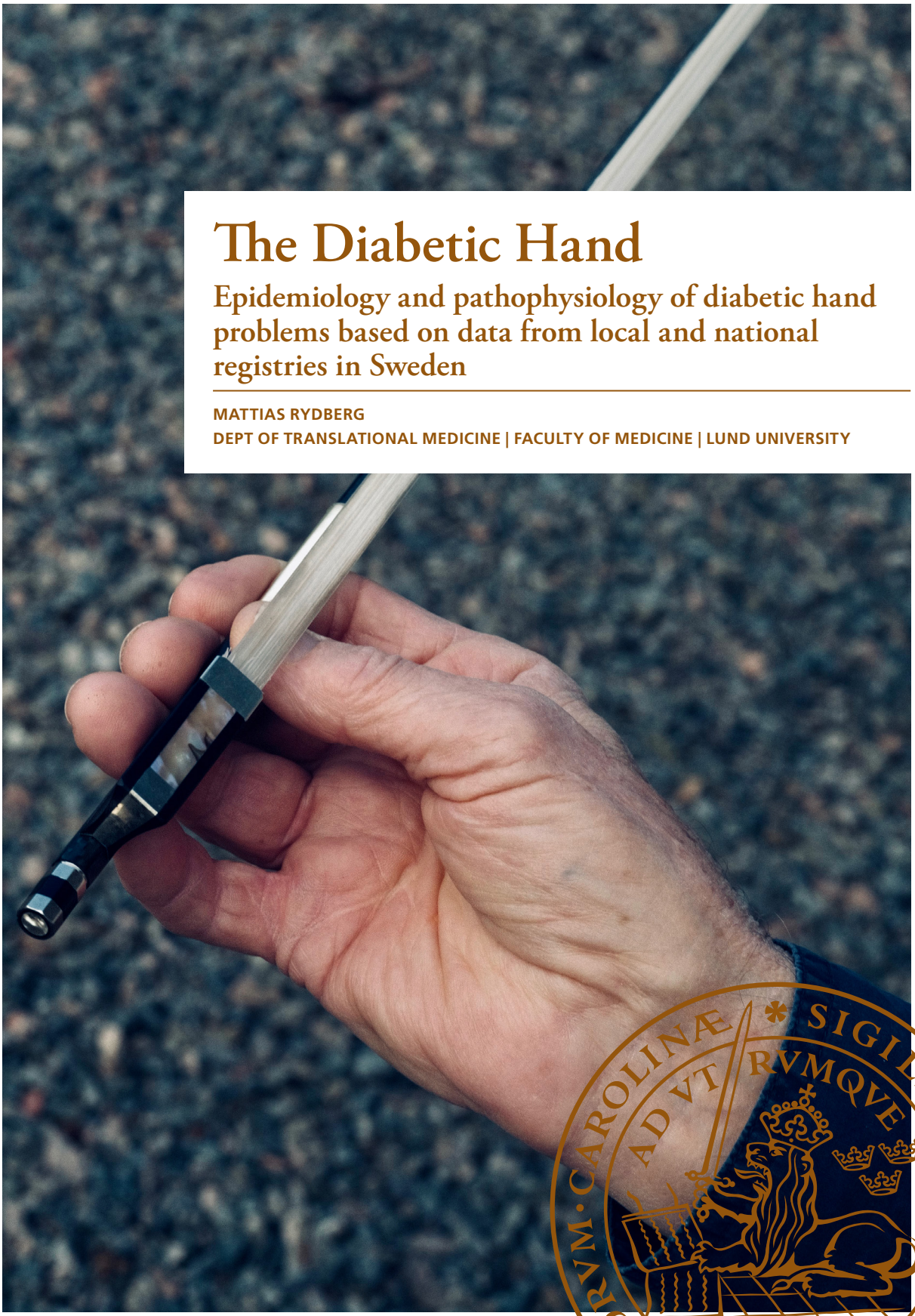
The Diabetic Hand. Epidemiology and pathophysiology of diabetic hand problems based on data from local and national registries in Sweden.

Rydberg, Mattias

2023

Document Version:
Förlagets slutgiltiga version



The Diabetic Hand

Epidemiology and pathophysiology of diabetic hand problems based on data from local and national registries in Sweden

MATTIAS RYDBERG
DEPT OF TRANSLATIONAL MEDICINE | FACULTY OF MEDICINE | LUND UNIVERSITY

The Diabetic Hand

- epidemiology and pathophysiology of diabetic hand problems based on data from local and national registries in Sweden

-

Mattias Rydberg

LUND
UNIVERSITY

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 June 2nd, 2023 at 09.00 in the Aula of CRC, Malmö, Department of Translational Medicine – Hand Surgery, Jan Waldenströms gata 35, S-205 02 Malmö, Sweden

Faculty opponent

Professor Dominic Furniss

University of Oxford, The Botnar Research Centre, Oxford, UK

Department of Plastic and Reconstructive Surgery, Oxford University Hospitals NHS Trust, Oxford, UK

Organization	Document name
LUND UNIVERSITY Department of Translational Medicine - Hand Surgery, Malmö, Sweden	DOCTORAL DISSERTATION
	Date of issue: 2023 – 06 – 02
Mattias Rydberg	-

Title:
The Diabetic Hand - epidemiology and pathophysiology of diabetic hand problems based on data from local and national registries in Sweden

Abstract
A normal hand function is crucial for human beings. The properties of the hand have enabled our species to evolve to our present state. Diabetes Mellitus (DM) is a rapidly growing public health problem with a current prevalence of over 10% in the adult global population. In addition, while the rapid increase in prevalence is alarming in itself, a manifold increase in the global burden of the disease is predicted in the coming years as the increasing prevalence of both type 1 (T1D) and type 2 (T2D) DM entails an increasing number of complications related to the disease.

The overarching aim of this PhD project was to draw attention to and shed light on a somewhat neglected area in diabetes complications, i.e., the diabetic hand. The project aimed to achieve this goal through a three-fold approach. First, the goal was to use big data from Swedish registers and cohorts to analyse the current state of the diabetic hand, including the incidence and prevalence of five common hand surgical diagnoses in the adult population of the Region of Skåne with a population of 1.1 million adult inhabitants. Second, I aimed to explore diabetic risk factors, metabolic factors and anthropometry, and their associations with different hand diagnoses. Finally, I aimed to explore patients' experiences and outcome after surgery for one of the most common diagnoses in the diabetic hand, i.e., trigger finger (TF), focusing on various patient reported outcome measures (PROMs).

The present results provide an insight into how common diabetic hand problems, such as carpal tunnel syndrome (CTS), ulnar nerve entrapment (UNE), Dupuytren's disease with contracture (DD), TF, and osteoarthritis of the first CMC joint of the thumb, are and how these complications affect individuals with DM. Study I presents data on an increased prevalence of all five studied diagnoses among T1D and T2D patients compared to controls, among men as well as women. Studies II and III followed a regional cohort, including over 30,000 individuals, for more than 20 years, and concludes that DM is a strong risk factor for CTS and UNE, as well as for DD. Study IV explored the relationship between high levels of plasma glucose (HbA1c) and TF during a 15-year period, concluding that among the population with DM, elevated HbA1c is a major risk factor for developing TF. Finally, study V explored PROMs after surgery for TF, and showed that patients with T1D and T2D can expect the same results after surgery as individuals without DM, after 12 months.

To summarise, using big data from Swedish national and regional registers and cohorts, this thesis presents unique insights into risk factors, prevalence, incidence and surgical outcome for various hand complications, all related to the Diabetic Hand. Primary prevention of T2D and optimal treatment of both T1D and T2D are crucial in order to prevent complications in the hand related to diabetes.

Key words: Diabetes mellitus, Carpal tunnel syndrome, Ulnar nerve entrapment, Dupuytrens disease, Hand surgery, Osteoarthritis, the Diabetic Hand, Trigger finger

Classification system and/or index terms

Supplementary bibliographical information Lund University, Faculty of Medicine Doctoral Dissertation Series 2023:77		**Language** English
ISSN and key title 1652-8220 -		**ISBN** 978-91-8021-417-9
Recipient's notes	**Number of pages** - 110	-
	-	

Signature Date 2023-04-26

The Diabetic Hand

Mattias Rydberg, M.D.

Faculty of Medicine, Department of Translational Medicine -
Hand Surgery, Lund University, Sweden

Supervisor: Professor Lars B. Dahlin, M.D., Ph.D.
Faculty of Medicine, Department of Translational Medicine -
Hand Surgery, Lund University, Sweden

Cover photo by Andrej Slavik. A.D. Emma Rydberg

The hand of Professor Rydberg with his beloved violin bow

Lund University
Faculty of Medicine
Department of Translational Medicine - Hand Surgery
Doctoral Dissertation Series
ISBN 978-91-8021-417-9
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2023

To my family

Table of Contents

"The hand is the visible part of the brain" - Immanuel Kant

Abstract

A normal hand function is crucial for human beings. The properties of the hand have enabled our species to evolve to our present state. Diabetes Mellitus (DM) is a rapidly growing public health problem with a current prevalence of over 10% in the adult global population. In addition, while the rapid increase in prevalence is alarming in itself, a manifold increase in the global burden of the disease is predicted in the coming years as the increasing prevalence of both type 1 (T1D) and type 2 (T2D) DM entails an increasing number of complications related to the disease.

The overarching aim of this PhD project was to draw attention to and shed light on a somewhat neglected area in diabetes complications, i.e., the diabetic hand. The project aimed to achieve this goal through a three-fold approach. First, the goal was to use big data from Swedish registers and cohorts to analyse the current state of the diabetic hand, including the incidence and prevalence of five common hand surgical diagnoses in the adult population of the Region of Skåne with a population of 1.1 million adult inhabitants. Second, I aimed to explore diabetic risk factors, metabolic factors and anthropometry, and their associations with different hand diagnoses. Finally, I aimed to explore patients' experiences and outcome after surgery for one of the most common diagnoses in the diabetic hand, i.e., trigger finger (TF), focusing on various patient reported outcome measures (PROMs).

The present results provide an insight into how common diabetic hand problems, such as carpal tunnel syndrome (CTS), ulnar nerve entrapment (UNE), Dupuytren's disease with contracture (DD), TF, and osteoarthritis of the first CMC joint of the thumb, are and how these complications affect individuals with DM. Study I presents data on an increased prevalence of all five studied diagnoses among T1D and T2D patients compared to controls, among men as well as women. Studies II and III followed a regional cohort, including over 30,000 individuals, for more than 20 years, and concludes that DM is a strong risk factor for CTS and UNE, as well as for DD. Study IV explored the relationship between high levels of plasma glucose (HbA1c) and TF during a 15-year period, concluding that among the population with DM, elevated HbA1c is a major risk factor for developing TF. Finally, study V explored PROMs after surgery for TF, and showed that patients with T1D and T2D can expect the same results after surgery as individuals without DM, after 12 months.

To summarise, using big data from Swedish national and regional registers and cohorts, this thesis presents unique insights into risk factors, prevalence, incidence and surgical outcome for various hand complications, all related to the Diabetic Hand. Primary prevention of T2D and optimal treatment of both T1D and T2D are crucial in order to prevent complications in the hand related to diabetes.

List of scientific publications

The thesis is based on the following scientific publications which have been reprinted with permission of the publishers. The five studies are all referred to throughout the book by their respective Roman numerals:

I: **Rydberg M,** Zimmerman M, Gottsäter A, Svensson A-M, Eeg-Olofsson K, Dahlin LB. The Diabetic hand: prevalence and incidence of diabetic hand problems using data from 1.1 million inhabitants in southern Sweden. BMJ Open Diabetes Research & Care. 2022;10(1). e002614.

II: **Rydberg M**, Zimmerman M, Gottsäter A, Nilsson PM, Melander O, Dahlin LB. Diabetes mellitus as a risk factor for compression neuropathy: a longitudinal cohort study from southern Sweden. BMJ Open Diabetes Research & Care. 2020. 1;8(1). e001298

III: **Rydberg M**, Zimmerman M, Persson Lofgren J, Gottsäter A, Nilsson PM, Melander O et al. Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years. Scientific Reports. 2021 (1). 14669.

IV: **Rydberg M**, Zimmerman M, Gottsäter A, Eeg-Olofsson K, Dahlin LB. High HbA1c Levels Are Associated With Development of Trigger Finger in Type 1 and Type 2 Diabetes: An Observational Register-Based Study From Sweden. Diabetes Care. 2022. dc220829.

V: **Rydberg M,** Zimmerman M, Gottsäter A, Åkesson A, Eeg-Olofsson K, Arner M, Dahlin LB. Outcome and patient experiences after open trigger finger release in patients with type 1 and type 2 diabetes - a retrospective study using PROMs and Swedish national quality registries. Accepted in Plastic and Reconstructive Surgery GO Open April 2023. In pre-print production.

Other scientific studies, published, but not included in the thesis:

Rydberg M, Dahlin LB, Gottsäter A, Nilsson PM, Melander O, Zimmerman M. High body mass index is associated with increased risk for osteoarthritis of the first carpometacarpal joint during more than 30 years of follow-up. Rheumatic and Musculoskeletal Diseases Open. 2020. 1;6(3). e001368.

Löfgren JP, Zimmerman M, Dahlin LB, Nilsson PM, **Rydberg M**. Diabetes Mellitus as a Risk Factor for Trigger Finger – a Longitudinal Cohort Study Over More Than 20 Years. Frontiers in Clinical Diabetes and Healthcare. 2021. 2;2. 708721.

Bergsten E, **Rydberg M**, Dahlin LB, Zimmerman M. Carpal Tunnel Syndrome and Ulnar Nerve Entrapment at the Elbow Are Not Associated with Plasma Levels of Caspase-3, Caspase-8 or HSP27. Frontiers in Neuroscience. 2022;16. 809537.

Linde F, **Rydberg M**, Zimmerman M. Surgically Treated Carpal Tunnel Syndrome and Ulnar Nerve Entrapment at the Elbow in Different Occupations and their Effect on Surgical Outcome. Journal of Occupational and Environmental Medicine. 2022 ;64(6):e369-e373.

Olsson C, **Rydberg M**, Zimmerman M. Diabetic retinopathy as a predictor for peripheral compression neuropathies, a registry-based study. PLoS ONE, 2022 (10): e0275598.

Abbreviations and definitions

A1-pulley	First annular pulley
AC	Adhesive capsulitis
AGE	Advanced glycation end products
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
CMC	Carpometacarpal
CTS	Carpal tunnel syndrome
DD	Dupuytren's disease
GAD	Glutamate decarboxylase
GWAS	Genome wide association study
HAKIR	National Quality Register for Hand Surgery
HbA1c	Glycosylated Haemoglobin A1c
ICD-10	International classification of disease 10
IR	Incidence ratio
IRr	Incidence rate ratio
MDCS	Malmö Diet and Cancer Study
NDR	National Diabetes Register
NPR	National Patient Register
MR	Mendelian randomisation
OA	Osteoarthritis
OR	Odds ratio
OCTR	Open carpal tunnel release
OTFR	Open trigger finger release
Pr	Prevalence ratio
PROM	Patient reported outcome measure
ROS	Reactive oxygen species
SHR	Skåne Healthcare Register
T1D	Type 1 diabetes

T2D	Type 2 diabetes
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TF	Trigger finger
UNE	Ulnar nerve entrapment

Thesis at a glance

Study I: the Diabetic hand: prevalence and incidence of diabetic hand problems using data from 1.1 million inhabitants in southern Sweden

Aim: To calculate prevalence and incidence of five common diabetic hand diagnoses among the adult population in the Region of Skåne.

Methods: The study included 1.1 million inhabitants in the Region of Skåne aged ≥18 years, of whom 50,000 had DM. Data on incident and prevalent CTS, UNE, TF, DD, and OA of the CMC-1 joint between 2004 and 2019 were collected from the Skåne Healthcare Register and cross-linked with the National Diabetes Register.

Results and conclusions: All five diagnoses studied were more prevalent in both T1D and T2D in both sexes ($p<0.01$). Apart from OA of the CMC-1 joint in men with T1D ($p=0.055$), the 10-year incidence rates for all diagnoses were higher among T1D and T2D patients ($p<0.0001$). In conclusion, individuals with T1D and T2D have a high prevalence of diabetic hand diagnoses. This should be kept in mind when examining patients with hand problems and concomitant DM.

Study II: Diabetes mellitus as a risk factor for compression neuropathy: a longitudinal cohort study from southern Sweden

Aim: To explore potential associations between DM, CTS, and UNE during 20 years of follow-up.

Methods: Between 1991-1996, 30,446 participants aged 46–73 years, were included in the population-based MDCS. Associations between prevalent DM at baseline and incident CTS or UNE were calculated using multivariate Cox proportional hazard models adjusted for known confounders.

Results and conclusions: Prevalent DM at baseline was independently associated with incident CTS (HR 2.10; 95% CI 1.65 to 2.70, $p<0.0001$) and incident UNE (HR 2.20; 95% CI 1.30 to 3.74, $p=0.003$). In conclusion, DM is a major risk factor for the development of both CTS and UNE.

Study III: Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years

Aim: To explore potential risk factors for DD using longitudinal data from the MDCS.

Methods: Baseline anthropometric data from the MDCS were cross-linked with data on incident DD, retrieved from Swedish national registers. Associations between DM, alcohol consumption, BMI, and serum apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) at baseline were analysed in multivariable Cox regression models during 20 years of follow-up.

Results and conclusions: 30,446 participants were recruited; 347 men and 194 women were diagnosed with DD during a median follow-up of 23 years. DM (men HR 2.23; 95% CI 1.50–3.30, women HR 2.69; 95% CI 1.48–4.90) and alcohol consumption (men HR 2.46; 95% CI 1.85–3.27, women HR 3.56; 95% CI 1.95–6.50) were associated with DD in the multivariate Cox regression models. Furthermore. there was an inverse association between DD and obesity among men, and ApoB/ApoA1 ratio among both sexes. In conclusion, DM and excess alcohol consumption constitute major risk factors for the development of DD in middle-aged individuals of both sexes.

Study IV: High HbA1c levels are associated with development of trigger finger in type 1 and type 2 diabetes

Aim: To examine whether an elevated HbA1c was associated with an increased risk of TF among individuals with T1D and T2D.

Methods: Data on incident TF between 2004-2019 in the Region of Skåne was cross-linked with data from the NDR. In total, 9,682 individuals with T1D and 85,755 individuals with T2D aged ≥18 years were included. Multivariate logistic regression models were used to calculate ORs for TF among individuals with elevated HbA1c.

Results and conclusions: Elevated HbA1c was associated with TF among T1D (women OR 1.26; 95% CI 1.1–1.4, p= 0.001, and men OR 1.4; 1.2–1.7, p< 0.001) and T2D (women OR 1.14; 95% CI 1.2–1.2, p< 0.001, and men OR 1.12; 95% CI 1.0–1.2, p= 0.003). In conclusion, elevated HbA1c is a risk factor for TF among both T1D and T2D. Optimal treatment of DM is important for prevention of diabetic hand complications.

Study V - Outcome and patient experiences after open trigger finger release in patients with type 1 and type 2 diabetes - a retrospective study using PROMs and Swedish national quality registries.

Aim: To explore patient outcome and experience after open trigger finger release in individuals with T1D and T2D

Methods: Data included all open trigger finger releases (OTFR) performed between 2010 – 2020 registered in HAKIR, cross-linked with data from NDR. PROMs included QuickDASH and HQ-8, a questionnaire designed for HAKIR, preoperative, and at three and 12 months postoperative. Outcome after surgery was calculated using linear mixed models to and presented as estimated means adjusted for age and stratified by sex.

Results and conclusions: A total of 6,242 OTFR were included; 22% with DM (496 with T1D [332 total, 67% female] and 869 with T2D [451 total, 52% female]). Women with T1D reported more symptoms of stiffness ($p<0.001$) and women with T2D described more pain at rest ($p<0.05$) as well as pain on load ($p<0.05$) and on motion without load ($p<0.01$) at three months. At 12 months, no differences were found in any of the HQ-8 PROMs. In conclusion, patients with T1D and T2D can expect the same good results after OTFR as individuals without DM, although the improvement might take longer, especially among women with T2D.

Preface

One of my first encounters with hand surgery was during the 8th semester of medical school at Lund University. I took a class held by Professor Lars Dahlin in the functional anatomy of the hand, which finished with 40-something case discussions. In a rapid flow, Dahlin assessed the different cases, showing his reasoning concerning the anatomical background of the case, giving us clues to the appropriate diagnosis. I was amazed by the complexity and intricacy of the surgery, the anatomy and the signs and hints that physical examination afforded the physician on his way toward the correct diagnosis.

Given the fact that I have always liked to fix things and repair items that are broken, hand surgery seemed the ideal speciality for me. At the time, however, hand surgery was a subspeciality within orthopaedic surgery and consequently, five wonderful years (2015-2020) followed at the Orthopaedic Department at Helsingborg Hospital, just north of Lund, Sweden.

It was during this period that I was introduced to the magnificent world of registry studies by my good friend and colleague Malin Zimmerman who had just defended her thesis, *The Diabetic Nerve*. That individuals with diabetes are prone to musculoskeletal disorders and are often severely afflicted by their disease, especially in the lower extremity, becomes fairly obvious during an orthopaedic residency.

When Dahlin and Zimmerman advocated that it was time to start my own PhD-studies back in 2018, introducing me to the large-scale registers and advanced statistical modelling required to mine the data sets for information, at the same time as I had also acquired the clinical background and experience needed to assess the concept of "*the diabetic hand",* I gladly accepted.

Looking back on the past five years, I have had some great experiences, learned things that I never thought I would; handled registers with 100,000,000 data points and travelled to faraway places to present my work. To have been given this opportunity is something that I will always be grateful for.

Context of the thesis

This thesis was carried out within the hand surgical group at the Department of Translational Medicine, Faculty of Medicine at Lund University, and at the clinical Department of Hand Surgery at Skåne University Hospital, Malmö, Sweden. The thesis is based on combined and cross-linked data from various Swedish quality and patient registers, together with data from regional cohort studies carried out in the city of Malmö, Sweden.

The hand surgical research group started its register-based research approximately 10 years ago and has been pioneering register-based hand surgical research in Sweden since then. Several original publications together with review papers have been published during these years. Much of this would not have been possible without our collaborators throughout Sweden and, of course, without the patients gladly supplying the registers with invaluable data.

As previously mentioned, a prerequisite for register-based studies and the cross-linking of data sets is not only good collaborations between various universities, but also between the various principals and managers of the registers. The scientific studies included in the thesis are all the results of collaboration between several different Swedish universities; Lund University, University of Gothenburg, Linköping University, and Karolinska Institutet. There are co-authors from different medical specialties (hand and orthopaedic surgery, endocrinology, and internal medicine) together with registry holders, statisticians, and data analysts. A lot of time has been spent on communication, emails, paperwork, and most of all statistical analysis. Ultimately, the goal has been to improve the care for individuals with DM and concurrent hand diagnoses, and at the same time improve knowledge and raise awareness concerning this group of patients.

This thesis presents a basis for understanding the complications which affect individuals with DM. It is intended not only for the interested hand surgeons, but also for hand therapists, physiotherapists, as well as endocrinologists and family physicians alike. Finally, it is intended for the patient who would like a broader understanding of the epidemiological basis of his or her hand complication(s).

Summary in Swedish

Populärvetenskaplig sammanfattning

Tänk dig att du vaknar upp och har sovit på handen. Hela handen sover, den lyder inte och känns fumlig. Varje dag är likadan. Du kan inte skriva – du tappar kaffekoppen – handen känns klumpig – fingrarna lyder dig inte. Och det gör ont, väldigt ont. Plötsligt fastnar ett finger inne i handflatan! Där ska det inte vara. Desperat försöker du räta ut det, men det sitter fast. Inte förrän du använder din andra hand till hjälp lyckas du räta på fingret med en knäpp. Karpaltunnelsyndrom (inklämning av medianusnerven i handledshöjd), inklämning av ulnarisnerven (änkestötsnerven) på armbågsnivå och triggerfinger är fenomen som många människor med diabetes upplever varje dag – utan att ha sovit på den! Dessutom är det vanligt med både Dupuytrens kontraktur (vikingasjukan – när fingret långsamt drar sig in i handflatan) samt ledsvikt i tummens grundled mot handflatan.

