1996	≥10 years. n=1027	49%	37.5%	9.5%	4%	66%	27%	6%
Japan [87]	2003-2006	≥15 years. n=509	36%	44%	10%	10%	n/a	n/a	n/a
Tübingen, Germany [140]	2006-2011	>17 years. n=815	13.9%	37.4%	26.6%	22.1%	46%	22%	32%
Nice, France [86]	Nov 2009-Nov 2010	≥0 years. n=329	42%	42%	8%	8%	n/a	n/a	n/a
Sweden [81]	2011-2013	≥16 years. n=1582	n/a	n/a	n/a	n/a	49.9%	44%	11.1%
Vigo, Spain [88]	2016-2018	≥18 years. n=638	24.3%	32.3%	30.9%	12.5%	49.2%	43.1%	7.7%

[a] Paper II

Proximal Humeral Fractures

Proximal humeral fractures (PHFs) are among the most common fracture types in the adult population and often lead to considerable suffering. Despite being common, many unanswered questions remain for these fractures.

This thesis aims to broaden the understanding of PHFs by exploring their epidemiology, classification systems, and long-term clinical outcome. Based on a review of radiographs spanning approximately eight decades in Malmö, Sweden, this thesis describes the epidemiology of PHF and examines whether the incidence and fracture patterns of PHFs have evolved over time. The clinical outcome following non-operative treatment 10 years after the fracture event for different types of PHF is also assessed.

This thesis answers some key questions regarding PHF and identifies new challenges for future research.

ANTON CEDERWALL was born in 1983 and grew up in Malmö, where he lived until 2004. He studied medicine at Linköping University from which he received his medical degree in 2010. After completing his internship in Halmstad, he returned home to Malmö in 2012 to begin his residency at the Department of Orthopaedics at Skåne University Hospital.

Towards the end of his residency, he began the work that forms the basis of this thesis, under the supervision of Professor Björn Rosengren. Anton received his qualification as specialist in orthopaedic surgery in 2018 and has since been working at the Shoulder Section at Skåne University Hospital in Malmö.

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