Diabetes är en folksjukdom som snabbt ökar i omfattning världen över. Hela 500 miljoner människor beräknas vara drabbade runt om i världen och i Sverige finns över 500 000 diabetespatienter. Nästan 5% av vår befolkning lever med sjukdomen. Medan insjuknandet i typ 1 diabetes, som oftast drabbar unga och leder till att kroppens insulinproduktion helt upphör, endast har ökat något framför allt i västvärlden, har typ 2 diabetes, också kallat ”åldersdiabetes”, ökat både i västvärlden och övriga världen.

I takt med att insjuknandet i diabetes ökar så ökar även antalet komplikationer till diabetes. Till de stora, ofta uppmärksammade diabeteskomplikationerna räknas njurskada, hjärt- och kärlsjukdom, skador på synnerven, nervsjukdom i fötter och underben samt fotsår. Mindre beforskat och betydligt mindre uppmärksammade är de diabeteskomplikationer som drabbar handen och dess funktion. Medan till exempel människor med diabetsfotsår ofta kontrolleras på en specialistmottagning med ortoped, diabetesläkare och ortopedtekniker, har personer med diabetes svårare att få vård för sin sjuka hand.

Genom denna avhandling, uppdelad i fem olika delprojekt, var syftet att belysa de problem och diagnoser som människor med diabetes upplever i sin hand.

I **studie I** undersökte vi förekomsten av fem vanliga handdiagnoser i Region Skåne. Vi använde registret Region Skånes vårddatabas som samkördes med det Nationella diabetesregistret för att på så sätt få fram data på hur vanliga dessa diagnoser är

bland människor med diabetes. Det visade sig att alla de fem undersökta diagnoserna som ovan nämnts var vanligare hos människor med både typ 1 och typ 2 diabetes.

I **studie II och III** undersökte vi dels förekomsten av nervinklämningssyndrom i handled och armbåge (II), dels förekomsten av Dupuytrens sjukdom (III) i en grupp invånare (kohort) i Malmö som följts sedan mitten av 90-talet. Under de 20 år som ca 30 000 deltagare i studien följdes kunde vi se att de individer som hade diabetes vid starten av studien hade dubbelt så hög risk att insjukna i både nervinklämningssyndrom och Dupuytrens sjukdom. Vi visade också att hög alkoholkonsumtion ökar risken för att drabbas av Dupuytrens sjukdom.

I **studie IV** ville vi ta reda på om högt blodsocker bland personer med diabetes ökar risken för triggerfinger, ett tillstånd där fingrarna fastnar i ett böjt läge. I denna studie samkörde vi data från Region Skånes vårddatabas med det Nationella diabetesregistret och kunde visa att högt långtidsblodsocker markant ökar risken för att drabbas av triggerfinger. Män med högst mått på långtidsblodsocker (HbA1c> 64 mmol/mol) hade över fem gånger så hög risk att insjukna jämfört med män med ett välreglerat blodsocker (HbA1c < 48 mmol/mol).

I **studie V** samkörde vi data från det handkirurgiska kvalitetsregistret (HAKIR) med Nationella diabetesregistret för att ta reda på hur personer med diabetes upplever sitt resultat efter operation för triggerfinger och om de förbättras i samma utsträckning som människor utan diabetes. Resultaten visade att för dem som opererades och samtidigt hade diabetes tog det längre tid att förbättras – men efter 12 månader var det ingen skillnad i resultaten. Personer med diabetes behöver alltså lite längre tid för att återhämta sig efter operation, men kan annars förvänta sig samma goda resultat som personer utan diabetes.

Sammanfattningsvis har denna avhandling belyst en tidigare relativt ouppmärksammad del av diabeteskomplikationerna - *den diabetiska handen.* Avhandlingen visar att diabetes påverkar inte bara nerverna i handled och armbåge, utan också bindväven i handen samt att många diagnoser är betydligt vanligare hos personer med såväl typ 1 som typ 2 diabetes. Den drivande faktorn verkar vara högt blodsocker där restprodukter från blodsockermolekylerna lagras in i senor, nerver och bindväv, vilket får dessa att fungera sämre och lättare fastna och ge symptom i form utav smärta, domningar och stickningar.

Att som person med diabetes drabbas av komplikationer i handen ger en signal om att man kanske bör tänka extra mycket på sin medicinering för att undvika höga blodsockernivåer. Med tanke på den diabetesepidemi som pågår i världen är det viktigt att förmedla budskapet om att även handens sjukdomar är kopplade till diabetes. Jag har också en förhoppning att vården kan anpassa sig efter behovet av en diabeteshandmottagning för att dessa patienter skall få en så bra och jämlik vård som möjligt.

Introduction

Epidemiology

The term epidemiology comes from the Greek words *Epi, Demos* and *Logos,* meaning upon, people, and study of, respectively. That is exactly what this thesis aims to accomplish, the study of people, in this case, individuals with diabetes mellius.

The Swedish National Diabetes Register (NDR), later described in detail in the method section, provides an extensive insight into the progress of the disease with its complications and pathophysiology. The NDR also provides Swedish researchers with the opportunity to study other disease associations and analyse the risk of various diseases developing among the population with DM.

Type 1 (T1D) and type 2 (T2D) diabetes are two different diseases regarding incidence, prevalence, pathophysiology, treatment, and complications, but also when it comes to survival and life expectancy. This introductory chapter will provide a very brief overview of the history, epidemiology, and pathophysiology of T1D and T2D with references to relevant studies.

Diabetes Mellitus

History

The etymology of the word diabetes is found in the ancient Greek word for "diabetes", which means to siphon or "to pass through", a reference to the large amount of urine produced when the pancreas stops producing insulin and the blood sugar spikes as a sign of T1D. The word mellitus comes from Latin and means sweet – a reference to the sweet urine produced.[1] The combination term "Diabetes Mellitus" was first popularised in the late 18th century but the disease was recorded by ancient Egyptians as far back as 1500 BC, describing polyuria, thirst and weight loss, seen today as signs of T1D.[2 3] However, it would take over 3,000 years before the prognosis for these patients improved, with the discovery and purification of insulin, a discovery for which F. Banting (*nota bene* an orthopaedic surgeon) and J.R.R. Macleod were awarded the Nobel Prize in 1923.[2]

Not long after the discovery of insulin, it was recognised that not all patients responded to it with the marked improvement seen in patients with what we now call T1D. The division into T1D (initially called insulin-dependent) seen in young patients and T2D (non-insulin dependent) seen in older, often overweight patients soon followed, with descriptions of different phenotypes and complications related to the respective diseases.[3] Today, additional categories of DM are recognised, apart from T1D and T2D, such as gestational DM.[1] Steps have also been taken to further improve patient outcome by classifying additional subgroups of DM depending on e.g., level of insulin resistance and insulin production, detection of antibodies, and anthropometrics at diagnosis, in order to individualise and improve the available treatment. Such developments constitute steps towards precision medicine in diabetes treatment. [4 5]

Epidemiology

Approximately 540 million individuals worldwide in the age range between 20 and 79 are estimated to have DM; an astounding 10.5% of the world's adult population. To make matters worse, the prevalence is rapidly growing, a trend seen both in T1D[6] and T2D,[7] and by 2045, it is estimated that the disease will affect about 780 million individuals.[8]

Diagnostic criteria

According to the latest WHO guidelines[9] and diagnostic criteria from the American Diabetes Association,[10] the diagnosis of diabetes is based on values of plasma glucose *or* HbA1c. The cut-off values are:

- Fasting venous plasma glucose ≥7.0 mmol/L
- Two-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT)
- HbA1c ≥ 48 mmol/mol
- Random plasma glucose value ≥11.1 mmol/L together with typical symptoms of DM

The test should be repeated if not accompanied by typical symptoms of hyperglycaemia, i.e. polyuria, or polydipsia as a sign of ketoacidosis.[10] Classification into T1D and T2D is often straightforward although difficulties can occur, especially when the phenotypes of the two diseases overlap.[11] As there is still no definitive test to differentiate between T1D and T2D at the time of diagnosis, the clinician has to rely on a combination of biomarkers, auto-antibodies, C-peptide, age, BMI, and other clinical characteristics, in order to make the classification.[12]

Pathophysiology

As previously stated, T1D and T2D are heterogenous diseases with two very different pathophysiological pathways.

The onset of T1D usually occurs in childhood or adolescence, and features autoantibodies against the insulin producing β-cells in the islets of Langerhans in the endocrine pancreas. This leads to insulin deficiency and, until 100 years ago, always led to death.[2 10] Several different autoantibodies have been found; GAD (glutamate decarboxylase), insulin-antibodies, and islet antigen-2.[12] Interestingly, some of these autoantibodies can be detected long before T1D is clinically diagnosed. Recent discoveries have enabled identification of the disease before insulin treatment is needed, i.e. before the destruction of the β-cells.[13] This has led to trials of effective screening programs,[10] but also trials of new immune therapies, targeting the different antibodies, in order to delay the onset of T1D or even to prevent the disease altogether.[14] Although rarely, T1D is sometimes diagnosed later in life and occasionally presents without autoantibodies; it is then referred to as idiopathic T1D or autoantibody-negative type 1 diabetes.[10]

T2D on the other hand, often starts gradually later in life and presents together with overweight or obesity and often in conjunction with a sedentary lifestyle. The marked biochemical features include both insulin resistance in the liver and peripheral tissue, and progressive loss of insulin production over time.[10] T2D also often presents together with hypertension, dyslipidaemia, i.e. features of the metabolic syndrome.[15]

The cause of T2D is thought to be multifactorial with a combination of inherited genetic traits together with adverse environmental exposures, such as a poor diet, pollution exposure, stress, and low physical activity, but it is also related to access to education, healthcare, and socioeconomic status.[10 16-18] With adequate control of these environmental risk factors, insulin resistance can be improved after initial diagnosis and the term *remission* has recently been introduced, referring to a prior T2D patient who has been able to maintain normal glucose levels (HbA1c < 48 mmol/mol) over three months without glucose-lowering medications.[17]

Complications

Complications from DM range from life-threatening gangrene in the lower extremity to heart failure, coronary heart disease, stroke, sensory loss in the feet, polyneuropathy, nephropathy, dementia, and pregnancy complications. Traditionally, complications are often divided into *microvascular* (i.e. neuropathy, nephropathy, and retinopathy) and *macrovascular* (i.e. atherosclerosis, stroke, cardiovascular disease) complications.[12 19] While mortality from these vascular complications is indeed in decline, as effective treatment has emerged during recent decades, diabetic complications and mortality caused by dementia, cancer, and

infections are instead on the rise.[20] In addition, and particularly in T1D, complications due to hyperglycaemia and diabetic ketoacidosis due to the lack of insulin production or insufficient treatment, resulting clinically in polyuria and polydipsia followed by confusion and coma, are life-threatening complications. Ketoacidosis is estimated to account for approximately 15% of all mortality related to T1D.[12 21]

In another complication spectrum, there is also an increased risk of osteoporosis and fractures in both T1D and T2D, although the causal link behind this association remains unclear. Both microvascular changes altering bone metabolism as well as increased risk of falls due to cerebral complications are thought to contribute.[22] Finally, musculoskeletal complications are also frequent in both T1D and T2D, but have been given much less attention compared to traditional vascular complications, despite having a severe impact on the quality of life of patients with diabetes.[23-25] This is particularly true of diabetic complications manifesting in the hand. Despite being described and discussed as early as in the 1970s,[26] they have not received as much attention as the complications described above.[27] Hence, the rationale presented below.

Rationale

When this thesis was initiated back in 2018, few large-scale epidemiological studies on the diabetic hand had been done in Sweden. Most previous international studies were carried out in small, specialized clinics, often with surgical outcome as the main endpoint. Furthermore, most previous studies were unable to appropriately stratify for T1D and T2D, conditions that, as previously described, have different pathophysiology and, as we hypothesized, might lead to different musculoskeletal and hand surgical complications.

Our research group had previously published data on outcome after surgery for CTS[28 29] among the population with DM in Sweden, but the large-scale epidemiological data from registers in Sweden were still missing. Given the unique opportunity that the Swedish 10-digit personal identity number offers for cross-linking of different registers, the next logical step was to assess the diabetic hand from an epidemiological perspective. Understanding both the epidemiology and pathophysiology behind the increased prevalence of hand problems among the population with DM is the first step towards evidence-based and improved treatment and care for these patients. Furthermore, this thesis could serve as a basis for improved preventive work and research, regarding both hand complications and DM as a whole. Finally, this thesis could hopefully contribute to motivating patients with DM to strive to meet their own individual long-term glycaemic targets, contributing to the prevention of complications and maintaining their quality of life.

Chapter 1 – Background

1.1 The diabetic hand

This chapter will give a brief background to the diabetic hand complications described and studied throughout this thesis, and the history, epidemiology, anatomy, pathophysiology, treatment, and outcome of the respective disease. The basic science, pathophysiology, and impact of DM on each diagnosis will, for clarity, be discussed in Chapter 5 – Discussion, while interpreting the results from the studies included in this thesis.

1.2 Nerve compression disorders

Carpal tunnel syndrome

CTS was first described by Sir James Paget in 1854, when identifying two cases of compression of the median nerve at wrist level.[30] CTS is the most common compression neuropathy in the upper extremity.[31] The first surgery for non-traumatic CTS was carried out 1946 but the term CTS did not actually come into general use until 1953.[30]

CTS is caused by a compression of the median nerve within the carpal tunnel at wrist level. The nerve passes through the tunnel together with nine flexor tendons, limiting the space for swelling and making the nerve susceptible to compression. While the carpal bones constitute the floor of the tunnel, the ceiling consists of a thick fibrous tissue layer called the transverse carpal ligament.[31]

A tingling sensation or numbness in the fingers (most often thumb, index, middle, and radial side of ring finger), clumsiness, and nocturnal pain are the classic symptoms of CTS, often indicating that the median nerve is compressed within the carpal tunnel. If the compression is long-standing, atrophy of the median nerve innervated thenar muscles (abductor pollicis brevis, opponens pollicis, and flexor pollicis brevis) can occur.[31 32]

The diagnosis is mainly clinical, based on specific tests for CTS together with information from the patient history. The use of electrophysiology to confirm the

diagnosis varies internationally, and surgeons have different opinions about when to use it.[32-34]

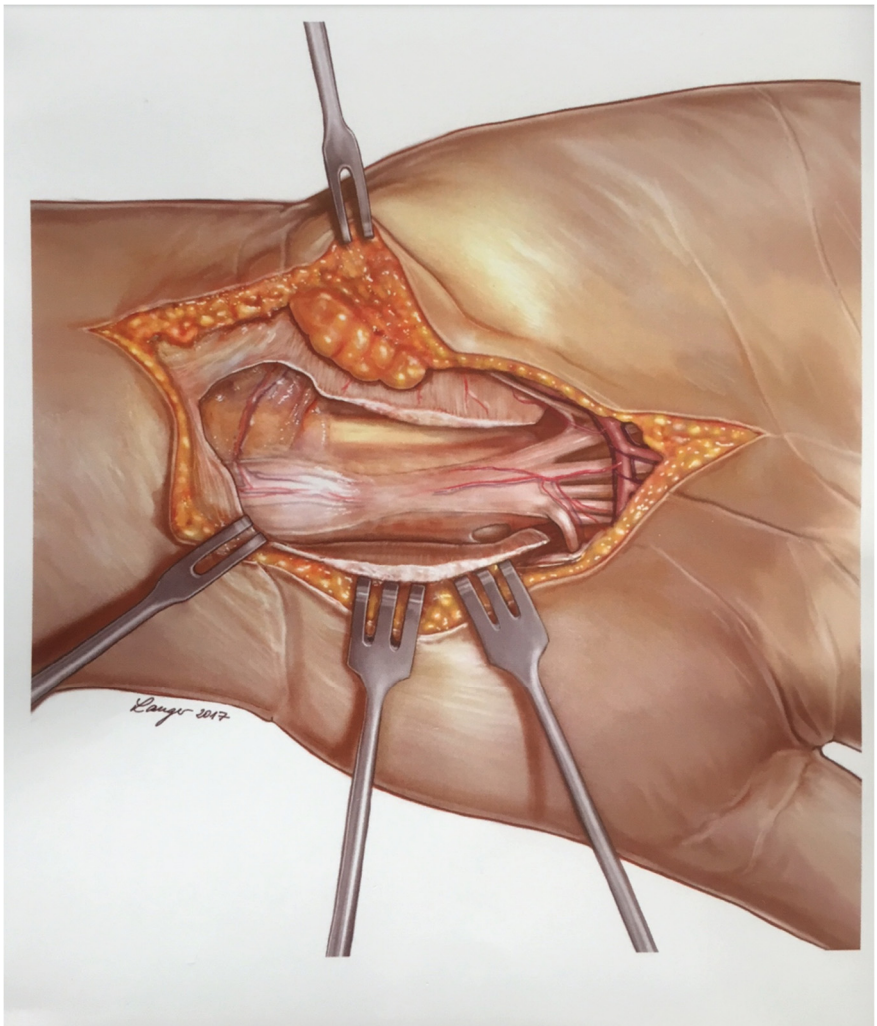


Figure 1.
Illustration by Martin Langer of open surgery for carpal tunnel syndrome. With permission.

There are several environmental and metabolic risk factors for CTS described in numerous publications, where the most robust evidence is for female sex,[35] DM,[33 36] increasing age,[37], high BMI,[31 38-40] distal radius fractures,[41] hypothyrodism,[31] and pregnancy.[42] Regarding occupational exposure, there are conflicting results in the literature and the exact causal link between certain types of work and CTS is yet to be determined.[43 44] A recent meta-analysis concerning occupational risk factors

found both high force and repetitious work, but not vibration exposure, to be associated with CTS.[45] Regarding smoking, a recent meta-analysis did not find sufficient evidence to support a causal relationship with CTS, similar to the findings in study II included in this thesis.[46]

There are several different treatments available for CTS, depending on the patient's symptoms, age, expectations, and preferences, and in some countries, access to healthcare or insurance.[47] If the symptoms are mild and mainly nocturnal, a nightly splint or a cortisone injection might be preferred. With worsening symptoms, OCTR is the gold standard of treatment. During OCTR, after injection of local anaesthesia, the carpal ligament is divided sharply and left to heal with prolongment **(Figure 1)**. This releases the median nerve from the compression. The procedure is often sufficient to stop the symptoms and has been described in the literature as having a mainly excellent outcome.[31]

Ulnar nerve entrapment at the elbow

UNE at the elbow (**Figure 2)** is the second most common nerve entrapment in the upper extremity. With a markedly lower prevalence and incidence compared to CTS, the patients are often younger,[48] and frequently report psychiatric comorbidities[49] and socioeconomic deprivation.[50 51] The ulnar nerve can be compressed in the cubital tunnel in the elbow, where it passes just dorsally to the medial epicondyle.[48 52] The nerve can also be compressed at wrist level where it passes in Guyon´s canal, although this condition is more rare compared to compression at elbow level.[53]

Symptoms include a tingling sensation and numbness in the ulnar side of the ring finger and little finger, and if the compression is proximal to the dorsal sensory branch, sensation is also affected in the dorsoulnar side of the hand. If long-standing and if the motor neurons in the nerve are affected, weakness and sometimes atrophy of the *flexor digitorum profundus* muscle to the little finger, hypothenar, and the ulnar nerve innervated intrinsic muscles of the hand can be seen.[54]

Risk factors for UNE are less thoroughly studied than those for CTS, possibly due to the much lower incidence of UNE, which limits the number of cases available for study.[48] Nevertheless, similar to CTS, DM has been proposed as a risk factor for UNE,[55 56] with the risk also being higher in men,[57] smokers,[58] and subjects exposed to vibration and a heavy workload.[59 60] However, it should be kept in mind that there are few pooled meta-analyses examining risk factors for UNE. Therefore, additional studies, particularly with regard to occupation, are warranted in order to further elucidate the pathologic basis of the disease.[61]

Treatment of UNE is often primarily conservative with a combination of night splinting, physical therapy, and elimination of external compression forces.[62] If remission is not obtained with conservative management, surgery might be

indicated for this subgroup of patients.[63] However, the numbers of randomised controlled trials comparing conservative versus operative treatments are scarce, and a systematic review in the Cochrane database from 2016 stated:

> "We do not know when to treat a person with this condition conservatively or surgically"[54]

Nevertheless, if no improvement is seen with conservative management, and when electrophysiological findings so indicate e.g. axonal loss, conduction block or slowed conduction velocity, several alternatives exists for surgical techniques.[64] The simplest technique involves in situ surgical release of the ulnar nerve in the cubital tunnel ("simple decompression"), dividing the compressing structures, particularly Osborne´s ligament, thus releasing the pressure on the nerve.[63] In recurrent cases, anterior transposition of the nerve might be performed. After careful dissection, the nerve is moved anteriorly of the medial epicondyle and positioned either subcutaneously, intramuscularly, or submuscularly. The best surgical technique is yet to be established, and practice varies from centre to centre.[63 64 65]

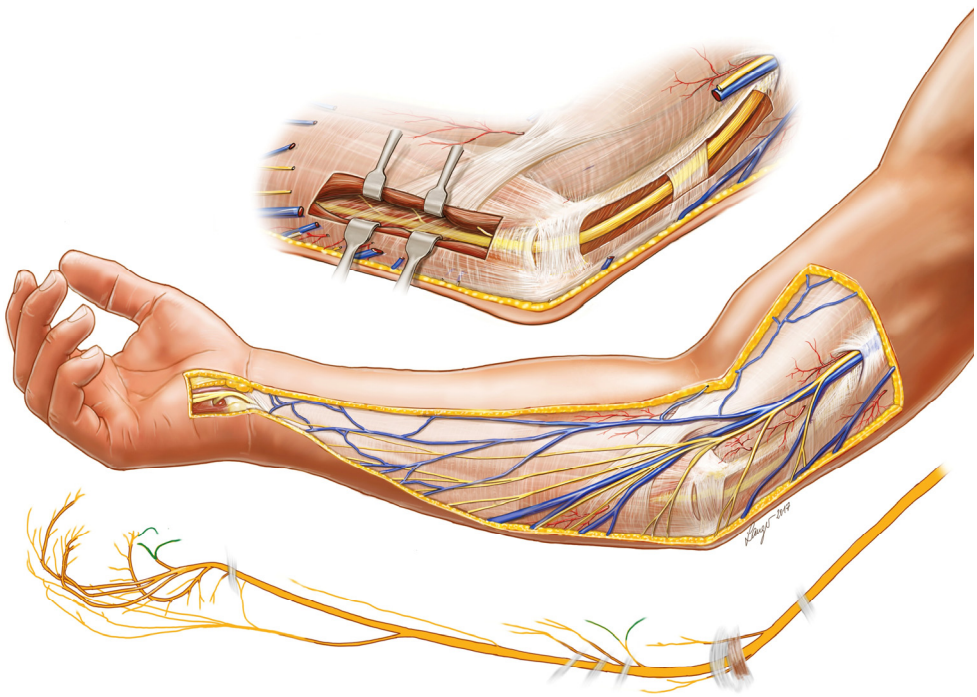


Figure 2.
Illustration by Martin Langer of the ulnar nerve and its pathway through the cubital tunnel at elbow level and Guyon's canal at wrist level. With permission.

In terms of outcome and patient experience after surgery, most RCTs included in the Cochrane analysis from 2016 reported improvement after surgery, although the evidence was insufficient to support any specific surgical technique. A recent Swedish study of 202 cases of UNE from a tertiary hand surgical centre concluded that in situ decompression is "a reliable first choice for surgery because of the relatively low level of complications and acceptable surgical outcome".[66] Another recent study from the UK also reported a relatively high level of patient satisfaction (86%) in patients with UNE who underwent in situ decompression.[67]

Anatomy and pathophysiology of compression neuropathies

Compression of a peripheral nerve in the upper extremity, either in the carpal tunnel in the wrist or in the cubital tunnel at elbow level, induces specific pathobiological changes within the nerve. The injury and nerve pathology are dependent on both the amount and duration of the local compression, together with environmental factors, such as heavy work-load, and metabolic factors such as DM, which act together with the individual's inherited genetic traits, as described below.[33 68 69]

In short, the peripheral nerve includes motor nerve fibres, with the cell body situated in the ventral horn of the spinal cord forming the anterior root, and sensory nerve fibres where the cell body is situated in the dorsal root ganglia forming the posterior root. Together with a small number of autonomic nerve fibres, the anterior and posterior roots form the spinal nerve. The cell bodies project axons that present both with and without myelin sheet, conveying signals from the CNS to the receptor organ, e.g. muscle, or conveying sensory signals from e.g. the skin or proprioceptive signals from a joint, to the CNS.[70 71]

Surrounding the myelinated nerve fibres are Schwann cells, a glial cell responsible for producing myelin. Myelin works not only as a conduit for the axon, enabling an increase in the speed (60 m/s) of the electrical impulses along the axon, compared to the non-myelinated fibres (2 m/s), but the Schwann cell also interacts and communicates closely with the axon. The individual axons are organised into fascicles, containing fibroblast, collagen, macrophages, and other cells, and the perineurium designates a layer consisting of flattened closely connecting cells. The perineurium also forms a diffusion barrier together with the intrinsic blood supply – vasa nervorum; the latter forming the blood-nerve barrier. Bundled together, the fascicles form the individual nerve which is covered and surrounded by the epineurium and finally the mesoneurium, a loose connective tissue enabling nerve gliding and also providing extrinsic blood supply to the nerve **(Figure 3)**.[72-74]

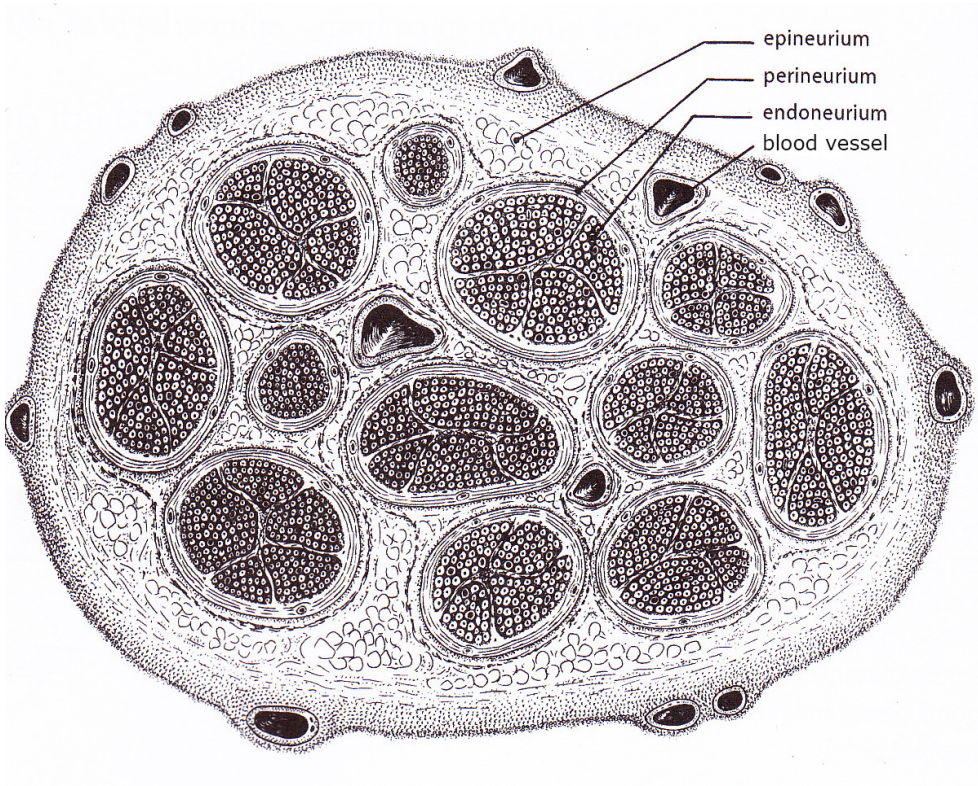


Figure 3
Anatomy of the peripheral nerve. Adapted from Handkirurgi.[75] With permission.

Several factors contribute to the pathophysiology of the peripheral nerve when compressed in CTS or UNE. In short, compression of the nerve can lead to diminished blood flow to the axon, initially interrupting the venous blood flow inducing venous stasis, formation of oedema, and ultimately leading to local ischemia. Furthermore, compression can cause fibrosis within the connective tissue surrounding the nerve, which also causes nerve swelling.[69 72 76] Indeed, ultrasound studies have shown an increased cross-sectional area of the ulnar and median nerve in both UNE and CTS respectively.[77 78]

On a cellular level, prolonged compression of the peripheral nerve eventually leads to compromise of the blood-nerve barrier with the described formation of oedema and local breakdown of the myelin sheets, so called demyelination. This triggers an attempt by the Schwan cells to remyelinate the axons, leading to a thinner myelin sheet and shorter internodal distances, as indicated by loss of conduction velocity on electrophysiology testing. If it is long-standing, the nerve compression will eventually lead to axonal damage and degeneration, as indicated by low amplitude in electrophysiology testing. The symptomatology of the patient is thought to follow

the extent of nerve injury with demyelination followed by a weak remyelination, leading to numbness and a tingling sensation in e.g., the fingers. A more severe compression with axonal loss and degeneration is often accompanied by muscle weakness and atrophies.[69 72]

Genetic traits

In recent years, both increasing interest and technological advances have made it possible to further explore the genetic background of compression neuropathies. Most studies have been done on CTS, possibly due to its increased prevalence compared to UNE. In 2002, a twin study analysed the risk of CTS among 4,488 females; 867 monozygotic (twins with the same genome) and 970 dizygotic twins (twins with different genomes). After adjusting for environmental factors, the estimated heritability for CTS was almost 50%.[79] Moreover, family studies have shown a markedly higher prevalence rate among relatives of patients with CTS,[80] and recent GWAS studies have identified several genetic loci associated with CTS.[81 82] Finally, variants of genes coding for e.g. collagen composition found in the connecting tissue in tendons within the carpal tunnel have been identified and shown to be overrepresented in patients with CTS.[68 83] Taking all this together, genetic traits are important for the development of compression neuropathies and studies have confirmed a strong hereditary factor. Calculation of an individual's own genetic risk score for CTS could be a tool for introducing early preventative measures in high-risk individuals, if it becomes more readily available in the future.

1.3 Soft-tissue disorders

Dupuytren´s disease

Dupuytren´s disease is a soft-tissue disorder that affects the palmar fascia of the hand. It was first described in 1614 by Felix Platter, a Swiss physician, who incorrectly attributed it to the flexor tendons.[84] Guillaume Dupuytren (1777–1835), whose name came to be associated with the disease, correctly described the anatomy and pioneered the surgical procedure of fasciectomy, a treatment still used today.[85] The prevalence varies widely depending on the region and population studied. It is most often diagnosed at the age of 70-80 years and is more common among men with a male-to-female ratio of 6:1, according to a recent review.[86 87 88]

The cause of DD is multifactorial with environmental and metabolic risk factors, including DM, smoking, alcohol consumption, hypertension, and manual work.[89-92] There is also a strong genetic trait with twin studies suggesting an 80% heritability on a population level.[93] In the last decade, research in the field of genetics has

identified several genetic loci associated with DD, further elucidating the pathogenesis and intricate interplay between genetic and environmental factors behind its development.[94 95]

The disease often starts with the formation of a small nodulus in the palm of the hand, seldom prompting the patient to seek healthcare. Slowly, often over several years or even decades, the characteristic chord formation starts in the hand and gradually contracts the affected finger, most often the ring finger. Everyday tasks, e.g., wearing a glove or shaking hands become increasingly difficult, at which stage the patient often seeks healthcare.[96]

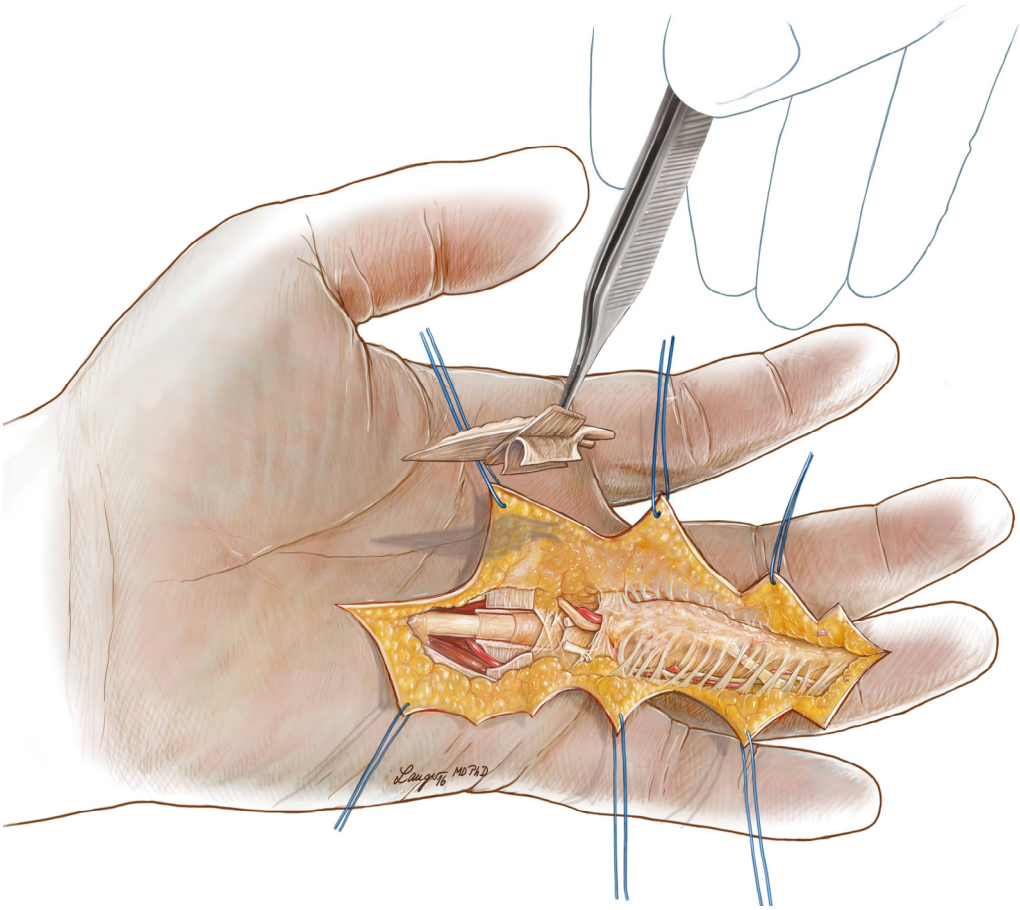


Figure 4:
Illustration by Martin Langer of open surgery for Dupuytren's disease and the removal of a palmar chord. With permission.

There are several different treatment options for DD, all dependent on the stage the disease has reached (i.e., the level of contraction and the joints in the affected finger), patient preference, previous treatments, and access to healthcare. In the initial phase, treatment frequently starts with simple stretching exercises and physiotherapy. After chord formation and after the finger has started to contract, needle fasciotomy is often the first line of treatment. If recurrent, or if the chord involves the proximal interphalangeal joint, the surgeon might propose open surgery and limited fasciectomy, due to the proximity of the neurovascular bundle to the chord in the basal phalanx **(Figure 4)**. Finally, if the patient has an aggressive form of DD, i.e., Dupuytren's Diathesis, dermofasciectomy and skin grafting can be performed.[96-98]

There are also injection treatments for DD, predominantly with collagenase, which have become more popular over the last decade. However, for several years, collagenase has principally only been available in the USA, and it can be a costly treatment. Needle fasciotomy shows equally good results, a low reintervention rate and is probably more cost-effective.[97 99] Finally, an interesting phase 2b study, injecting the anti-TNF monoclonal antibody adalimumab, has shown promising results regarding softening and size reduction of early-stage DD noduli.[100]

Trigger Finger

Trigger finger is a disease of the hand causing the affected finger to lock in flexion. It is sometimes referred to as stenosing flexor tenosynovitis. The affected finger, most often the ring finger or thumb, often has to be manually extended with the contralateral hand, resulting in a snapping or triggering sensation which can sometimes be felt in the palm of the hand.[101]

TF was first described by the French physician Alphonse Henri Notta in 1850, hypothesising that the aetiology of the triggering came from either a swollen tendon sheet or swelling of the tendon itself. Although surprisingly modern in his hypothesis, Notta offered no effective treatment to his patients. In fact, it would be almost another century before modern treatment with A1-pulley release or cortisone injections was popularised.[102]

TF is one of the more common diagnoses in hand surgery clinics, with a lifetime prevalence of 2-3% in the general population. It is reported to be up to ten times more common among individuals with DM, more common among women, and most often diagnosed at the age of 50-60 years. [32 48 103] **Figure 5** demonstrates the incidence rates for women in the Region of Skåne from 2010 – 2019, for individuals without diabetes, with T1D, and with T2D, respectively (data from Study I).

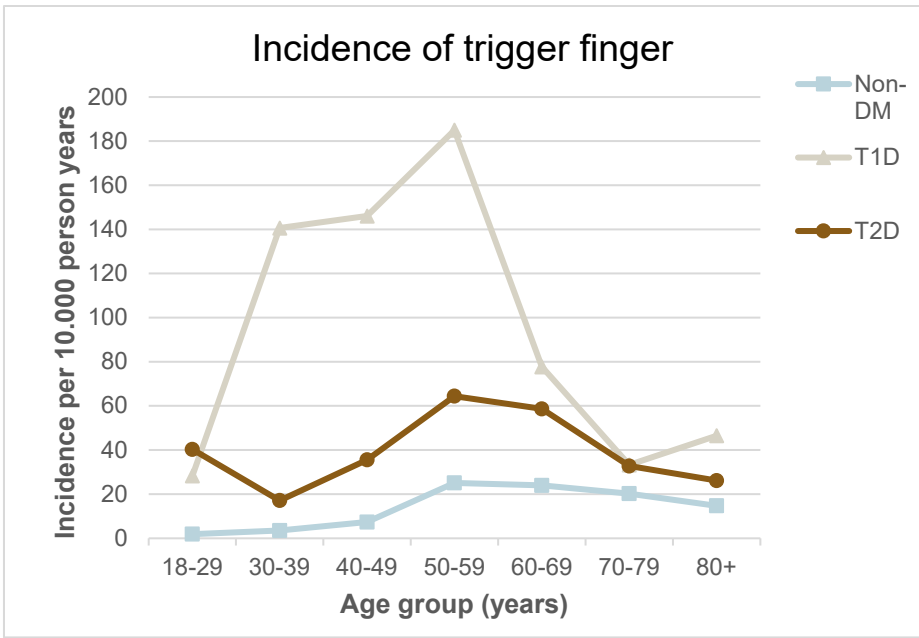


Figure 5:
Age-stratified incidence rates for trigger finger in women between 2010 and 2019 in the Region of Skåne. DM; diabetes mellitus, T1D; type 1 diabetes, T2D, type 2 diabetes.[48]

The exact cause of TF is still being debated, although most researchers agree that an imbalance in the size of the flexor tendon and the flexor tendon sheet, usually at the level of the A1 pulley, is the causative factor of the triggering phenomena. This imbalance may originate from a thickening of the A1 pulley, inflammation of the tenosynovium, or thickening of the flexor tendon (noduli) of the affected digit, or a combination of these factors, causing the digit to stay in a bent position, unable to extend without additional force.[104-107] Risk factors for TF include DM, female sex, and rheumatoid arthritis.[108 109] Recent publications in the field of genetic research using GWAS have identified several genetic loci associated with TF, and further elucidated its pathology, indicating an hereditary component.[110]

There are several different treatment modalities available for TF; the first line including hand therapy with different orthoses, is often initiated in primary care. If this approach is not satisfactory, cortisone injections over the A1 pulley are usually tried and a success rate of 50-60% has been reported.[111] If the condition is recurrent or if the cortisone injections are unsuccessful, open surgery and OTFR is often the next line of treatment. During OTFR, the surgeon makes a small incision in the skin of the palm under local anaesthesia, debriding down to the level of the tendon sheet and the A1 pulley. The pulley is divided longitudinally, creating more space for

normal tendon gliding. This is often enough to resolve the triggering in the affected finger.[112 113]

Outcome after OTFR has mainly been reported as favourable with improvement in hand function.[114] A recent Cochrane analysis from 2018 stated that 92% of patients had resolution of symptoms after OCTR, compared with 61% after steroid injection. The authors conclude that the number of high-quality studies is limited, however, especially with regard to functional outcome after cortisone injections vs OTFR, highlighting the need for high-quality randomized control studies.[115] A recent multi-centre study, including 1879 OTFR cases, reported improved hand function among the majority of patients, and a relatively low risk of serious complications with a 2% re-operation rate over 3 months.[116] The most effective treatment for patients with TF and DM is still being debated, although recent publications favour cortisone injections as the first line of treatment, even among individuals with DM, before discussing OTFR.[117]

In terms of our clinical practice, the patient is often offered a steroid injection at the hand surgical clinic if they have not had prior injections in primary care, before discussing OTFR.

1.4 Osteoarthritis of the CMC-1 joint

Osteoarthritis of the hand is a common, heterogeneous disease in which aetiology, epidemiology, radiology, and disease course differ depending on the affected joint (*nota bene*, there are in total 27 joints in the hand). General hand OA is more common among women and the prevalence increases with age, although both prevalence and incidence vary substantially depending on the population studied and definitions used for OA (e.g., only radiographic and/or clinical symptoms). [118-120]

The base of the thumb, i.e., the CMC-1 joint, is one of the more common joints to be affected by OA in the hand and for clarity, OA of the CMC-1 is the joint that henceforth will be discussed in this section. The prevalence of radiographic signs of OA of the CMC-1 joint also increases with age, affecting over 90% of individuals aged over 80 years. However, there is a low correlation between clinical symptoms and radiographic signs of OA and this condition can probably be considered part the normal ageing process. [121 122 123] Nevertheless, when symptomatic, OA of the CMC-1 joint can be detrimental to hand function, especially to the thumb grip, and can significantly reduce both quality of life and ability to work.[124 125]

There are several proposed risk factors for OA of the CMC-1 joint including various occupations, obesity, genetic factors, age, and female sex. DM has also been suggested as a risk factor for hand OA, although the causative link remains unclear.

Previous studies have shown conflicting results regarding this association. It has been proposed that individuals with DM experience more hand pain than non-DM controls; thus, potentially increasing symptoms of OA.[120 126 127]

The cardinal symptom is pain in the base of the thumb and subsequent loss of function and thumb grip. Diagnosis is based on a typical patient history together with radiographic signs of OA in the CMC-1 joint which can be combined with specific tests, such as the grinding test, i.e., application of axial and rotational force on the thumb base causing crepitations and pain. As the disease progresses, the joint progressively becomes subluxated and the thumb is often positioned in adduction (adduction contracture), limiting the functional grip (**Figure 6)**.[32 128]

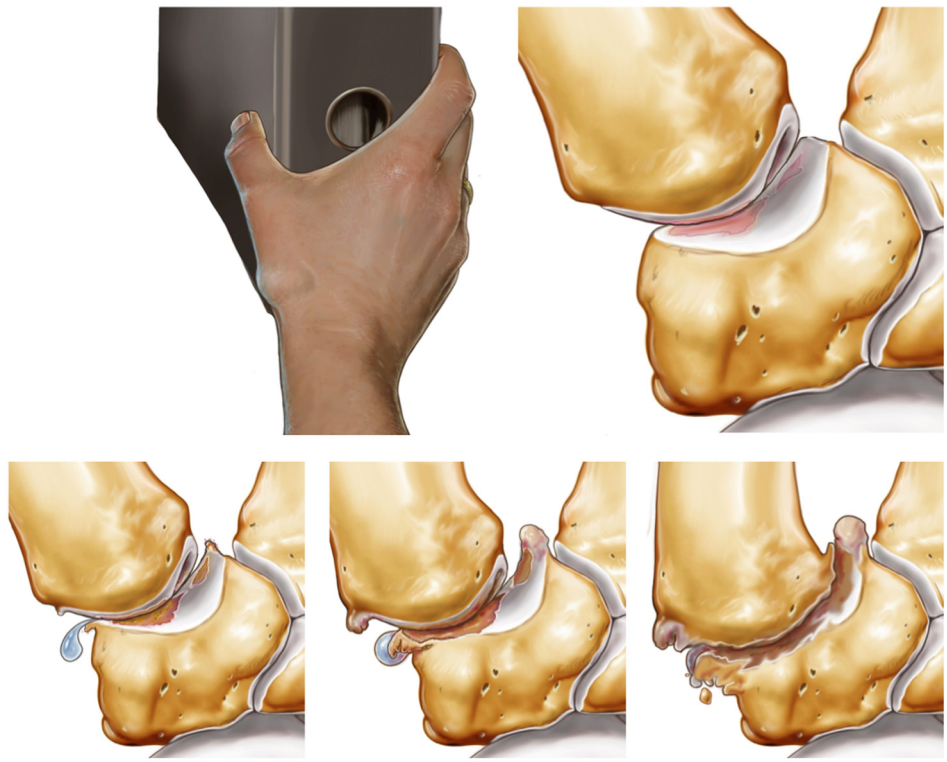


Figure 6:
Illustration by Martin Langer of the progression of osteoarthritis of the CMC-1 joint. With permission.

The first line of treatment in early-stage, symptomatic OA of the CMC-1 joint is typically hand therapy, orthosis, and oral medications with NSAID and/or paracetamol. Activity and occupational adjustment are sometimes necessary and are often discussed with the patient.[119 129] If these methods fail, intra-articular cortisone

injection is the next line of treatment and it has shown low complication rates in a recent study from the UK on 19,120 injections over a period of 19 years. In the same study, 22% of the individuals subsequently had surgery after their injection during the study period, most within a year of injection.[130]

If conservative methods fail, there are several different surgical techniques available to restore function and reduce pain. These include arthroscopic debridement, joint fusion, trapeziectomy with or without ligament reconstruction, or interposition with the joint capsule and joint replacement with a prothesis. The individual procedures and indications are beyond the scope of this summary. It should be noted that while there is still controversy regarding the superiority of any one surgical technique, there are reports of favourable outcome among the majority of patients, irrespective of the surgical technique used.[131] [132] [133]

Chapter 2 - Aims

2.1 General aims of the thesis

The overarching aim of this thesis was to shed light on the diabetic hand, in order to improve the care provided for individuals with DM and concomitant hand disorders. Using the data made available in different Swedish registers and using already existing local cohort studies in Malmö, the aim was to present new, large-scale, longitudinal data regarding risk factors and epidemiology for hand surgical patients with concomitant DM.

In addition, most previous studies on the diabetic hand, more specifically investigating patient experience and surgical outcome, have been carried out internationally in small, highly specialized clinics. This thesis aims to contribute to the understanding of the diabetic hand, its pathogenesis and surgical treatment and outcome, analysing PROMs from the large-scale, national Swedish hand surgical quality register – HAKIR.

Finally, this thesis aims to become a basis of knowledge for surgeons and therapists alike, and to direct attention towards diabetic hand problems in order to continue further research within the field of hand surgery and DM.

2.2 Specific aims of the individual publications

Study I

To calculate prevalence and incidence of five common diabetic hand diagnoses among the population in the Region of Skåne in Sweden.

Study II

To explore potential associations between DM, CTS, and UNE during 20 years of follow-up using the MDCS cohort from Malmö, Sweden.

Study III

To explore metabolic and environmental risk factors for DD using longitudinal data from the MDCS cohort.

Study IV

To examine whether an elevated HbA1c was associated with an increased risk of TF among individuals with T1D and T2D.

Study V

To explore surgical outcome and patient experience after OTFR in individuals with T1D and T2D, compared to individuals without DM.

Chapter 3 - Methods

3.1 The Swedish registers

This thesis would not exist without the availability and meticulous registrations made in all the different Swedish registers. This chapter will first give a brief history of Swedish registers, including that of the Swedish personal identity number, followed by a more detailed description of the registers and cohorts used throughout this thesis. Finally, this chapter will describe the main statistical methods used in the individual studies (I-V) included in the thesis and also reflect on some of the ethical aspects of register studies.

History of quality registers

In order to improve our diagnostic and treatment strategies, it is my firm belief that we have to track our patients, report, learn from their outcomes and experiences, and adapt our strategies accordingly. One of the pioneers in this field was the American surgeon Amory Codman (1869 – 1940), who was educated at Harvard Medical School from which he graduated in 1894. Codman developed the first American register on bone sarcoma, pursuing his idea that patient follow-up, transparency, and learning from mistakes could improve patient care and treatments. While he only added a total of 17 patients to his register, Codman was obviously a pioneer, acting ahead of his time.[134 135]

> "Every hospital should follow every patient it treats long enough to determine whether the treatment has been successful, and then to inquire 'if not, why not' with a view to preventing similar failures in the future." – A. Codman [134]

The first Swedish quality register was founded in 1975 in Lund by the professor in orthopaedic surgery, Göran Bauer, who developed a register for improving outcomes after total knee replacement.[136] Today, there are over 100 different Swedish quality registers, all with the goal of improving patient care, quality, and research within their field.[137]

History of the Swedish personal identity number

The Swedish personal identity number provides a unique opportunity for register studies. It was introduced in 1947 after a government proposition and initially included the individual's date of birth and three digits. In 1967, a fourth digit was added indicating the individual's sex, giving the personal number the 10-digit form it has today. Once introduced, the personal identity number was quickly accepted and is still a very important part of everyday life in Sweden today. It is basically needed in all parts of society, from paying bills, visiting the healthcare sector to buying concert tickets, etc. Since the digitalisation of the personal identity number, its main use in research has firstly been to identify cases and patients; it is often used as the identification variable in a dataset. Second, it allows quick linkage between registers, adding and sharing individual data, resulting in larger databases allowing researchers to study, interpret, and subsequently draw conclusions.[138]

The Swedish National Patient Register (Studies II and III)

The National Patient Register (NPR) was first introduced in 1962 and initially only included psychiatric disorders and diagnoses. Before 1962, only sporadic details of diagnoses and surgical procedures were reported to the Swedish National Board of Health and Welfare (Sw. *Socialstyrelsen*). In 1964, a pilot register, including for the first time all somatic diseases, was introduced in the Region of Uppsala, but it would take almost 25 years for all regions in Sweden to be included in the register. Up until 1997, only diagnoses in hospital-based clinics for inpatients were registered in the NPR. Starting in 1997, all diagnostic and procedure codes (KVÅ) from day surgery were included, and from 2001 all diagnoses from the outpatient clinics were included. To date, there are no Swedish national registers including data from primary care, thus researchers have to rely on administrative regional registers, e.g. the Skåne Health Care Register (SHR), for information and data including primary care.[139 140]

The variables included in the NPR are patient age, sex, diagnosis, surgical codes, admission/discharge dates, and various administrative variables. No anthropometric variables, medications, comorbidities, or lifestyle factors, such as smoking, are registered, hence the need for cross-linking with other registers or the use of population-based cohorts. Since it is mandatory for healthcare providers to transfer data to the NPR, it has a high coverage rate. Finally, the NPR has previously been validated in a number of studies, including musculoskeletal diagnoses, indicating high validity and completeness.[140-142] It should be noted that no validation studies on the NPR have yet been published regarding elective hand surgical diagnoses, an area that would be an obvious target for further research.

Skåne Healthcare Register (SHR; Studies I and IV)

The SHR was started in 1998 with the overarching aim of providing a database containing data on healthcare trends, information for policymakers and politicians, but also to provide data for researchers and administrators when planning for future healthcare services within the Region of Skåne. The register includes diagnoses and data from primary care as well as outpatient and inpatient care from the Region of Skåne, which has approximately 1.1 million adult inhabitants.[143] The data are automatically transferred from the healthcare providers, private as well as public, to the database, and as the diagnoses also serve as the basis for financial reimbursement for the clinic, it is thought to cover the majority of all visits in the region. The diagnosis codes transferred are based on ICD-10,[144] and include codes (KVÅ) for various surgical procedures. SHR also provides data on sex, age, date of visit, and level of healthcare (primary, secondary, or tertiary care), but no anthropometric or laboratory data are included. The register has previously been validated and has been used for research in several medical fields.[143 145] In studies I and IV, only a first-time diagnosis was used when calculating prevalence and incidence, as a patient might visit a physician several times for CTS, for example.

National Diabetes Register (NDR; Studies I – V)

The National Diabetes Register (NDR) was started in 1996, aiming to improve the care for all individuals with DM in Sweden following the so-called St. Vincent Declaration.[146] Building on evidence-based development of care, the goal was for the participating units, both in primary care and in hospital-based clinics, to improve their quality of care and provide feedback to patients and individual units. Today, it is possible for each unit to see its own patients' results, enabling easy comparison on both regional and national levels.[147]

The NDR includes data on DM type, date of diagnosis, duration of DM, medications, laboratory values such as HbA1c, blood lipids, fasting glucose, anthropometric measurements, such as BMI, lifestyle variables, e.g., smoking, and physical activity, and data on complications, e.g., stroke, retinopathy, and albuminuria. It has a coverage rate of approximately 85-90% of patients with DM in Sweden, and all individuals provide written or oral informed consent before registration. The NDR has traditionally focused on outcomes related to medical aspects of diabetes complications, e.g., retinopathy, foot ulcers, HbA1c levels, etc. However, a pilot project has recently started in 30 primary care units and 30 hospital-based units, focusing on patient-reported outcomes, such as quality of life, how patients experience their disease, as well as how they experience the support and care offered by each clinic.[147 148 149]

Swedish National Quality Register for Hand Surgery (HAKIR; Study V)

The Swedish national quality register for hand surgery (HAKIR) was started in 2010 on the initiative of the Swedish Society for Hand Surgery. It has gradually expanded to include all seven university hospitals as well as several private hand surgery units in Sweden. When initiating the register, the aim was to improve healthcare, by e.g., identifying complications and enabling research in order to improve treatments.[150] In 2022, over 90% of all operations in the participating units were included in HAKIR. However, the exclusion of children, patients with nationalities other than Swedish, and individuals with a protected personal number prevents the registry coverage from reaching 100%.

Patients included in HAKIR are asked to fill out two different PROMs preoperatively, then at three and 12 months after surgery. The first is the Swedish version of QuickDASH, an 11-point questionnaire resulting in a disability score ranging from 0 – 100, where a higher score indicates increasingly worse function. QuickDASH is a shortened version of the commonly used Disabilities of the Arm Shoulder and Hand (DASH), including 30 questions about upper extremity function.[151] The second PROM is HQ-8, a specially designed 8-point questionnaire for HAKIR addressing pain on load, pain on motion without load, pain at rest, stiffness, weakness, numbness, cold sensitivity, and ability to perform daily activities. While QuickDASH mainly focuses on exploring the patient's ability to perform certain activities in daily life, e.g., opening a jar or washing their back, the HQ-8 focuses more on hand and finger function, e.g., stiffness and weakness. HQ-8 has previously been validated, showing good validity (the ability of the PROM to measure what it is intended to measure) as well as responsiveness (the ability to detect a change in a patient's clinical condition over time).[152] Both QuickDASH and HQ-8 questionnaires can be found in the Appendix.

3.2 Malmö Diet and Cancer Study cohort (MDCS; Studies II and III)

The Malmö Diet and Cancer Study (MDCS) cohort was started in 1991 in the city of Malmö in southern Sweden and was initially intended to study the relationship between self-reported food intake and risk of various forms of cancer. The baseline examinations were conducted between March 1991 and September 1996 with participants aged 45 to 73 years. All individuals born between 1926 and 1945, and living within the city of Malmö, were invited to participate. The only exclusion criterion was inadequate Swedish language skills. The attendance rate was approximately 41% (30,446 individuals) and 40% of the included participants were men. Subjects were invited to participate in the study by a letter of invitation, but also through advertisements in local newspapers and in public places.[153] [154]

All participants filled out several questionnaires, including questions regarding lifestyle choices, such as physical activity, alcohol consumption, diet, and smoking habits. In addition, socioeconomic variables, such as occupation and education level, as well as medications, previous and current diseases, and family history of diseases were recorded. During baseline examinations, trained nurses measured anthropometric variables, e.g., height, weight, and waist circumference, and participants' blood pressure. A collection of blood samples was drawn and analysed from all patients after an overnight fast. Diabetes status was reported as a self-reported physician's diagnosis, use of anti-diabetic medication, or fasting plasma glucose concentration of ≥7.0 mmol/L. A diabetes diagnosis during follow-up was validated by register linkage to NDR, and several other local and regional diabetes registers within the Region of Skåne.[155 156]

Depending on the research question of the intended study, end-point assessment and outcome variables were retrieved through cross-linking with other Swedish registers, as previously described. In studies II and III, cross-linking with NPR allowed for retrieval of endpoint diagnosis (study II; CTS and UNE and study III; DD) up until Dec 31, 2018.[56 90] Maximum follow-up time for the participants recruited in 1991 is now over 30 years.

Over the years, the MDCS cohort has provided data for an abundance of publications in several different medical fields, covering areas from cardiology and urology, to orthopaedics, and now also, for the first time, hand surgery.[90 157-159]

3.3 Acquiring and extracting data

Working with registers involves several steps; from formulating a research idea, to formation of a hypothesis, applications for ethical permissions, data extraction, to the completion of a manuscript. As there are also numerous steps involved in obtaining ethical permissions, in data handling, data storage, and transfer of files to data management, statistical programming, and manuscript writing, years of preparation and planning become necessary. Furthermore, the implementation of GDPR and increasingly regulatory data laws in Sweden will not make things easier. A flowchart of the data extracted for study I, from the research idea in 2019 to the final publication in "BMJ Open Diabetes Research & Care" in 2022 is displayed below **(Figure 7)**. On a final note, the cost of data handling has risen in the last few years. For study I, the total cost for data extraction alone, including fees for both ethical and data applications and the cost for data managers at the respective registers exceeds 15,000 Euros.

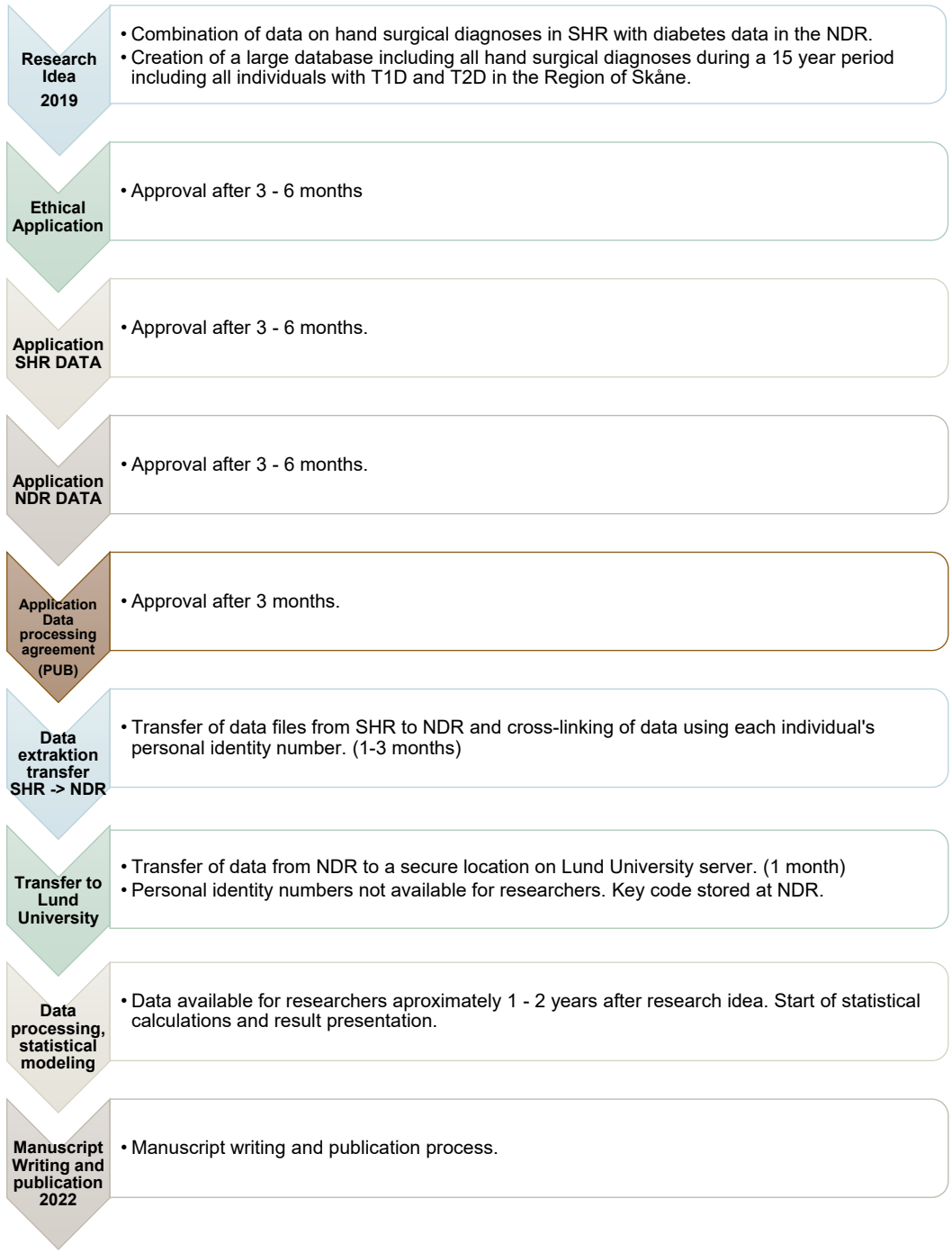


Figure 7.
Flowchart with time frames involved in each step from research idea to final publication for study I.

3.4 Statistical methods

Several different statistical models have been used in the studies included in this thesis. The major statistical models used for the main findings in each study will be described briefly below with reference to the respective study. For the interested reader, references to statistical papers are also provided.

Study I - Incidence rate ratios / prevalence ratios

Study I investigated the prevalence and incidence of five common hand surgical diagnoses in the population with T1D and T2D, compared to the population without DM within the Region of Skåne. Based on the yearly number of individuals living in the Region of Skåne with and without DM, estimates of incidence (new cases / 10,000 person-years) and prevalence (number of cases during the last 15 years among the population alive on December 31, 2019) were calculated. For statistical comparison, incidence rate ratios (IRr) and prevalence ratios (Pr) were calculated. All calculations were stratified for sex and T1D and T2D, and data on age-specific incidence were also included in the supplement.[160]

To give an example, the incidence rate of CTS among women with T1D was 95.5 per 10,000 person-years compared to 26.1 per 10,000 person-years among controls. The IRr was thus calculated as:

$$IRr = \frac{(95.5/10{,}000)}{(26.1/10{,}000)} = \mathbf{3.7}$$

Likewise, the prevalence on December 31, 2019 of CTS among women with T1D was 18,515/52,8310 = 3.5 and 412/3,045 = 13.5 among controls. The *prevalence ratio* was then calculated:

$$Pr = \frac{(412/3{,}045)}{(18{,}515/52{,}8310)} = \mathbf{3.9}$$

Finally, age- and sex-stratified incidence curves were calculated and plotted for each diagnosis, stratified in 10-year intervals **(Figure 8)**.

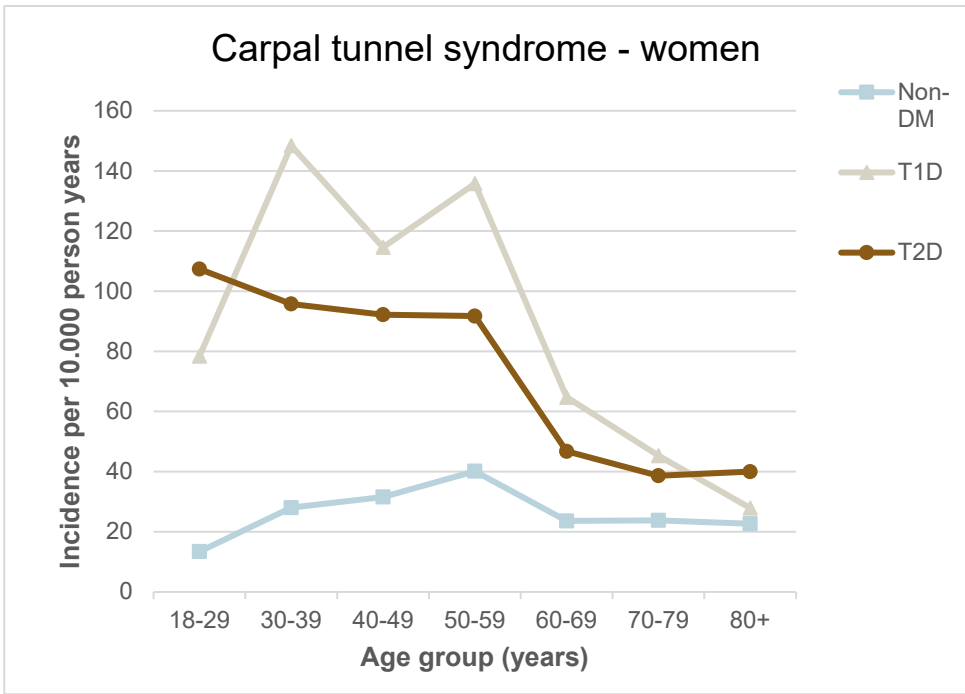


Figure 8:
Age-stratified incidence rates for carpal tunnel syndrome among women between 2010 and 2019. Data from Study I.

Studies II and III - survival analysis

In studies II and III, data from the longitudinal cohort study MDCS were used, as described above. Participants in both studies II and III were followed from the baseline registration (1991 – 1996) until either a diagnosis of interest, i.e., CTS or UNE (study II) or DD (study III) was established, or until emigration, death, or the end of follow-up on December 31, 2018. In this way, each individual in the study has a unique follow-up time, allowing for statistical survival analysis.

Two main statistical survival analyses were used for survival data. In study II, a Kaplan-Meier plot with an enclosed log-rank test was used to calculate differences in event-free time, i.e., the time from baseline until an established diagnosis of CTS or UNE in individuals with and without DM at baseline **(Figure 9)**.[161]

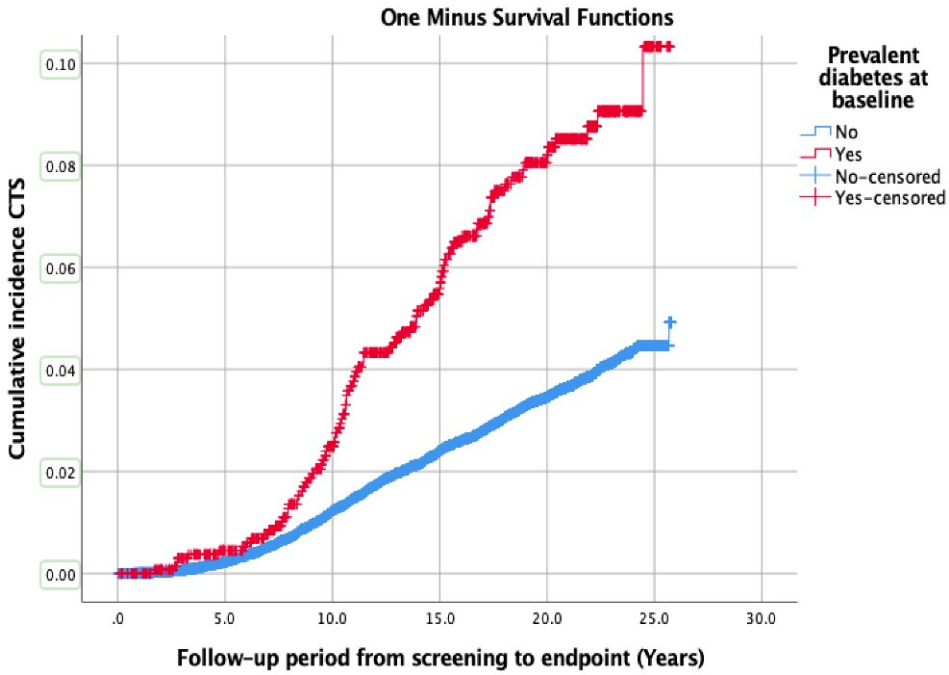


Figure 9:
Kaplan-Maier plot on the cumulative incidence of CTS in the MDCS-cohort with and without DM. Data from study II.

However, since the Kaplan-Meier plot is a univariate analysis, it only describes survival in relation to the factor studied and ignores the impact of others, meaning it has no ability to adjust for confounding factors, e.g., sex, age, and smoking, further discussed in Chapter V. Moreover, although the log-rank test indeed provides a p-value for a statistical difference between the groups, it does not give an estimation of the effect size, i.e., it does not provide an actual impact of DM on the risk of developing CTS. It only states whether there is a difference between the studied groups. In order to calculate both the effect size and also include adjustment of confounders, multivariate analysis in the form of multivariate Cox Regression models was used in both studies II and III.[162 163]

A key element in the Cox regression model is the assumption of proportionality, i.e., the assumption that the ratio between the hazards is relatively proportional over time. This assumption was tested in studies II and III by calculation of log-log plots and by graphically analysing the curves and confirming proportionality. In both studies II and III, the underlying timescale was the time from baseline registration to an established diagnosis, emigration, death, or end of follow-up on December 31, 2018. Hazard ratios with 95% confidence intervals were calculated firstly in crude, unadjusted models, and subsequently in multivariate models adjusted for potential

confounders. The confounders added into the models in each study were based on both previous research into risk and protective factors for respective diagnoses, as well as on clinical experience, and finally on data available in the registers. In addition, in study III, a directed acyclic graph (DAG) was constructed to illustrate potential associations and pathways between exposures, risk factors, and DD.[162 164]

Study IV – Binary logistic regression

Study IV investigated the effect of an elevated HbA1c on the risk of TF among individuals with T1D and T2D between 2004 and 2019. Data from SHR were crossed-linked with NDR, creating a database with approximately 10,000 and 86,000 individuals with T1D and T2D, respectively. Multivariate binary logistic regression models stratified for sex and type of DM were performed in order to calculate the impact of an elevated HbA1c (predictor variable) on the risk of developing TF (binary outcome variable).[165]

To better reflect an individual's long-term glycaemic control over the years included in the register, a mean value was calculated from all the registered HbA1c data for each individual (HbA1c is usually registered once a year). Since the mean values had a slightly left-skewed distribution (normality was visually assessed via a histogram) a z-score standardization *([variable level - mean] / standard deviation)* was performed. This resulted in a variable with a mean of 0 and a standard deviation of 1. Results were expressed as ORs for each standard deviation (SD) increase in HbA1c, to facilitate interpretation of the results.[166]

Furthermore, individuals included in the study were divided into tertiles according to their glycaemic control with optimal control (≤ 48 mmol/mol), acceptable control (48.1–64 mmol/mol), and poor control (>64 mmol/mol), an adaptation of the American Diabetes Association and National Institute for Health and Care (NICE) guidelines for glycaemic control.[167 168] Two different regression models were created. The first was a crude age-adjusted model while the second model included further adjustment for BMI, smoking, systolic blood pressure, and duration of DM.

Study V – mixed model linear regression

Study V investigated the patient-reported outcome after OTFR using data from HAKIR that were crosslinked with NDR. The two questionnaires used in HAKIR; HQ-8 and QuickDASH, have already been addressed and explained above. The patients fill in the questionnaires three times i.e., preoperatively, and at three and 12 months postoperatively. The data from HAKIR is thus seen as repeated measures data with predetermined time intervals. Additionally, with a relatively low response rate (50% of included patients responded to at least one questionnaire) the problem of missing data has to be addressed statistically. In both these cases, i.e., repeated measures with missing data, a mixed model linear regression can be applied for statistical analysis. Firstly, this model does not require complete data from all patients, it uses all observations available and thus makes use of the available

information effectively. Furthermore, it considers differences in e.g., variation in baseline values in each individual when comparing outcomes between the groups studied. Mixed model linear regression can also handle and statistically address both fixed effects (e.g., diabetes status, age, specific time intervals), and random effects (improvement over time, baseline function) on the outcome in question. Fixed effects are seen as fairly constant across individuals in each group, while random effects vary across individuals in each group. [169 170]

In study V, the outcomes studied were improvement in QuickDASH and the HQ-8 between assessments preoperatively, at three months, and at 12 months, respectively. Since the outcome after OTFR might differ between men and women, all calculations were stratified for sex and adjusted for age at surgery. Finally, the models presented estimated means for each group at each time interval. Differences in outcome between T1D, T2D, and the controls were calculated in the mixed linear regressions models.

3.5 Ethical considerations

Several ethical approvals were obtained before the writing of the studies included in this thesis. For studies I and IV, a new ethical application was submitted, and permission was obtained from the National Swedish Ethical Review Board in 2019 for the cross-linking of data from the SHR and NDR (DNR: 2019-02042). For studies II and III, several complementary ethical approvals were obtained (DNR: 2019-01433; 2019-01439) in addition to the general ethical permissions for the MDCS study (DNR: LU51-90; 2009-633). For study V, complementary ethical permission was obtained (DNR: 2021-00902) in addition to the already overarching ethical permission for HAKIR (DNR: 2017/2023-31; 2019-00880).

Several interesting ethical aspects and considerations must be reflected on with regard to register and cohort studies. One of these aspects is the principle of autonomy – that all individuals have the right to make their own decisions and choices, especially with regard to informed consent.[171]

In studies II and III, informed consent was obtained from all participants before enrolment in the MDCS. However, as previously stated, the aim of the MDCS when initiated was to explore a potential link between diet and cancer risk – there were no study protocols for exploring associations between DM and hand surgical diagnoses. Nevertheless, over the years the MDCS evolved to include several other outcomes in a variety of medical fields, including the ones in this thesis. In study V, informed consent was obtained from the participants in HAKIR and also for registration in the NDR. Common to the MDCS, NDR, and HAKIR is the possibility of not participating or withdrawing and having one's data removed. However, this is exceedingly uncommon and to our knowledge, only 2-3 participants (1/10,000)

have withdrawn from the MDCS and even fewer from HAKIR. Nevertheless, the possibility to do so is in accordance with the principle of autonomy.

For studies I and IV, however, informed consent was obtained for inclusion in the NDR, but not in the SHR. In the SHR, the data on diagnoses are automatically transferred from the caregiver, as previously stated, and a diagnosis is also a requirement for reimbursement from the Region's administration to the clinic. An individual is not able to withdraw his or her data from the SHR. However, the SHR is more than a patient register used for research, it works as an administrative source for administrators, politicians, and policymakers in the region.[143] The same is also true for the NPR; individuals are not able to remove their already registered data and no informed consent is obtained before collecting the data.[172] One could argue that the data in the SHR and NPR are less sensitive since they only include the diagnosis and surgical codes that are transferred to the register (as opposed to the MDCS and NDR, which include laboratory data, anthropometrics, genetic information, socioeconomic status, etc). Nevertheless, diagnostic data are collected without consent from the patient.

With this being said, it is agreed that the information collected in these registers fits well within the principle of beneficence, the will to act for the benefit of the patients and promote the welfare of the patient and others.

> *"… it is assumed that the study participants do not object to registry-based research, provided that such research is deemed ethical by the ethics committee. This assumed agreement to contribute personal data to research is part of the informal contract between the individual and the state… given that health care is traditionally virtually free of charge."* – Jonas Ludvigsson 2015 [173]

Also, as previously stated, very few individuals actively opt out of other types of registers, e.g., from the Swedish biobank,[174] and the sheer number of patients (sometimes millions) would make it impossible for researchers to acquire informed consent from everyone involved.

It is thus my firm belief that within the field of register studies, where the present thesis lies, the good outweighs the potential harm for the individual person whose data we are collecting and analysing without their consent. Nevertheless, it is of the utmost importance that researchers first obtain ethical permission from the National Ethical Review Board before extracting data and, of course, that they handle the data with respect for the individual's privacy and integrity.

Chapter 4 – Results

The results from the original studies included in this thesis are briefly summarised below. For detailed results, the interested reader is referred to the individual studies.

4.1 Study I

The Diabetic hand: prevalence and incidence of diabetic hand problems using data from 1.1 million inhabitants in southern Sweden.

Study I investigated the prevalence and incidence of CTS, UNE, DD, TF, and OA of the CMC-1 joint in the Region of Skåne in southern Sweden among the population with T1D and T2D, using the population without DM as a control. All calculations were stratified for sex and calculated separately for T1D and T2D. Data collected between 2004 and 2019 were available.

The prevalences of all five diagnoses were higher among both men and women with T1D and T2D ($p < 0.01$). The prevalence ratio ranged from 1.8 (95% CI; 1.4 – 2.4, $p < 0.01$) for OA of the CMC-1 joint to 9.4 (95% CI; 8.6 – 10.3, $p < 0.0001$) for TF among women with T1D **(Figure 10)**.

All the 10-year incidence rates were higher among both T1D and T2D patients ($p < 0.0001$) compared to the controls with the exception of OA of the CMC-1 joint in men with T1D ($p = 0.055$) (**Table 1)**.

Finally, there were more individuals with T1D and T2D who had a second, concomitant prevalent diagnosis (T1D; women 34%; 95% CI 30.6 – 37.5, men 24%; 95% CI 20.7 – 27.8; T2D; women 22%; 95% CI 21.1 – 23.8, men 19%; 95% CI 17.5 – 20.1), compared to the population without DM (women 17%; 95% CI 16.3 – 17.1, men 13%; 95% CI 13.0 – 14.1; Chi-square $p < 0.0001$ for all analyses).

Table 1.
Sex-stratified incidence rates 2010 - 2019 among individuals ≥ 18 years in the Region of Skåne, Sweden, with corresponding incidence rate ratios of respective diagnoses in the populations with T1D and T2D, with the population without DM as control. CI; confidence interval, CMC; carpometacarpal, IR; Incidence ratio, IRR; incidence rate ratio, OA; Osteoarthritis. *p < 0.0001, ** p = 0.055

Women	**Without Diabetes**			**Type 1 Diabetes**			**Type 2 Diabetes**		
Diagnosis	No. Events	IR/10000	IRr (ref)	No. events	IR/10000	IRr (95% CI)	No. events	IR/10000	IRr (95% CI)
Carpal tunnel syndrome	13086	26.1	1.0	250	95.5	3.7 (3.2 – 4.2)*	1007	52.1	2.0 (1.9 – 2.1)*
Ulnar nerve entrapment	1942	3.9	1.0	37	14.1	3.7 (2.6 – 5.0)*	145	7.5	1.9 (1.6 – 2.3)*
Trigger finger	6253	12.5	1.0	263	100.5	8.1 (7.1 – 9.1)*	813	42.0	3.4 (3.1 – 3.6)*
Dupuytren's disease	1648	3.3	1.0	60	22.9	7.0 (5.4 – 9.0)*	182	9.4	2.9 (2.5 – 3.3)*
OA of the CMC-1 joint	3711	7.4	1.0	37	14.1	1.9 (1.4 – 2.6)*	281	14.5	2.0 (1.7 – 2.2)*

Men	**Without Diabetes**			**Type 1 Diabetes**			**Type 2 Diabetes**		
Diagnosis	No. Events	IR/10000	IRr (ref)	No. events	IR/10000	IRr (95% CI)	No. events	IR/10000	IRr (95% CI)
Carpal tunnel syndrome	6178	12.9	1.0	188	58.1	4.5 (3.9 – 5.2)*	837	31.6	2.5 (2.3 – 2.6)*
Ulnar nerve entrapment	1715	3.6	1.0	51	15.8	4.4 (3.3 – 3.8)*	232	8.8	2.5 (2.1 – 2.8)*
Trigger finger	3662	7.6	1.0	165	51.0	6.7 (5.7 – 7.8)*	782	29.5	3.9 (3.6 – 4.2)*
Dupuytren's disease	3952	8.2	1.0	119	36.8	4.5 (3.7 – 5.4)*	590	22.3	2.7 (2.5 – 3.0)*
OA of the CMC-1 joint	1248	2.6	1.0	14	4.3	1.7 (0.9 – 2.8)**	157	5.9	2.3 (1.9 – 2.7)*

4.2 Study II

Diabetes mellitus as a risk factor for compression neuropathy: a longitudinal cohort study from southern Sweden.

Study II aimed to explore associations between DM at the time of recruitment to the MDCS cohort and incident CTS and UNE during long-term follow-up. Of the 30,446 participants who were aged 46-73, 1,081 developed CTS and 223 developed UNE during a median follow-up of 21 years.

First, when using Kaplan-Meier plots there was a higher cumulative incidence of CTS (log-rank test $p < 0.0001$) as well a higher cumulative incidence of UNE (log-rank test $p < 0.0001$) among participants with DM at baseline compared to participants without DM.

Second, in the multivariate Cox regression models, prevalent DM at baseline was associated with incident CTS (HR 2.1; 95% CI: 1.6 – 2.7 $p < 0.0001$) as well as incident UNE (HR 2.2; 95% CI: 1.3 – 3.7 $p = 0.003$) **(Table 2)**. The analyses were made first in a crude model, adjusted only for age at study entry and sex, then in a model further adjusted for sex, age at study entry, alcohol consumption, BMI, hypertension, the use of antihypertensive treatment, and smoking.

Table 2.
Multivariable Cox regression analysis with hazard ratios for incident CTS and UNE in relation to diabetes mellitus. * Adjusted for sex, age at study entry, alcohol consumption, BMI, hypertension, the use of antihypertensive treatment, and smoking. DM; Diabetes Mellitus, CTS; Carpal Tunnel Syndrome, UNE; Ulnar Nerve Entrapment, HR; Hazard Ratio, CI; Confidence interval

Variable	**Model II***	
CTS (n = 1081)	**HR (95% CI)***	**P - value**
Prevalent DM	2.10 (1.65 - 2.70)	< 0.0001
UNE (n = 223)	**HR (95% CI)***	**P - value**
Prevalent DM	2.20 (1.30 – 3.74)	0.003

4.3 Study III

Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years.

Study III aimed to explore metabolic and environmental risk factors for DD in the MDCS cohort during long-term follow-up. Of the 30,446 participants included in the study, 347 men DD and 194 women developed DD during a median follow-up time of 23 years.

In the multivariate Cox regression model, DM among both men (HR 2.2; 95% CI: 1.5 – 3.3; p <0.001) and women (HR 2.7; 95% CI: 1.5 – 4.9 p = 0.001) as well as moderate and heavy alcohol consumption among both sexes, were highly associated with increased risk of DD during the follow-up time.

Obesity was inversely associated with DD among men (HR 0.66; 95% CI: 0.44 – 0.98 p = 0.04). This trend was also found among women, although borderline significant (p = 0.05). Furthermore, when analysing the blood lipid levels, the ApoB/ApoA1 ratio was also negatively associated with incident DD in both men (HR 0.85; 95% CI: 0.75 – 0.96; p = 0.01) and women (HR 0.80; 95% CI: 0.66 – 0.97; p = 0.02) **(Table 3)**.

Table 3.
Sex-stratified, multivariable Cox regression models with corresponding HR for incident DD in relation to ApoA1, ApoB and the ApoB/ApoA1 ratio. The model is adjusted for age, DM, hypertension, alcohol consumption, smoking, manual work, and BMI. *HR are expressed as per one SD increase of the respective Z-score converted variable.

Variable		
Men	**HR (95% CI)***	**P - value**
ApoA1	1.22 (1.09 – 1.38)	**< 0.01**
ApoB	0.97 (0.86 – 1.09)	= 0.64
ApoB/ApoA1	0.85 (0.75 – 0.96)	**= 0.01**
Women		
ApoA1	1.17 (1.01 – 1.36)	**= 0.03**
ApoB	0.83 (0.70 – 0.99)	**= 0.03**
ApoB/ApoA1	0.80 (0.66 – 0.97)	**= 0.02**

4.4 Study IV

High HbA1c levels are associated with the development of trigger finger in type 1 and type 2 diabetes: an observational register-based study from Sweden.

Study IV aimed to examine whether an elevated HbA1c was associated with an increased risk of TF among individuals with T1D and T2D in the Region of Skåne, Sweden between 2004 and 2019. Individuals diagnosed with TF during the study period had higher mean HbA1c levels, in both sexes and in T1D ($p < 0.01$) as well as T2D ($p < 0.01$), when analysing the quantitative variable characteristics.

In all logistic regression models, there was an association between TF and elevated HbA1c levels among subjects of both sexes with both types of DM. This was true both when using HbA1c as a continuous z-score converted variable, and when analysing HbA1c in tertiles, with individuals with optimal HbA1c control (mean HbA1c ≤ 48 mmol/mol) as reference. The logistic regression models were first analysed in a crude, age-adjusted model, then in a model further adjusted for the duration of DM, smoking, BMI, and systolic blood pressure **(Table 4)**.

Moreover, two sensitivity analyses were performed in the study; the first excluding all individuals ≤ 40 years, the second excluding all individuals with a duration of DM < 10 years. When analysing the data in these subpopulations, an elevated HbA1c was still associated with TF in men and women, and in T1D and T2D, both when used as a continuous variable and when divided into tertiles.

Table 4.
Multivariate logistic regression models for individuals with T1D and T2D, stratified for sex, with OR for TF in relation to HbA1c. Firstly, a **continuous z-score converted variable is presented and also different groups of glycaemic control among DM; optimal control ≤ 48 mmol/mol, acceptable control 48 – 64 mmol/mol, and poor control > 64 mmol/mol using the individuals with optimal glycaemic control as reference. * Adjusted for age at last registration in NDR, duration of DM, BMI, smoking, and systolic blood pressure. ** expressed as OR per 1 standard deviation (SD) increase in HbA1c.

	Type 1 diabetes		**Type 2 diabetes**	
Women	**OR (95% CI)***	**P - value**	**OR (95% CI)***	**P - value**
HbA1c continuous**	1.16 (1.05 – 1.29)	**< 0.001**	1.09 (1.02 – 1.17)	**= 0.011**
Optimal glycaemic control	*Reference*	**-**	*Reference*	**-**
Acceptable glycaemic control	1.88 (1.10 – 3.23)	**= 0.021**	1.38 (1.18 – 1.61)	**< 0.001**
Poor glycaemic control	2.36 (1.38 – 4.04)	**= 0.002**	1.39 (1.14 – 1.70)	**= 0.001**
Men				
HbA1c continuous **	1.30 (1.14 – 1.49)	**< 0.001**	1.10 (1.03 – 1.19)	**= 0.009**
Optimal glycaemic control	*Reference*	**-**	*Reference*	**-**
Acceptable glyacemic control	3.26 (1.31 – 8.11)	**= 0.011**	1.29 (1.10 – 1.52)	**= 0.002**
Poor glycaemic control	5.56 (2.24 – 13.78)	**< 0.001**	1.39 (1.13 – 1.70)	**= 0.002**

4.5 Study V

Outcome and patient experiences after open trigger finger release in patients with type 1 and type 2 diabetes - a retrospective study using PROMs and Swedish national quality registries.

Study V aimed to explore patient experiences and surgical outcome after OTFR in patients with T1D and T2D compared to individuals without DM, using two different PROMs described above. During the study period between 2010 and 2020, 6,242 OTFR were included from HAKIR, where 496 had T1D (332, 67% female) and 869 T2D (451, 52% female).

There were improvements in patients with T1D and T2D and the controls regarding overall QuickDASH scores and all the HQ-8 questions studied, three months after surgery ($p < 0.001$).

When comparing T1D and T2D patients to the control group, women with T1D had more symptoms of stiffness ($p < 0.001$) and women with T2D had more pain on load ($p < 0.05$) and motion without load ($p < 0.01$) at three months after surgery compared to the control group. At 12 months, there were no longer any differences in any of the HQ-8 PROMs. Men with T1D and T2D experienced more pain preoperatively ($p < 0.01$). However, at neither three nor 12 months were there any difference in HQ-8 PROMs compared to the control group.

In total, 52.6% of the participants responded to at least one of the PROMs and there was only a slightly higher number of T2D in the non-responder group. Age and sex did not differ between the responders and non-responders.

Finally, the number of individuals who underwent ≥ 2 OTFR during the study period was higher both among patients with T1D (130/496, 22%, Chi^2 $p < 0.001$) and T2D (153/869, 18%, Chi^2 $p = 0.01$) compared to the control group (711/4,877, 15%).

Chapter 5: Discussion

5.1 General discussion

Throughout this thesis, I have used Swedish national and regional registers and population-based cohorts to study the impact of T1D and T2D on common hand surgical diagnoses. This chapter will first discuss the epidemiological findings of the studies included and relate these to previous studies. Second, the pathophysiological background to how DM affects the various diagnoses will be briefly discussed and related to different theories regarding why DM seems to lead to a marked increase in incidences and prevalences. Finally, important methodological considerations will be discussed followed by some study-specific strengths and limitations.

The diabetic nerve (Studies I, II)

Study I presents data showing a markedly higher prevalence as well as incidence of CTS and UNE among individuals of both sexes with T1D and T2D, respectively, when compared to individuals without DM. Compression neuropathies were up to 3-4 times more common among individuals with DM and the incidences were also markedly higher. Study II corroborated these findings, adding longitudinal data in a different study design, following the MDCS cohort over 20 years, presenting data on a markedly higher risk for incident CTS and UNE during follow-up.

The results from studies I and II confirm the findings of several previous studies on compression neuropathies, results from metanalyses on CTS and DM, and conclusions from recent review articles, all showing an increased risk for CTS among individuals with DM.[27 33 36 175] This thesis also adds particularly valuable data on the ulnar nerve and UNE among the population with DM. Earlier epidemiological data on UNE are scarce, and large studies have so far been missing, possibly due to the clearly lower prevalence of UNE compared to CTS. Nevertheless, our findings are in line with previous smaller studies as well as the clinical and electrophysiological findings among patients with UNE and DM.[55 176 177 178 179]

These findings allow us to state with reasonable confidence that, at an epidemiological level, DM is one of the major risk factors for the development of

compression neuropathies in the upper extremity. However, the question of how DM affects the peripheral nerves on a biochemical and anatomical level remains and will be described and discussed below.

Glucose neurotoxicity

Several biochemical explanations have been presented concerning why DM increases the incidence of compression neuropathies. One of the recognised explanatory factors is that DM induces pathological alterations in the intracellular metabolism within the neurons. In a normoglycaemic state, glucose is converted into glucose-6-phosphate by the enzyme hexokinase, as part of normal glycolysis. When exposed to hyperglycaemia, hexokinase becomes saturated, inducing glucose metabolism via the so-called *polyol pathway*. In this pathway, the enzyme aldose reductase reduces glucose to sorbitol. Because sorbitol is a hyperosmotic protein with low permeability through the cell membrane, it gets confined or trapped within the axons of the neuron, working as an osmotic driver. This osmotic drive traps fluid within the cell which can possibly lead to cellular oedema and subsequent nerve trunk swelling.[176 180 181 182 183] Moreover, in the hyperglycaemic state, the neuron is exposed to increased oxidative stress, leading to cell damage and axonal degeneration. This is partly due to the polyol pathway depleting intracellular antioxidants such as glutathione when metabolizing glucose to sorbitol, but also to increased production of reactive oxygen species (ROS) within the mitochondria as a result of hyperglyceamia.[180 183 184]

DM can also affect the axonal transport within the neuron, something that is crucial for the neuronal homeostasis. Axonal transport is the process whereby proteins, lipids and cellular compounds are transported along the axon of the neuron from the cell body and vice versa.[185] Animal studies have, for example, shown that compression of the sciatic nerve in rats caused an increased inhibition of axonal transport of proteins to a greater extent in diabetic rats compared to health rats, indicating an increased susceptibility to compression.[186 187]

Furthermore, DM also affects the supporting cells surrounding the axons within the nerve trunk. Hyperglycaemia, but also dyslipidaemia frequent in T2D, is thought to contribute to increased Schwann cell stress and lead to endothelial dysfunction in the small blood vessels approaching and within the nerve trunk. This in turn can lead to demyelination of the axon with impaired nerve conduction and nerve dysfunction as a result. Part of the effect can be attributed to the polyol pathway, impairing homeostasis of the Schwann cells by accumulation of sorbitol, as previously described, but also to the formation of advanced glycaemic end products (AGEs) creating further intracellular oxidative stress as a result, as further discussed below.[188] Additionally, as described in the introduction section, DM induces microvascular alterations, particularly true for endoneurial capillaries. These alterations include capillary basement thickening and hyperplasia of the endothelium, leading to both diminished microcirculation to the axons and

supporting cells causing ischemia, but also capillary dysfunction with reduced extraction of oxygen as a result.[189] Finally, the rheological properties of the erythrocytes, the carriers of oxygen, are also altered in patients with DM. Studies have shown an impaired deformability of the erythrocytes in the presence of DM, possibly leading to disrupted perfusion of the nerve resulting in hypoxia, as the erythrocytes can no longer easily pass through the small endoneurial capillaries. [190]

Unfortunately, there are very few nerve biopsy studies since nerve biopsies are associated with a risk of morbidity in the form of neuromas, sensory deficit and chronic pain.[191] However, biopsies have been obtained from the posterior interosseus nerve (PIN), just proximal to the wrist, from patients undergoing open surgery for CTS at the Hand Surgical Department in Malmö, Sweden, subsequent to ethical permission from the regional ethics board and informed consent from the patient. Data from these biopsies suggest a reduction in myelinated nerve fibre density and endoneurial capillary density in individuals with DM and CTS compared to the non-DM control patients with CTS. Interestingly, a reduction in myelinated fibre density could also be shown also in non-DM patients with CTS compared to the control group *without* CTS.[192] Nota bene, biopsies were taken from a non-compressed nerve, possibly indicating a predisposition to compression neuropathies among patients with CTS. Indeed, since it is suggested that approximately half of the liability to develop CTS is contributed by genetic traits,[79] one might hypothesise that the population with CTS is already prone to compression due to existing pathology within the nerve fibres. Additional data from the same biopsies demonstrated upregulation of vascular endothelial growth factor (VEGF) in patients with DM, possibly indicating reduced microcirculation and endoneurial hypoxia.[193]

Finally, sheer mechanical pressure on the nerve due to swelling of the surrounding ligaments or tenosynovium, as discussed below, might also impair the return of venous blood, resulting in venous statis, hypoxia and further oedema within the nerve trunk.[69] Indeed, hypertrophy of the transverse carpal ligament (**Figure 11)** has been associated with disease progression in CTS, possibly increasing pressure within the carpal tunnel.[194]

Thus, the diabetic nerve becomes trapped in a vicious cycle. Already frail and oedematous from prolonged hyperglycaemia, inducing pathological alterations within the neurons and surrounding tissue, combined with the low density of nerve fibres within the nerve trunk, the nerve is prone to compression. Adding insult to injury, when compressed the nerve becomes even more oedematous, and together with venous stasis due to compression, the threshold for symptom development is imminent and is possibly reached earlier than in a non-diabetic nerve.

Anatomical basis of compression neuropathies

Several theories have been presented over the years concerning how and why DM affects the peripheral nerve, making it more prone to compression in the carpal tunnel at the wrist and in the cubital tunnel at elbow level. In the case of CTS, the median nerve resides within the carpal tunnel together with nine flexor tendons surrounded by tenosynovium, below the transverse carpal ligament. If one or more of these three structures (the nerve, tendons with synovia, or the carpal ligament) increases in size, the functional area for the well-vascularized median nerve, with its axons and surrounding Schwann cells, is reduced in the tunnel, increasing the risk of compression and symptom development among patients. DM could possibly affect all of these three structures, inducing nerve trunk swelling, proliferation and oedema of the tenosynovium, as well as thickening of the carpal ligament.[195 196 197] Likewise, if a ganglion cyst originating from the bottom of the carpal tunnel starts to grow, symptoms of CTS often arise as the cyst enlarges and the median nerve becomes progressively compressed **(Figure 11)**.[198]

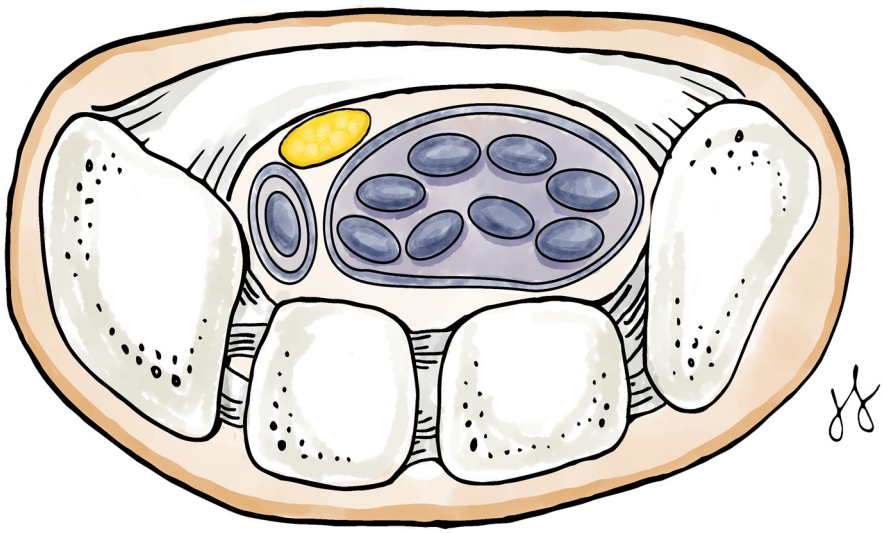


Figure 11.
Illustration by Linnea Arvidssson. Cross-section of the carpal tunnel in the wrist. The median nerve (yellow) residing under the carpal ligament together with the nine flexor tendons (blue) with surrounding tendon sheet. With permission.

As for the ulnar nerve, it passes dorsally to the medial epicondyle, through the cubital tunnel and is kept in place by tight ligament structures; Osborne's ligament being the roof of the tunnel and the medial collateral ligament and the joint capsule constituting the floor. The cubital tunnel constitutes a tight space that does not allow for swelling of the nerve, analogues to the carpal tunnel.[199] Indeed, several studies

of the ulnar nerve, using ultrasound, have reported that it has a larger cross-sectional area in patients with UNE than in controls, indicating that nerve swelling is indeed a part of the anatomic basis of the disease.[200 201 202] Similarly, ultrasound studies of the ulnar nerve in individuals with DM have shown a larger CSA in patients with DM compared to controls, particularly in individuals with established polyneuropathy.[203]

Studies I and II add population-based longitudinal data, confirming that both CTS and UNE should be included as two of the diagnoses in the concept of the diabetic hand; the findings thus corroborate the pathophysiological pathways and alterations described above. However, as previously briefly mentioned, DM also affects the ligaments, tendons and tenosynovium surrounding the peripheral nerves. This pathogenesis is in many ways shared with both TF and DD and will be further discussed below.

Dupuytrens disease and trigger finger (Studies I, III, IV, V)

Studies III, IV, and V all investigated DM and its association with soft tissue disorders, i.e., TF and DD. Study III used the MDCS cohort and provided robust evidence and population-based data in a longitudinal setting suggesting that DM is a major risk factor for the development of DD in middle-aged individuals. This study confirms previous conclusions from systematic reviews[204 205] and adds valuable longitudinal data which have previously been lacking. Together with Study I, which also provides large-scale population-based data on a clearly higher incidence as well as prevalence of DD among both T1D and T2D, we can now be reasonably certain that individuals with DM have an increased risk of developing DD during their lifetime. Study III also analysed additional metabolic and environmental risk factors for DD, presenting evidence for heavy alcohol consumption being one of the explanatory factors for its development, in accordance with a recently published systematic review.[205] **Figure 12** presents a directed acyclic graph (DAG) with arrows representing the complex interplay and potential interactions and pathways between exposures, risk and protective factors. and DD.

Interestingly, study III also presented data on a *lower* risk of DD in obese individuals in the MDCS cohort, particularly among men, even after adjustment for several confounding factors. When analysing the blood lipid levels, a high ApoB/ApoA1-ratio (a strong predictor of cardiovascular risk and an indication for unfavourable blood lipid status) was also negatively associated with DD among both sexes. This somewhat surprising association has previously been shown in both observational epidemiological studies,[206 207] but also in a genetic study[95] as well as in a recent mendelian randomisation (MR, discussed in detail below) study, indicating a causal protective role of an elevated BMI for the development of DD.[208]

As the exact biological mechanisms for this association are yet to be elucidated, one proposed mechanism is lower serum testosterone among obese individuals compared to individuals with normal weight.[208] Testosterone has indeed been shown to stimulate fibroblast proliferation and androgen receptors are increasingly expressed in palmar fascia in DD.[209 210] This hypothesis is supported by the fact that testosterone levels have been shown to decrease with increasing BMI and potentially reduce the disease progress of DD.[211 212]

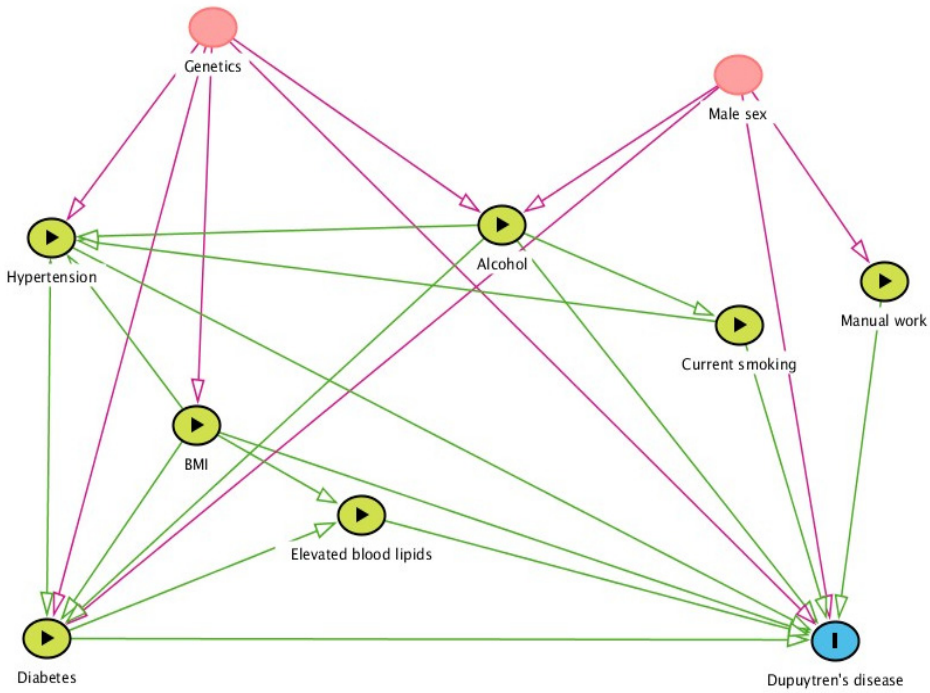


Figure 12.
Directed acyclic graph (DAG) with arrows representing potential explanatory pathways and interactions between exposures, risk and protective factors and Dupuytrens disease (DD).

Regarding TF, Study I reports a staggering 8-fold increase in incidence among women with T1D, and higher prevalence and incidence rates among both sexes and both types of DM. This association between TF and DM has been known for a long time and is now well established.[108 117 213] While Study I defines the present epidemiological and demographic status of the diabetic hand, including TF, Study IV adds in-depth data on glycaemic control and its association with TF, providing evidence of a dose-response relationship between HbA1c levels and the risk of TF, irrespective of DM type or sex. Study IV also adds valuable data concerning the causal relationship between DM and TF, as a biological gradient (or dose-

relationship) is one of the nine Bradford Hill criteria for causation, further discussed below. On this subject, all individuals with TF before their DM diagnosis were excluded from Study IV, thus ensuring a correct temporal association, which is another cornerstone of causation.[214] Putting all this evidence together, as with DD, we can now with reasonable confidence confirm that DM, and especially T1D, is one of the *causal* and major risk factors for the development of TF.

Having confirmed DM as a risk factor for TF (Studies I and IV), the next logical step was to investigate the way in which patients with DM experienced the surgical treatment we offer them at the hand surgical department, i.e., OTFR. As the most cost-efficient treatment algorithm for TF in the presence of DM is still being debated,[215] knowledge of patient experience and outcome after OTFR is important in order to correctly inform and advise our patients. Study V analysed PROs from a large number of individuals undergoing OTFR and is one of the largest studies to date to do so. In accordance with several previous studies, all reporting similar, mainly favourable, outcomes among individuals with DM and controls,[216 217] data from Study V show no difference in any of the HQ-8 questions studied twelve months after surgery. However, women with T2D reported more symptoms at *three* months, which seemed to resolve over time. Taking all the findings together, Study V contributes large-scale data on surgical outcome and patient experience after OTFR, confirming the clinical view that it sometimes takes longer for patients with TF and concomitant DM to experience symptom relief after surgery. Given the fact that almost 22% of all patients undergoing a first-time OTFR in Study V had DM, and that individuals with DM more often had a secondary OTFR compared to the controls, it is important that these findings are communicated to our patients during consultations, enabling them to make an informed decision regarding their treatment.

Advanced glycation end products – a driving force in diabetic complications

One of the proposed biochemical processes behind diabetic complications is the formation of advanced glycated end products (AGEs). In brief, AGEs are a result of hyperglycaemia leading to different proteins and lipids becoming glycated after reacting with excess glucose. Connective tissue components, extracellular matrix, and proteins with a slow turnover rate are extra vulnerable, and components such as collagen, abundant in tendons and fascia tissue, become cross-linked, losing their properties.[218 219] The formation of AGEs has previously been associated with several fibroproliferative diagnoses e.g., idiopathic pulmonary fibrosis[220] and diabetic cardiomyopathy,[221] but also with musculoskeletal diagnoses, such as frozen shoulder.[222] In the case of DD, biopsies from the palmar fascia have shown higher levels of AGEs among patients with DD compared to a control group,[223] but whether these findings are consistent in individuals with DM is currently unknown. However, one of the proposed cellular mechanisms responsible for the *contracture* in DD is the conversion of fibroblasts to myofibroblasts. It has been proposed that

AGEs interact with fibroblasts by upregulating intracellular transforming growth factor (TGF)-β through their cell surface AGE-receptor.[224 225] Indeed, an increased genetic expression of TGF-β has been shown in biopsies from palmar fascia in DD.[226] Finally, TGF-β is thought to increase collagen synthesis as the typical palmar chord is formed but also increase the contracture of the finger as the disease progresses.[227] Taking this together, it appears that, as a result of prolonged hyperglycaemia in DM, AGEs can act through intracellular signalling, increasing the activity and conversion rates of fibroblasts to myofibroblasts, which in turn contributes to disease progress in DD.

The pathogenesis of TF is not as well understood and researched as that of DD, especially in the presence of DM. As described in Chapter 1.2, the trigger phenomenon is thought to occur due to a disproportion in size between the tendon and surrounding tendon sheet, causing the finger to lock in a flexed position,[112] usually at the level of the A1 pulley. There are studies using ultrasound that indicate a thicker A1 pulley in TF, but also signs of tenosynovitis as well as flexor tendinosis, flexor tendon thickening, and formation of tendon nodules, suggesting that tendon pathology is a factor in TF.[104 106 228 229] Furthermore, biopsies from the tendon in patients with TF have shown signs of tendinosis, i.e., histological signs of micro-ruptures and synovial inflammation.[230] Such findings could potentially be induced or aggravated by hyperglycaemia and DM. Undoubtedly, biopsies from the A1 pulley in individuals with DM do show increased oxidative stress as well as neovascularization, a possible sign of diabetes-induced hypoxia, especially in individuals with poor glycaemic control.[231 232] DM has also been shown to induce tendinopathy with subsequent thickening of tendons.[233] It has been proposed that activation of the polyol pathway, as described above, also contributes to tendon swelling due to the accumulation of hyperosmotic proteins within the tendon. Finally, AGEs are also thought to contribute to the pathogenesis in TF by disrupting tendon homeostasis by the cross-linking of collagen, thus increasing stiffness of the tendon.[234 235] A thicker tendon, tendon sheet or A1 pulley due to fibrosis and collagen deposition, partly as a consequence of DM, might all contribute to the pathogenesis of TF **(Figure 13)**.

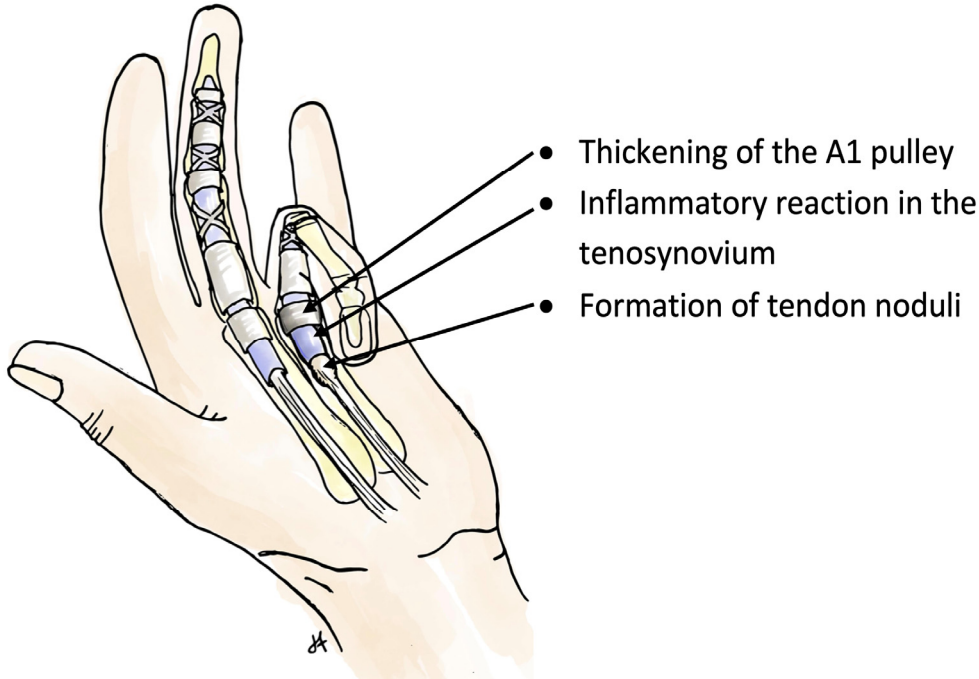


Figure 13.
Illustration by Linnea Arividsson. Potential explanatory factors behind the trigger phenomena in TF. With permission.

Interestingly, genetic studies from biopsies collected from the A1 pulley in patients undergoing OTFR show an upregulation in several genes linked to collagen production, but also an upregulation in TGF-β, indicating a possible shared pathogenesis with DD as well as other fibroproliferative disorders.[236] It remains unknown whether an increased formation of AGEs as a consequence of DM also contributes to increased fibrosis through the TGF-β signalling pathway in TF, analogous with DD, but it is an interesting pathway for continued research. In addition, TGF-β signalling has been linked to increased fibrosis in the connective tissues also within the carpal tunnel among patients with CTS.[237 238] Finally, a recent GWAS study from the UK Biobank found a shared genetic susceptibility between CTS and TF and increased levels of insulin-like growth factor (IGF)-1, another marker of fibrosis, in plasma samples in individuals with both TF and CTS. The study suggests that IGF-1 signalling contributes to the pathogenesis in both conditions.[110 239]

To summarise, it appears that DD and TF, and possibly also CTS, share several distinct pathological pathways related to fibrosis, all contributing to the development and progress of the diseases, both on a biochemical and possibly also on a genetic level. Several of these pathways seem to be amplified by DM, as indicated not only by the epidemiological findings of increased prevalence and

incidence rates in the diagnoses, but also by the evidence of a dose-relationship between HbA1c levels and TF found in the studies included in this thesis.

Osteoarthritis of the CMC-1 joint (Study I)

As described in Chapter I, hand osteoarthritis is a heterogenous disease, which can affect any of the 27 joints in the hand, although with a preponderance in the distal interphalangeal joints and the CMC-1 joint. Study I presents observational data indicating an increased prevalence of OA of the CMC-1 joint in both men and women with either T1D or T2D, compared to controls. Furthermore, the incidences were all higher in individuals with DM, with the exception of T1D among men where there was no difference to controls. As previously mentioned, there are conflicting results in the literature with regard to DM and the risk of hand OA. Indeed, some observational studies indicate that DM is a risk factor for OA, while others only observed it within subsets of hand OA, in specific age groups, or found no correlation at all.[240 241 242] The causative elements in hand OA, and especially OA of the first CMC-1 joint, are still unclear, and further research is warranted to elucidate the intricate interplay between OA and metabolic factors.

In Study I, although the prevalence rates were certainly higher among individuals with DM, the effect sizes for OA of the CMC-1 joint were markedly lower than for, e.g., CTS and TF. Furthermore, the presented data were not adjusted for potential confounders, as described in detail below. As BMI most likely acts as a confounder,[243] correlating both with DM and the risk of OA, the results must be interpreted with this limitation in mind. On this subject, there are a number of studies indicating that both overweight and obesity are risk factors for hand OA.[126 244 245] Indeed, our group has also presented data concerning an increased risk for OA of the CMC-1 joint among obese individuals of both sexes, in a large cohort study where over 30,000 individuals were followed for 40 years.[120] Proposed pathophysiological mechanisms for this somewhat unexpected association, since the CMC-1 joint is not a weight-bearing joint, include a low-systemic inflammation in obesity, secretion of pro-inflammatory cytokines from the adipose tissue and also an upregulation of certain hormones, e.g., relaxin, in obese individuals, possibly inducing joint instability and disease progress.[246 247]

In summary, the current evidence is limited and a potential causal link between DM, hyperglycaemia, and OA of the CMC-1 joint is yet to be established or discarded through further research. Nevertheless, Study I adds valuable large-scale data on the increased prevalence of OA of the CMC-1 joint among the population with DM.

Correlation or causation – the case of the diabetic hand

As described above, there is strong evidence that CTS, UNE, TF, and DD should be included in the diabetic hand and that the pathogeneses of these diagnoses have many similarities and share several biochemical pathways. Both metabolic and environmental as well as genetic and occupational factors interplay and contribute to the development of the presented diagnoses. To single out one exposure as the main driving factor and to prove causation is always perilous. With that being said, causation is always an interpretation of available evidence, it is an issue of judgment and inference, not an entity or a fact in observational studies. Causation has been called a continuum from very unlikely to very likely and it is seldom proven or absolute.[248] One of the most cited frameworks for causal inference is the Bradford Hill criteria, published in 1965 by Sir Austin Bradford Hill.[249] This framework has helped epidemiologists and researchers throughout the years to justify their verdicts concerning potential causation.[43] [250] The Bradford Hill criteria include nine viewpoints that will, very briefly, be assessed in relation to the results and conclusions stated in this thesis.

First, there is certainly *strong* evidence for causation presented in this thesis. Several of the diagnoses were up to 6-8 times as prevalent among individuals with DM and, except for OA of the CMC-1 joint, all had an incidence rate ratio above 1.9.

Second, there is *consistency* in the findings across different study designs and populations, both in the presently included studies and particularly when earlier studies and meta-analyses from different research groups in different parts of the world are included.

Third, regarding *specificity*, DM causes several other diseases apart from the diagnoses included in the diabetic hand, but a causative factor only seldom has one single effect. Likewise, there are several other factors, apart from DM, that influence the risk of developing the diagnoses in the diabetic hand. Adjusting for these confounding factors in studies II-IV is a way of increasing *specificity*.

Fourth, throughout this thesis, a diagnosis of DM preceded the outcome, thus ensuring correct *temporality* and minimising the risk of reverse causation.

Fifth, greater exposure to a risk factor (in study IV: HbA1c) led to greater risk of developing the disease (TF) and study IV presents a dose-response relationship between HbA1c and TF, thus confirming a *biological gradient.* Further studies are warranted to investigate whether these findings also apply to CTS, UNE, and DD.

Sixth, concerning *plausibility*, the discussion in this chapter has provided a pathologic basis and framework, explaining the potential causal relationship between DM and the diabetic hand. My own clinical experience, and probably that of many other hand surgeons, indicates that the clinical view also supports *plausibility*. As previously stated, 22% of all patients undergoing a first time OTFR in study V had DM.

Seventh, *coherence* is the assessment of whether the association found is compatible with existing theory, evidence, and knowledge. Indeed, the diabetic hand has been discussed since the 1970s and the data presented throughout this thesis are in line with previous studies and meta-analyses, all referred to in respective chapters.

Eighth, the results and conclusions presented are in line with *experimental* pre-clinical, genetic and animal studies (especially on diabetic neuropathy in rats)[187] as well as e.g., *experimental* studies using sonography and MRI, as previously referred. This thesis adds *experiments* in the form of population-based cohort and register studies. What is missing is the form of experiment comprising larger, randomized controlled trials, e.g., investigating whether strict glycaemic control reduces the risk of hand complications, discussed further below.

Finally, the ninth criterion of *analogy* can be assessed by considering the abundance of evidence that exists for other diseases that are caused by DM. Cardiovascular disease, retinopathy, nephropathy, as well as other musculoskeletal complications, as discussed in the introduction section, are known and established complications stemming from DM, and analogous with the diabetic hand.

On a final note, the gold standard for proving causal inference in epidemiology today is a randomised controlled trial in which individuals are allocated into an exposure and a control group and followed over time. In the case of the diabetic hand, a study design allocating individuals into a "high HbA1c" or "poor glycaemic control" group would be neither ethical nor particularly practical. Instead, a so-called mendelian randomisation (MR) analysis could possibly be used to further strengthen the causal relationship between DM and the diabetic hand. Very briefly, MR relies on the measurements of genetic variants that have already been associated with the exposure of interest (DM) in, for example, a prior GWAS. Using these genetic variants, often converted into a polygenetic risk score, as proxies for the exposure of interest, associations between the genetic variants and the outcome are calculated and analysed. Although outside the scope of this thesis, MR is less prone to bias and confounding (discussed below) compared to traditional observational studies in epidemiology.[251 252] Interestingly, MR studies have previously been used to provide evidence for a causal relationship between T2D and various diseases, e.g., increased risk of coronary heart disease,[253] but have also been introduced in the field of hand surgery. In a recent publication using MR, an association between T2D and CTS was found, adding data to support the causal relationship between DM and compression neuropathies presented in this thesis.[254] Finally, a recent study using MR in data from the UK biobank found a lower risk of DD among individuals with a raised BMI, where the authors concluded that adiposity is causally protective against DD,[208] a result similar to the findings in study III in this thesis as previously mentioned.

With this being said, and the Bradford Hill criteria assessed, none of these nine criteria alone can provide a verdict on causation. However, after writing this thesis,

I have the highest confidence in the conclusion presented which is: that there is an entity in the diabetic hand; that hand surgical diagnoses cluster among individuals with DM; and that CTS, UNE, TF, and DD should all be included when referring to the diabetic hand. As for OA of the CMC-1 joint, there is, in my view, insufficient evidence and too many conflicting results to state a causal inference between the diseases. Finally, further studies are warranted, especially in the genetic field, to assess the shared genetic traits between DM and the diagnoses in the diabetic hand.

> "All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." - Austin Bradford Hill, 1965

Taking all this together, I sincerely believe that this thesis has added valuable work, especially for individuals with DM, and that the results I have presented will contribute positively to the field of hand surgery by providing better and evidence-based care for patients with DM.

5.2 Methodological considerations

Most studies within the field of epidemiology, including those in this thesis, investigate the relationship between an exposure (DM) and disease (hand surgical diagnoses) using various statistical methods. One of the challenges in epidemiology is to assess whether the observed statistical association actually reflects a true causal association between the exposure and disease. The Bradford Hill framework for causation has already been discussed, but a more thorough examination of alternative explanations, limitations, and misclassification of the data, as well as potential bias and confounding, is needed if one is to draw conclusions about causality. This section will discuss the strengths and limitations of the individual studies, but will first describe some important methodological concepts, such as internal and external validity, confounding and bias in relation to this thesis.

External validity

It is often necessary due to various factors in epidemiology, to draw conclusions from a small study sample. External validity **(Figure 14)** refers to whether such conclusions are valid and can be generalised to the whole population.[255] One of the main strengths of this thesis and the studies included is the large size of the populations in the registers and cohorts, as well as the ability to cross-link data between the registers, combining them into massive data sets. This allows for different kinds of studies, both cohort studies (studies II and III) as well as retrospective register studies (studies I, IV, and V), possibly increasing external

validity and generalisability. Furthermore, the large data sets also allow for stratification for sex and diabetes type, which is not always possible in smaller data sets. This stratification adds to the external validity as we can draw conclusions regarding both sexes and both major types of diabetes, at the same time minimising the risk of confounding. A large population also reduces the risk of random sampling bias (discussed below) which in turn increases the generalisability of the results and conclusions. One limitation of the external validity is that all the studies included were conducted within Sweden. Inclusion of data from international registers in attempts to repeat the findings in this thesis would certainly improve the external validity. Additional threats to the external validity are discussed in the individual limitations of the studies below.

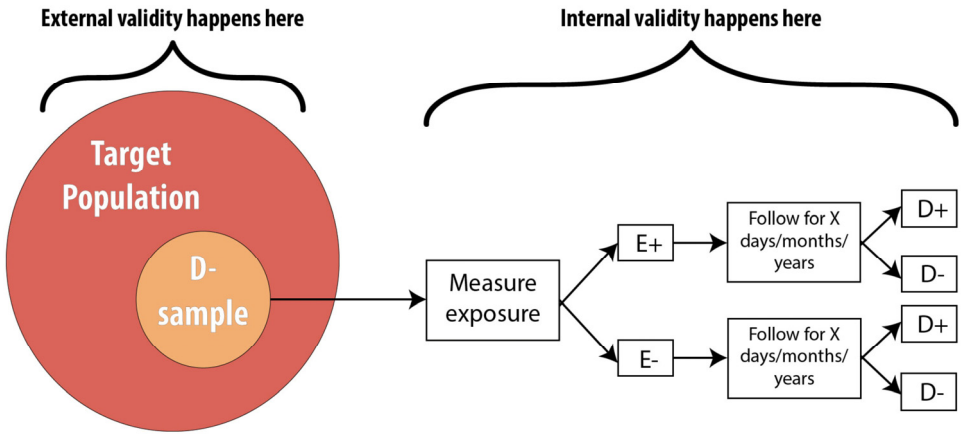


Figure 14.
Illustration of external versus internal validity in a cohort study design. Reprinted with permission from the publisher under CC BY-NC. [256]

Internal validity

Internal validity refers to the accuracy of the study design and whether the study can establish a trustworthy relationship or association between exposure and outcome; i.e. if the study reflects the truth and if there is indeed cause-and-effect between exposure and outcome. Both systematic and random errors in the study can affect the internal validity. As random errors are harder for the researcher to control because they occur by chance and include imprecise measures (some individuals forgetting to fast before a fasting glucose test, physicians entering a wrong diagnosis code by mistake, etc.), they are often evaluated by conducting a statistical test with confidence intervals and a corresponding p-value (indicating the probability / likelihood that the observed finding is a result of chance). Increasing sample size and meticulous input of variables and laboratory values in the registers are ways in which random errors could be reduced. As mentioned above, the large sample sizes throughout this thesis represent one of its strengths. Significant systematic errors,

or bias, that affect the internal validity are selection bias, misclassification bias, and confounding, as discussed below.

Selection bias

Selection bias occurs when there is a systematic difference in selection of the exposure and control groups in, for example, a cohort study. Individuals with DM entering the MDCS cohort might be more motivated and more actively seeking healthcare than individuals without DM, thus introducing a selection bias into the study. This is further discussed below in Chapter 5.3. Selection bias can also affect the external validity of the study if the population entering the cohort is substantially different from the entire population This is also further discussed in Chapter 5.3. Studies I, IV, and V use population-based data from the entire population in the Region of Skåne and all patients undergoing OTFR in the HAKIR database, respectively. This minimises the risk of selection bias, adding to the validity of the studies. [256 257 258]

Misclassification bias

Misclassification bias can be divided into misclassification of exposure and misclassification of outcome. With reference to exposure, this thesis has relied mainly on high quality data from the NDR, previously described in detail in Chapter II, to minimize the risk of systematic misclassification of exposure. Individuals in the NDR are also often followed over several years, and have multiple measurements of exposure, e.g., HbA1c levels, further reducing the risk of misclassification bias.[259 260] Concerning outcome misclassification, one of the limitations in this thesis is that to date there is no accepted Swedish national consensus about diagnostic criteria for any of the hand-arm diagnoses included throughout this thesis. Most diagnoses are based solely on clinical examination, although sometimes electrophysical examinations are used to aid the clinician in diagnosing e.g., compression neuropathies. When data from primary care (studies I and IV) are included the risk of misclassification is possibly increased, as some physicians might only rarely encounter the more uncommon diseases, such as UNE. However, potential misclassification of outcome probably does not vary between individuals with and without DM and can therefore be classified as nondifferential misclassification (rates of misclassification are the same in each exposed group). Furthermore, studies II, III, and V include only diagnoses from hospital-based, specialist care, mainly made by specialists in hand or orthopaedic surgery familiar with the diseases included in the diabetic hand. Having several study designs, using different data sets from both primary and hospital-based care, with results pointing in the same direction, strengthens the causal inference between exposure and outcome, as discussed above.

Confounding

Finally, an important concept in epidemiological studies is confounding. As *random errors* in a study are attributed to *chance* and handled by statistical modelling with confidence intervals and p-values, and *bias* is systematic errors handled by the investigator by using the best study design possible, confounding is the effect of a third variable that is associated with both the exposure and the outcome. If it is not handled correctly, confounding can distort the true relationship between exposure and outcome and lead the researcher into drawing inaccurate conclusions.[260] This is particularly true in a cohort study, where the exposed and un-exposed groups might differ in baseline characteristics, e.g., individuals with DM being older at baseline. As age is also associated with the risk of CTS, age acts as a confounder and must be handled accordingly **(Figure 15)**.

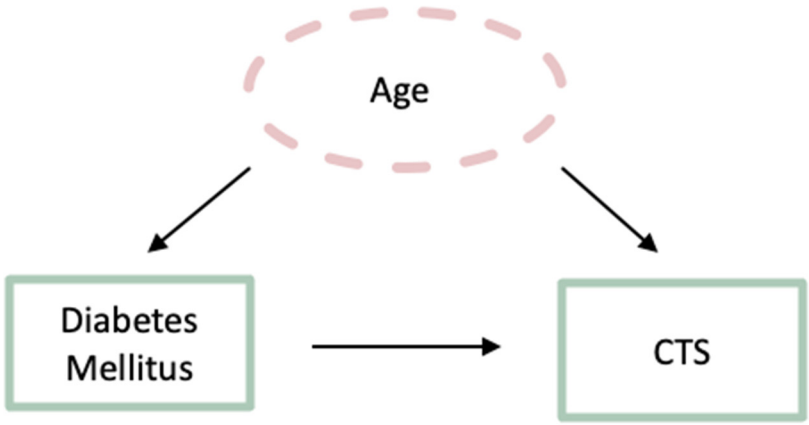


FIGURE 15.
Age as a confounding variable, associated with both diabetes mellitus (exposure) and CTS (outcome).

There are multiple ways of handling confounding. Stratification of the data (studies I, III, IV, and V) and adjusting for confounders (studies II – V) in a multivariate regression analysis are two common ways which are further discussed below in Chapter 5.2.[261] However, in real life it is virtually impossible to collect all data that could possibly affect both exposure and outcome. The term *residual confounding* is therefore used to refer to the confounding effect remaining after stratification and adjustment.[260] Throughout this thesis, the lack of genetic data could definitely be seen as residual confounding and is an obvious limitation. It is possible that DM and hand surgical diagnoses share some common genetic factors and shared genetic variations may be considered a potential source of confounding and a potential explanation for, at least some, of the observed associations and conclusions presented. Further studies are warranted to explore potential shared genetic traits

between DM and the diagnoses included in the diabetic hand to further strengthen conclusions presented throughout this thesis regarding the causal inference.

5.3 Study-specific strengths and limitations

Study I

The major strength of study I is the large, population-based data from over 1.1 million adult inhabitants in the Region of Skåne, making this study one of the larger epidemiological studies conducted concerning diabetic hand complications. Moreover, the inclusion of data from both primary and specialised care is one of the strengths and unique features of the study. Studies that include data from hospital-based care alone might underestimate the true prevalence of a diagnosis, since many cases are handled only in primary care and never get referred to a specialised clinic. Nevertheless, the data presented here only reports the epidemiology of physician-based diagnoses. There will be individuals who are only treated by hand therapists or physiotherapists, and also individuals who do not seek healthcare at all for their symptoms. One might thus argue that this study presents data concerning clinically relevant diagnoses within the study population rather than data concerning the "true" prevalence in the general population. A survey carried out in the general population, like that conducted by Atroshi et al.[262] for CTS, might be an interesting complement and could include additional diagnoses. On a final note, the true prevalence in the general population might also be higher since data were only available for the years between 2004 and 2019, and patients diagnosed before 2004 are not included in the prevalence calculations.

Studies II - III

Both studies II and III used data from the MDCS cohort, previously described in detail in Chapter 3.2. The major strength of this cohort is firstly its prospective, longitudinal design, allowing for a long follow-up time (20+ years), but also its size, making these studies some of the largest epidemiological studies addressing risk factors for compression neuropathies (study II) and DD (study III) published to date. The longitudinal design, with meticulous collection of baseline data, allows the verification of a correct temporal association between the exposures and outcomes studied, i.e., DM occurring *before* a hand diagnosis. This minimises the risk of recall bias among the participants, which is frequent in other study designs, such as case-control studies.[263] Furthermore, it also constitutes one of the cornerstones of causal inference, as described above.

However, it is possible that participants with a chronic disease, such as DM, were more often examined by a physician during follow-up, making it easier for them to mention symptoms of the hand thereby increasing the incidence in the group with

DM, and introducing detection bias**.** However, the large number of individuals, randomly selected over several years, counteracts this bias. Moreover, the recruitment process and attendance rate (41%) at baseline can potentially introduce other forms of bias that have to be addressed before interpreting results and reaching conclusions. As previously mentioned, whether these conclusions are valid and can be generalised to the whole population is called external validity. Previous studies on the representativity and selection bias of the MDCS cohort have reported better health among participants in the MDCS compared to non-participants, as well as higher mortality among non-participants.[154] However, at the time of recruitment, there were no plans for research within the field of hand surgery, thus limiting the chance of selection bias in relation to the outcomes studied throughout this thesis. In addition, demographics in the city of Malmö have changed dramatically since the recruitment of the individuals in the MDCS cohort. Approximately 89% of the MDCS cohort were born in Sweden whereas closer to 30% of the Malmö population in 2022 were born outside Sweden.[154 264] This, of course, has wide implications for the external validity of the studies and conclusions drawn from the cohort. The results might not be generalisable to the population living in Malmö today. This obviously needs to be kept in mind when interpreting the results.

Further limitations include not being able to reliably stratify for T1D and T2D in the MDCS cohort. Individuals with DM were, at the time of recruitment, often classified as "insulin-dependent" and "non-insulin dependent" since the diagnostic criteria of T1D and T2D were not then as stringent as they are today. Another limitation of the study design is that it only includes baseline characteristics, e.g., smoking, alcohol consumption, and BMI that were measured only once. These habits and characteristics might, of course, have changed over time among some participants. In contrast, and to avoid this limitation, study IV uses a different study design, where a mean value was created from several measures over time, sometimes up to 15 years, creating a variable that might better reflect an individual's fluctuation over time.

Study IV

Study IV cross-linked data from the SHR and NDR, creating a large data base covering the vast majority of individuals with T1D and T2D within the Region of Skåne, including all individuals with a diagnosis of TF in both primary and secondary care. This design and the cross-linking of data are the major strengths of the study together with the size of the population studied. The study design allows firstly stratification and separate risk calculations for T1D and T2D, but also stratification for sex. The study is, to the best of my knowledge, one of the first and largest studies to do this. Furthermore, the high quality of the registers used is a major asset; the NDR, particularly, because of its meticulous registrations of laboratory values, anthropometrics and medications and the SHR for its high

coverage rate, mandatory registration, and data transfer of physician-made diagnoses from caregivers.

It is worth noting one limitation of study IV which is that it only included individuals within the Region of Skåne, meaning that the findings might not be generalisable to a different population. Replication of the findings in the study with a different population is necessary in order to improve external validity. Moreover, the study is dependent on accurate registration in the registers used. Misclassification, as previously discussed, is an important concept in epidemiological research. The NDR has taken steps towards limiting misclassification as registrations are either derived from automatic electronic transfer of physician-made diagnoses, or by a nurse, often in primary care, who specializes in diabetes care. The SHR relies on an automatic transfer of diagnoses to the register and there have been several validation studies, discussed above in Chapter 3.1. Finally, the adjustment for confounding factors, also discussed above, is a further step towards improving the internal validity of the study, providing proof of the causal relationship between hyperglycaemia and the risk of TF.

Study V

Study V investigated surgical outcome and patient experience after OTFR in individuals with T1D and T2D in comparison with individuals without DM. Like the other studies in this thesis, its major strength lies in the large population studied, allowing for stratification for diabetes type and sex. In comparison, two recent studies investigating outcome after OTFR in patients with DM included 192 and 69 patients, respectively, well below the nearly 7,000 individuals included in this study.[216 217] However, the major limitation in study V, as in many studies using patient-reported outcome data, is the low response rate from patients undergoing OTFR.[265] As only 53% of the population answered just one questionnaire, it is essential to improve the response rate in the future in order to more accurately describe the outcomes studied in HAKIR. Measures have been taken in order to achieve this, e.g., automatization and digitalisation of the questionnaires and by simplifying the login functions in HAKIR to make registration easier for the patients. Having dedicated staff at each participating unit, responsible for the quality and management of the register data, are also steps towards increasing the response rate.

An interesting note is that there have recently been some studies conducted, analysing PROs among non-responders. One study from a hand surgical centre in the UK reported no difference in predicted QuickDASH response when comparing responders (55% in the study) to non-responders, indicating an acceptable loss to follow-up at 45%.[266] Similarly, equally satisfactory results were reported among responders and non-responders after hip and knee arthroplasty when the non-responders were contacted by telephone.[267] This study also reported a preference among elderly patients aged ≥ 67 years to be contacted through postal, rather than

electronic, questionnaires. It is not known whether this also applies to patients undergoing hand surgery, but allowing patients to choose the form of contact might be one way of increasing the response rate.

Finally, with regard to the previous discussion on confounding, the regression models in study V were adjusted for age at surgery and stratified for sex but included no adjustments for other comorbidities. This limitation regarding the internal validity should be kept in mind when analysing the result from the study, as discussed above.

> "If you eliminate the impossible, whatever remains, *however improbable*, must be the truth." – Sherlock Holmes

Chapter 6: Conclusions

6.1 Main Conclusions

DM is a major risk factor for, and contributes to, the pathogenesis of several hand surgical diagnoses as presented in this thesis. There is strong evidence that CTS, UNE, TF, and DD should be included in the diabetic hand and that there are many similarities in their pathogenesis and several shared biochemical pathways. Below follows the major conclusions presented in the individual studies included in the thesis:

Summary and key findings:

- There is a high prevalence of the diagnoses included in the diabetic hand in individuals with T1D and T2D. This should be kept in mind when examining patients with hand problems and concurrent DM. (Study I)
- DM is a major risk factor for the development of both CTS and UNE among middle-aged individuals during long-term follow-up. (Study II)
- DM and excess alcohol consumption constitute major risk factors for the development of DD in middle-aged individuals of both sexes. (Study III)
- An elevated HbA1c is a risk factor for TF among individuals with T1D or T2D. Optimal treatment of DM seems to be of importance for the prevention of diabetic hand complications. (Study IV)
- Patients with T1D and T2D can achieve the same results after OTFR as individuals without DM, although the improvement might take longer, especially among women with T2D. (Study V)

6.2 Clinical implications

Although the care of patients with DM in Sweden is mainly excellent, the data presented in this thesis provide solid evidence that individuals with DM still suffer from more hand complications than individuals without DM. The results of this

thesis will hopefully have several clinical implications and will ultimately contribute to improved care for individuals with DM. Regarding clinical implications, I see four main areas of interest: *information*, *collaboration*, *prevention*, and *expectations*.

Information is key to raising awareness of the diabetic hand among patients, but also among physicians, nurses, physiotherapists, and occupational therapists alike. As previously mentioned, many patients never see a hand surgeon and mainly receive their diagnosis and treatment from healthcare providers in primary care, who then play a critical role in the early detection and management of these diagnoses. It is thus important to raise awareness among healthcare providers in primary care of the increased prevalence, but also of the fact that hand symptoms co-exist with other diabetes-related complications, such as neuropathy, nephropathy, and retinopathy. Furthermore, information provided to primary care that optimal treatment of both T1D and T2D can be preventive, could possibly prevent several cases of hand complications each year. Thus, provision of better information, and optimal treatment of DM, could possibly prevent several cases of diabetes-related hand problems which would otherwise require treatment at departments of hand surgery or orthopaedics.

As for *collaboration*, initiating an outpatient clinic together with endocrinologists, physiotherapists, occupational therapists, and hand surgeons or orthopaedic surgeons for patients with severe hand symptoms, could possibly improve the care for patients with DM. This type of multidisciplinary team care is already well established for patients with diabetic foot ulcers but is yet to be started for individuals with hand diagnoses. In this type of outpatient clinic, more aspects of the patient's disease would be addressed and coordination of care between specialists could ensure the best possible outcome for the patients. With this dissertation, I hope to be able to motivate the creation of such an outpatient clinic, with the goal of ultimately reducing, or at least postponing, morbidity associated with diabetes.

As for *prevention*, the ultimate goal for individuals with DM is to prevent the development of complications related to their disease. I hope that, with the writing of this thesis, I may further motivate patients to control their blood sugar levels by providing solid evidence of a reduced risk of complications in the hand with lower HbA1c levels. I also hope that this thesis can work as motivation for high-risk individuals to prevent T2D altogether, inspiring individuals at risk to initiate early life-style interventions and management. This is crucial, not only for preventing hand complications but for the prevention of other life-threatening complications and morbidity alike.

Finally, regarding *expectations*, this thesis provides valuable data concerning patients' experiences after surgery for TF. Being able to correctly inform patients with TF and concomitant DM about rehabilitation time and the somewhat slower

recovery rate compared to individuals without DM, particularly since patient expectations are closely related to postoperative outcome and experience,[268] will hopefully improve the care for these patients.

6.3 Future perspectives

I am hopeful that this thesis will serve as a foundation for both future research in the field of DM complications of the hand, but also for improved treatment of hand surgical diagnoses. For the future, I see six main areas for continued research that I would like to explore.

The first research area is the continued investigation into whether strict glycaemic control effectively reduces the risk for all diagnoses related to the diabetic hand. This could be done in a clinical setting, e.g., by prospectively following a number of patients with T1D and T2D, carefully monitoring glycaemic control and noting the incidence of both hand surgical diagnoses and operations prospectively over a number of years. It could also be done in a retrospective way, using the same study design as in study IV and data from the NDR and SHR.

The second research path is further investigation of surgical outcome and patient experience among individuals with DM for other types of hand surgical operations (trigger finger already being investigated in this thesis). Our group has previously reported surgical outcomes after OCTR among patients with DM,[28] but solid research into outcomes after surgery for DD and OA of the CMC-1 joint is still lacking.

The third area I hope to be able to explore is the further development of HAKIR, modernising the register to improve the response rate, among other things. One way to improve the register could, for example, be to individualise the PRO questionnaires for each diagnosis. For example, cold sensitivity and numbness might not be a necessary outcome to study after OTFR. Minimizing the number of questions needed in a PROM might improve the willingness to respond among patients. Furthermore, interesting research efforts have been conducted using computerised algorithms (MCAT - multidimensional computerized adaptive testing) in order to automatise and reduce the number of questions in the DASH questionnaires after surgery for Dupuytrens disease, but still accurately estimate patient outcome.[269] It would be interesting to adapt a similar MCAT for HAKIR in order to reduce the number of questions, limiting the time consumed and hopefully increasing the response rate.

Fourth, there are a number of patients with serious complications related to their DM, e.g., patients with lower limb amputations, who also have concurrent hand diagnoses. To start a new outpatient clinic, managed together with a team of

endocrinologists, hand therapists and hand surgeons, could potentially improve the care for these patients. As previously mentioned, this type of multidisciplinary team is yet to be started for individuals with hand diagnoses. Qualitative methodology e.g., interviewing patients in focus groups or in one-on-one interviews could be used to further investigate patient experience in this type of outpatient clinic.

A fifth area would be further investigation of the genetic background to the diabetic hand, to find common genetic traits between DM and hand diagnoses. For example, previous studies have found a shared genetic background between CTS and TF.[110] Expanding this research to include genetic traits for DM, possibly through a mendelian randomisation study, would be an interesting next step. Studies of this type are of importance in order to further elucidate the causal link between DM and hand surgical diagnoses.

A sixth path, and a natural continuation from this thesis, would be to further explore additional musculoskeletal diagnoses that could possibly be related to DM. It would be especially interesting to further investigate the diabetic shoulder, including diagnoses, such as adhesive capsulitis (AC).[270] AC is also a fibroproliferative disorder, which possibly shares some pathobiology with DD. Indeed, a recent study from the UK Biobank found several genetic loci involved in pathologic fibrosis, shared among the diseases.[271]

On a final note, it is important to remember that the vast majority of patients with the diagnoses described throughout this thesis do not have DM. However, a number of patients presenting with e.g., TF or CTS will develop DM *after* being diagnosed. A recent publication from the USA found a staggering 60% prevalence of prediabetes among individuals with bilateral compression neuropathies when investigating 183 patients with an oral glucose test and fasting plasma glucose levels.[272] One might then hypothesise that it might be possible to predict who will develop, or at least who has a higher risk of developing, T2D using the data from our Swedish registers. To create a prediction model for T2D, including variables such as sex, age, various comorbidities, and anthropometrics to identify high risk individuals might be possible using today's modern registers. An early diagnosis of TF or CTS could then act as a first warning sign of T2D, for example in patients with a positive family history of DM. Identifying these patients at increased risk could potentially prevent several cases of T2D every year, improving quality of life and minimising future morbidity for the patients.

Acknowledgements

Lars Dahlin

The second Professor Lars to enter my life. I have so much to thank you for. First for giving me this opportunity and for trusting Malin that to take on one last doctoral student could be a good thing – even in your 60s, but also for giving me the freedom to go on my own scientific journey, always trusting in me to deliver manuscripts and meet deadlines. Your never-ending curiosity and interest in new ideas and methods are an inspiration to all of us. Your will to guide me into the world of hand surgery and PhD studies is something that I will always be grateful for.

Lars Rydberg

The first Professor Lars to enter my life and my beloved father, to you I owe everything. Having a professor as a father is not always easy. On our adventures, from being stopped at military roadblocks in rural Mozambique to high altitude climbing in the Alps, we have had some fantastic times. For a child, it was hard to know what a professor in oceanography did on a day-to-day basis. Having completed my own PhD studies, I think I understand more of what it meant for you to have your own PhD students in different parts of the world – always being the first one up in the morning, reviewing manuscripts and papers. You are indeed my strongest source of inspiration.

Malin Zimmerman

My dear friend and co-supervisor Malin first introduced me to the wonderful world of register studies back in 2018. Never did I expect to end up at this place when you first showed me your excel documents, packed with CTS data. Your enthusiasm and ability to get things done will always be an inspiration to me.

Anders Gottsäter and Peter Nilsson

My dear co-supervisors. Thank you for sound advice and introducing me to the world of diabetes and cohort studies. Your input during manuscript revision and the sometimes tiresome publication process have been invaluable.

Anette Chemnitz and Antonio Abramo

My clinical supervisors and mentors. Thank you for being an inspiration in the clinical field of hand surgery and for pushing me in the operation room. Your skills are great and awe-inspiring. May I one day be as skilled and knowledgeable as you.

Niklas and Lars

Sons of Inger crew. Research is indeed a funny thing. I am tremendously grateful for our long friendship.

Christian, Christian and Martin

Gunz n golf crew. Nothing would have been done without the heavy liftin', saunas, beers and golf. Ph.Done.

Fredrik

My life-long friend. Thank you for bringing me along to the orthopaedic department back in 2010, starting it all, and for all the support during tough times. And for all the laughs and fish.

Linnea Arvidsson

For the help with amazing illustrations.

Tina and Sharon

For all the administrative help and laughs at "plan 3".

Inger Rydberg

My dear mother – thank you for always being there for me and for all the love and support. And also for all the help with little August, it has truly been invaluable and has given me the time to write this thesis.

Emma and Andrej

Thank you for the help with artwork and fantastic cover photo. And thank you for being such a lovely extended family for August.

Maja and Johanna

My dear sisters. Thank you for all the support over these years.

Linnea and August

My beloved family. You are everything. Thank you for your patience over all these years. And thank you August – little one – for coming into this world, early and restless like your father. You are the light of my life. I love you both.

Finally, all dear colleagues and friends at the Hand Surgical Department in Malmö and Orthopaedic Department in Helsingborg. Without your support, nothing would have been done.

References

1. Sapra A, Bhandari P. Diabetes Mellitus. StatPearls. Treasure Island (FL): StatPearls Publishing LLC. 2022.
2. Zajac J, Shrestha A, Patel P, et al. The Main Events in the History of Diabetes Mellitus. In: Poretsky L, ed. Principles of Diabetes Mellitus. Boston, MA: Springer US 2010:3-16.
3. Tattersall RB. The History of Diabetes Mellitus. Textbook of Diabetes 5ed2017:1-22.
4. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *The Lancet Diabetes & Endocrinology* 2018;6(5):361-69.
5. Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;63(9):1671-93.
6. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *The Lancet Diabetes & Endocrinology* 2022;10(10):741-60.
7. Khan MAB, Hashim MJ, King JK, et al. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* 2020;10(1):107-11.
8. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice* 2022;183:109119.
9. World Health Organization. Diagnosis and Management of Type 2 Diabetes. 2020(WHO/UCN/NCD/20.1)
10. American Diabetes Association Professional Practice C. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2021;45(Supplement_1):S17-S38.
11. Holt RIG, DeVries JH, Hess-Fischl A, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44(11):2589-625.
12. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *The Lancet* 2018;391(10138):2449-62.
13. Dayan CM, Besser REJ, Oram RA, et al. Preventing type 1 diabetes in childhood. *Science* 2021;373(6554):506-10.

14. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Science Translational Medicine* 2021;13(583):eabc8980.
15. Fernández-Verdejo R, Galgani JE. Exploring the sequential accumulation of metabolic syndrome components in adults. *Scientific Reports* 2022;12(1):15925.
16. Volaco A, Cavalcanti AM, Filho RP, et al. Socioeconomic Status: The Missing Link Between Obesity and Diabetes Mellitus? *Curr Diabetes Rev* 2018;14(4):321-26.
17. Riddle MC, Cefalu WT, Evans PH, et al. Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism* 2022;107(1):1-9.
18. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *The Lancet* 2017;389(10085):2239-51.
19. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nature Reviews Nephrology* 2020;16(7):377-90.
20. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. *Nature Reviews Endocrinology* 2022;18(9):525-39.
21. Wolfsdorf J, Glaser N, Sperling MA. Diabetic Ketoacidosis in Infants, Children, and Adolescents: A consensus statement from the American Diabetes Association. *Diabetes Care* 2006;29(5):1150-59.
22. Sellmeyer DE, Civitelli R, Hofbauer LC, et al. Skeletal Metabolism, Fracture Risk, and Fracture Outcomes in Type 1 and Type 2 Diabetes. *Diabetes* 2016;65(7):1757-66.
23. Choi JH, Kim HR, Song KH. Musculoskeletal complications in patients with diabetes mellitus. *Korean J Intern Med* 2022;37(6):1099-110.
24. Adriaanse MC, Drewes HW, van der Heide I, et al. The impact of comorbid chronic conditions on quality of life in type 2 diabetes patients. *Qual Life Res* 2016;25(1):175-82.
25. Kamiab Z, Shafaee N, Askar PS, et al. Prevalence and Prevention of Rheumatologic Manifestations and their Relationship with Blood Glucose Control in Patients with Type II Diabetes. *Int J Prev Med* 2021;12:142.
26. Jung Y, Hohmann TC, Gerneth JA, et al. Diabetic hand syndrome. *Metabolism* 1971;20(11):1008-15.
27. Papanas N, Maltezos E. The diabetic hand: a forgotten complication? *J Diabetes Complications* 2010;24(3):154-62.
28. Zimmerman M, Eeg-Olofsson K, Svensson A-M, et al. Open carpal tunnel release and diabetes: a retrospective study using PROMs and national quality registries. *BMJ Open* 2019;9(9):e030179.
29. Zimmerman M, Dahlin E, Thomsen NOB, et al. Outcome after carpal tunnel release: impact of factors related to metabolic syndrome. *Journal of Plastic Surgery and Hand Surgery* 2017;51(3):165-71.
30. Stecco C, Aldegheri R. Historical review of carpal tunnel syndrome. *La Chirurgia degli Organi di Movimento* 2008;92(1):7-10.

31. Padua L, Coraci D, Erra C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. *Lancet Neurol* 2016;15(12):1273-84.
32. Currie KB, Tadisina KK, Mackinnon SE. Common Hand Conditions: A Review. *Jama* 2022;327(24):2434-45.
33. Zimmerman M, Gottsäter A, Dahlin LB. Carpal Tunnel Syndrome and Diabetes-A Comprehensive Review. *J Clin Med* 2022;11(6)
34. Osiak K, Mazurek A, Pękala P, et al. Electrodiagnostic Studies in the Surgical Treatment of Carpal Tunnel Syndrome—A Systematic Review. *Journal of Clinical Medicine* 2021; 10(12).
35. Wiberg A, Smillie RW, Dupré S, et al. Replication of epidemiological associations of carpal tunnel syndrome in a UK population-based cohort of over 400,000 people. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2022;75(3):1034-40.
36. Pourmemari MH, Shiri R. Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis. *Diabetic medicine : a journal of the British Diabetic Association* 2016;33(1):10-6.
37. Cazares-Manríquez MA, Wilson CC, Vardasca R, et al. A Review of Carpal Tunnel Syndrome and Its Association with Age, Body Mass Index, Cardiovascular Risk Factors, Hand Dominance, and Sex. *Applied Sciences* 2020; 10(10).
38. Becker J, Nora DB, Gomes I, et al. An evaluation of gender, obesity, age and diabetes mellitus as risk factors for carpal tunnel syndrome. *Clin Neurophysiol* 2002;113(9):1429-34.
39. Otelea MR, Nartea R, Popescu FG, et al. The Pathological Links between Adiposity and the Carpal Tunnel Syndrome. *Current Issues in Molecular Biology* 2022; 44(6).
40. Boz C, Ozmenoglu M, Altunayoglu V, et al. Individual risk factors for carpal tunnel syndrome: an evaluation of body mass index, wrist index and hand anthropometric measurements. *Clinical Neurology and Neurosurgery* 2004;106(4):294-99.
41. Cooke ME, Gu A, Wessel LE, et al. Incidence of Carpal Tunnel Syndrome after Distal Radius Fracture. *J Hand Surg Glob Online* 2022;4(6):324-27.
42. Padua L, Pasquale AD, Pazzaglia C, et al. Systematic review of pregnancy-related carpal tunnel syndrome. *Muscle & Nerve* 2010;42(5):697-702.
43. Lozano-Calderón S, Anthony S, Ring D. The Quality and Strength of Evidence for Etiology: Example of Carpal Tunnel Syndrome. *The Journal of hand surgery* 2008;33(4):525-38.
44. Shiri R, Falah-Hassani K. Computer use and carpal tunnel syndrome: A meta-analysis. *Journal of the Neurological Sciences* 2015;349(1):15-19.
45. Hassan A, Beumer A, Kuijer PPFM, et al. Work-relatedness of carpal tunnel syndrome: Systematic review including meta-analysis and GRADE. *Health Science Reports* 2022;5(6):e888.
46. Lampainen K, Hulkkonen S, Ryhänen J, et al. Is Smoking Associated with Carpal Tunnel Syndrome? A Meta-Analysis. *Healthcare* 2022; 10(10).

47. Baker NA, Feller H, Freburger J. Does Insurance Coverage Affect Use of Tests and Treatments for Working Age Individuals With Carpal Tunnel Syndrome in the United States? Analysis of the National Ambulatory Medical Care Survey (2005-2014). *Archives of Physical Medicine and Rehabilitation* 2019;100(9):1592-98.
48. Rydberg M, Zimmerman M, Gottsäter A, et al. Diabetic hand: prevalence and incidence of diabetic hand problems using data from 1.1 million inhabitants in southern Sweden. *BMJ Open Diabetes Research & Care* 2022;10(1):e002614.
49. Dahlin LB, Perez R, Nyman E, et al. Carpal Tunnel Syndrome and Ulnar Nerve Entrapment Are Associated with Impaired Psychological Health in Adults as Appraised by Their Increased Use of Psychotropic Medication. *J Clin Med* 2022;11(13)
50. Zimmerman M, Nyman E, Steen Carlsson K, et al. Socioeconomic Factors in Patients with Ulnar Nerve Compression at the Elbow: A National Registry-Based Study. *Biomed Res Int* 2020;2020:5928649.
51. Johnson NA, Darwin O, Chasiouras D, et al. The effect of social deprivation on the incidence rate of carpal and cubital tunnel syndrome surgery. *J Hand Surg Eur Vol* 2021;46(3):265-69.
52. Cambon-Binder A. Ulnar neuropathy at the elbow. *Orthopaedics & Traumatology: Surgery & Research* 2021;107(1, Supplement):102754.
53. Aleksenko D, Varacallo M. Guyon Canal Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing copyright © 2022, StatPearls Publishing LLC. 2022.
54. Caliandro P, La Torre G, Padua R, et al. Treatment for ulnar neuropathy at the elbow. *Cochrane Database Syst Rev* 2016;11(11):Cd006839.
55. Acosta JA, Hoffman SN, Raynor EM, et al. Ulnar neuropathy in the forearm: A possible complication of diabetes mellitus. *Muscle Nerve* 2003;28(1):40-5.
56. Rydberg M, Zimmerman M, Gottsäter A, et al. Diabetes mellitus as a risk factor for compression neuropathy: a longitudinal cohort study from southern Sweden. *BMJ Open Diabetes Res Care* 2020;8(1):e001298.
57. Osei DA, Groves AP, Bommarito K, et al. Cubital Tunnel Syndrome: Incidence and Demographics in a National Administrative Database. *Neurosurgery* 2016;80(3):417-20.
58. Hulkkonen S, Auvinen J, Miettunen J, et al. Smoking is associated with ulnar nerve entrapment: a birth cohort study. *Scientific reports* 2019;9(1):9450-50.
59. Miettinen L, Ryhänen J, Shiri R, et al. Work-related risk factors for ulnar nerve entrapment in the Northern Finland Birth Cohort of 1966. *Sci Rep* 2021;11(1):10010.
60. Mezian K, Jačisko J, Kaiser R, et al. Ulnar Neuropathy at the Elbow: From Ultrasound Scanning to Treatment. *Front Neurol* 2021;12:661441.
61. Fadel M, Lancigu R, Raimbeau G, et al. Occupational prognosis factors for ulnar nerve entrapment at the elbow: A systematic review. *Hand Surgery and Rehabilitation* 2017;36(4):244-49.

62. Poenaru D, Ojoga F, Sandulescu M, et al. Conservative therapy in ulnar neuropathy at the elbow (Review). *Exp Ther Med* 2022;24(2):517.
63. Anderson D, Woods B, Abubakar T, et al. A Comprehensive Review of Cubital Tunnel Syndrome. *Orthop Rev (Pavia)* 2022;14(3):38239.
64. Dy CJ, Mackinnon SE. Ulnar neuropathy: evaluation and management. *Curr Rev Musculoskelet Med* 2016;9(2):178-84.
65. Carlton A, Khalid SI. Surgical Approaches and Their Outcomes in the Treatment of Cubital Tunnel Syndrome. *Front Surg* 2018;5:48.
66. Giöstad A, Nyman E. Patient Characteristics in Ulnar Nerve Compression at the Elbow at a Tertiary Referral Hospital and Predictive Factors for Outcomes of Simple Decompression versus Subcutaneous Transposition of the Ulnar Nerve. *BioMed Research International* 2019;2019:5302462.
67. Yeoman TFM, Stirling PHC, Lowdon A, et al. Patient-reported outcomes after in situ cubital tunnel decompression: a report in 77 patients. *J Hand Surg Eur Vol* 2020;45(1):51-55.
68. Malakootian M, Soveizi M, Gholipour A, et al. Pathophysiology, Diagnosis, Treatment, and Genetics of Carpal Tunnel Syndrome: A Review. *Cellular and Molecular Neurobiology* 2022
69. Tapadia M, Mozaffar T, Gupta R. Compressive neuropathies of the upper extremity: update on pathophysiology, classification, and electrodiagnostic findings. *The Journal of hand surgery* 2010;35(4):668-77.
70. Kahle W, Frotscher M. Color Atlas of Human Anatomy, Vol. 3: Nervous System and Sensory Organs. [Elektronisk resurs]. 7 ed: Thieme Medical Publishers Incorporated 2015.
71. Hagert E. Proprioception of the Wrist Joint: A Review of Current Concepts and Possible Implications on the Rehabilitation of the Wrist. *Journal of Hand Therapy* 2010;23(1):2-17.
72. Mackinnon SE. Pathophysiology of nerve compression. *Hand Clin* 2002;18(2):231-41.
73. Lanier ST, Brogan DM. Nerve Compression, Nerve Injury, and Nerve Regeneration: An Overview: Springer International Publishing 2022:3-26.
74. King R. Anatomy of the peripheral nerve. Peripheral nerve disorders2014:32-37.
75. Lundborg G, Björkman A. Handkirurgi - skador, sjukdomar, diagnostik och behandling. 3ed. Lund: Studentlitteratur 1999.
76. Doughty CT, Bowley MP. Entrapment Neuropathies of the Upper Extremity. *Med Clin North Am* 2019;103(2):357-70.
77. Yoon JS, Walker FO, Cartwright MS. Ulnar neuropathy with normal electrodiagnosis and abnormal nerve ultrasound. *Arch Phys Med Rehabil* 2010;91(2):318-20.
78. Nakamichi KI, Tachibana S. Enlarged median nerve in idiopathic carpal tunnel syndrome. *Muscle Nerve* 2000;23(11):1713-8.
79. Hakim AJ, Cherkas L, El Zayat S, et al. The genetic contribution to carpal tunnel syndrome in women: A twin study. *Arthritis Care & Research* 2002;47(3):275-79.

80. Puchalski P, Szlosser Z, Żyluk A. Familial occurrence of carpal tunnel syndrome. *Neurologia i Neurochirurgia Polska* 2019;53(1):43-46.
81. Wiberg A, Ng M, Schmid AB, et al. A genome-wide association analysis identifies 16 novel susceptibility loci for carpal tunnel syndrome. *Nature Communications* 2019;10(1):1030.
82. Skuladottir AT, Bjornsdottir G, Ferkingstad E, et al. A genome-wide meta-analysis identifies 50 genetic loci associated with carpal tunnel syndrome. *Nature Communications* 2022;13(1):1598.
83. Dada S, Burger MC, Massij F, et al. Carpal tunnel syndrome: The role of collagen gene variants. *Gene* 2016;587(1):53-58.
84. Elliot D. The early history of contracture of the palmar fascia. Part 1: The origin of the disease: the curse of the MacCrimmons: the hand of benediction: Cline's contracture. *J Hand Surg Br* 1988;13(3):246-53.
85. Holzer LA, de Parades V, Holzer G. Guillaume Dupuytren: His Life and Surgical Contributions. *The Journal of hand surgery* 2013;38(10):1994-98.
86. Nordenskjold J, Englund M, Zhou C, et al. Prevalence and incidence of doctor-diagnosed Dupuytren's disease: a population-based study. *J Hand Surg Eur Vol* 2017;42(7):673-77.
87. Lanting R, Broekstra DC, Werker PM, et al. A systematic review and meta-analysis on the prevalence of Dupuytren disease in the general population of Western countries. *Plast Reconstr Surg* 2014;133(3):593-603.
88. Hindocha S, McGrouther DA, Bayat A. Epidemiological evaluation of Dupuytren's disease incidence and prevalence rates in relation to etiology. *Hand (N Y)* 2009;4(3):256-69.
89. Godtfredsen NS, Lucht H, Prescott E, et al. A prospective study linked both alcohol and tobacco to Dupuytren's disease. *J Clin Epidemiol* 2004;57(8):858-63.
90. Rydberg M, Zimmerman M, Löfgren JP, et al. Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years. *Scientific Reports* 2021;11(1):14669.
91. Descatha A, Bodin J, Ha C, et al. Heavy manual work, exposure to vibration and Dupuytren's disease? Results of a surveillance program for musculoskeletal disorders. *Occupational and Environmental Medicine* 2012;69(4):296-99.
92. Wijnen V, Buntinx F, De Smet L, et al. Comorbidity in Dupuytren disease. *Acta Orthopaedica Belgica* 2016;82(3):643-48.
93. Larsen S, Krogsgaard DG, Larsen LA, et al. Genetic and environmental influences in Dupuytren's disease: A study of 30,330 Danish twin pairs. *Journal of Hand Surgery (European Volume)* 2014;40(2):171-76.
94. Dolmans GH, Werker PM, Hennies HC, et al. Wnt signaling and Dupuytren's disease. *N Engl J Med* 2011;365(4):307-17.
95. Major M, Freund MK, Burch KS, et al. Integrative analysis of Dupuytren's disease identifies novel risk locus and reveals a shared genetic etiology with BMI. *Genet Epidemiol* 2019;43(6):629-45.
96. Karbowiak M, Holme T, Khan K, et al. Dupuytren's disease. *BMJ* 2021;373:n1308.

97. Yoon AP, Kane RL, Hutton DW, et al. Cost-effectiveness of Recurrent Dupuytren Contracture Treatment. *JAMA Network Open* 2020;3(10):e2019861-e61.
98. Armstrong JR, Hurren JS, Logan AM. Dermofasciectomy in the management of Dupuytren's disease. *J Bone Joint Surg Br* 2000;82(1):90-4.
99. Leafblad ND, Wagner E, Wanderman NR, et al. Outcomes and Direct Costs of Needle Aponeurotomy, Collagenase Injection, and Fasciectomy in the Treatment of Dupuytren Contracture. *The Journal of hand surgery* 2019;44(11):919-27.
100. Nanchahal J, Ball C, Rombach I, et al. Anti-tumour necrosis factor therapy for early-stage Dupuytren's disease (RIDD): a phase 2b, randomised, double-blind, placebo-controlled trial. *Lancet Rheumatol* 2022;4(6):E407-e16.
101. Brozovich N, Agrawal D, Reddy G. A Critical Appraisal of Adult Trigger Finger: Pathophysiology, Treatment, and Future Outlook. *Plast Reconstr Surg Glob Open* 2019;7(8):e2360-e60.
102. Clapham PJ, Chung KC. A Historical Perspective of the Notta's Node in Trigger Fingers. *The Journal of hand surgery* 2009;34(8):1518-22.
103. Merry SP, O'Grady JS, Boswell CL. Trigger Finger? Just Shoot! *J Prim Care Community Health* 2020;11:2150132720943345.
104. Cheng Y-S, Chieh H-F, Lin C-J, et al. Comprehensive simulation on morphological and mechanical properties of trigger finger – A cadaveric model. *Journal of Biomechanics* 2018;74:187-91.
105. Uchihashi K, Tsuruta T, Mine H, et al. Histopathology of tenosynovium in trigger fingers. *Pathol Int* 2014;64(6):276-82.
106. Guerini H, Pessis E, Theumann N, et al. Sonographic appearance of trigger fingers. *J Ultrasound Med* 2008;27(10):1407-13.
107. Liu KJ, Thomson JG. Experimental model of trigger finger through A1 pulley constriction in a human cadaveric hand: A pilot study. *J of Hand Surg* 2013;38(10):1933-40.
108. Löfgren JP, Zimmerman M, Dahlin LB, et al. Diabetes Mellitus as a Risk Factor for Trigger Finger –a Longitudinal Cohort Study Over More Than 20 Years. *Frontiers in Clinical Diabetes and Healthcare* 2021;2
109. Vasiliadis AV, Itsiopoulos I. Trigger Finger: An Atraumatic Medical Phenomenon. *The journal of hand surgery Asian-Pacific volume* 2017;22(2):188-93.
110. Patel B, Kleeman SO, Neavin D, et al. Shared genetic susceptibility between trigger finger and carpal tunnel syndrome: a genome-wide association study. *The Lancet Rheumatology* 2022;4(8):e556-e65.
111. Fleisch SB, Spindler KP, Lee DH. Corticosteroid injections in the treatment of trigger finger: a level I and II systematic review. *J Am Acad Orthop Surg* 2007;15(3):166-71.
112. Lunsford D, Valdes K, Hengy S. Conservative management of trigger finger: A systematic review. *Journal of Hand Therapy* 2019;32(2):212-21.
113. Ryzewicz M, Wolf JM. Trigger digits: principles, management, and complications. *The Journal of hand surgery* 2006;31(1):135-46.

114. Gil JA, Hresko AM, Weiss AC. Current Concepts in the Management of Trigger Finger in Adults. *J Am Acad Orthop Surg* 2020;28(15):e642-e50.
115. Fiorini HJ, Tamaoki MJ, Lenza M, et al. Surgery for trigger finger. *Cochrane Database of Systematic Reviews* 2018(2)
116. Koopman JE, Hundepool CA, Duraku LS, et al. Complications and Functional Outcomes following Trigger Finger Release: A Cohort Study of 1879 Patients. *Plast Reconstr Surg* 2022;150(5):1015-24.
117. Kuczmarski AS, Harris AP, Gil JA, et al. Management of Diabetic Trigger Finger. *The Journal of hand surgery* 2019;44(2):150-53.
118. Haugen IK, Englund M, Aliabadi P, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. *Annals of the rheumatic diseases* 2011;70(9):1581-86.
119. Fuggle N, Bere N, Bruyère O, et al. Management of hand osteoarthritis: from an US evidence-based medicine guideline to a European patient-centric approach. *Aging Clin Exp Res* 2022;34(9):1985-95.
120. Rydberg M, Dahlin LB, Gottsäter A, et al. High body mass index is associated with increased risk for osteoarthritis of the first carpometacarpal joint during more than 30 years of follow-up. *RMD Open* 2020;6(3):e001368.
121. Moriatis Wolf J, Turkiewicz A, Atroshi I, et al. Prevalence of doctor-diagnosed thumb carpometacarpal joint osteoarthritis: an analysis of Swedish health care. *Arthritis Care Res (Hoboken)* 2014;66(6):961-5.
122. Sodha S, Ring D, Zurakowski D, et al. Prevalence of osteoarthrosis of the trapeziometacarpal joint. *J Bone Joint Surg Am* 2005;87(12):2614-8.
123. Becker SJ, Briet JP, Hageman MG, et al. Death, taxes, and trapeziometacarpal arthrosis. *Clin Orthop Relat Res* 2013;471(12):3738-44.
124. Tenti S, Ferretti F, Gusinu R, et al. Impact of thumb osteoarthritis on pain, function, and quality of life: a comparative study between erosive and non-erosive hand osteoarthritis. *Clinical Rheumatology* 2020;39(7):2195-206.
125. Marks M, Vliet Vlieland TPM, Audigé L, et al. Healthcare costs and loss of productivity in patients with trapeziometacarpal osteoarthritis. *Journal of Hand Surgery (European Volume)* 2015;40(9):927-34.
126. Plotz B, Bomfim F, Sohail MA, et al. Current Epidemiology and Risk Factors for the Development of Hand Osteoarthritis. *Current Rheumatology Reports* 2021;23(8):61.
127. Wolf JM, Turkiewicz A, Atroshi I, et al. Occupational load as a risk factor for clinically relevant base of thumb osteoarthritis. *Occup Environ Med* 2020;77(3):168-71.
128. Villafañe JH, Valdes K, Angulo-Diaz-Parreño S, et al. Ulnar Digits Contribution to Grip Strength in Patients with Thumb Carpometacarpal Osteoarthritis is Less than in Normal Controls. *HAND* 2014;10(2):191-96.
129. Marotta N, Demeco A, Marinaro C, et al. Comparative Effectiveness of Orthoses for Thumb Osteoarthritis: A Systematic Review and Network Meta-analysis. *Archives of Physical Medicine and Rehabilitation* 2021;102(3):502-09.

130. Lane JCE, Craig RS, Rees JL, et al. Low rate of subsequent surgery and serious complications following intra-articular steroid injection for base of thumb osteoarthritis: national cohort analysis. *Rheumatology* 2021;60(9):4262-71.
131. Lane JCE, Rodrigues JN, Furniss D, et al. Basal thumb osteoarthritis surgery improves health state utility irrespective of technique: a study of UK Hand Registry data. *J Hand Surg Eur Vol* 2020;45(5):436-42.
132. Wilcke MK, Evans K, Franko MA, et al. Trapeziectomy with or without a tendon-based adjunct: a registry-based study of 650 thumbs. *Journal of Hand Surgery (European Volume)* 2022;47(7):728-33.
133. Wolf JM, Turkiewicz A, Englund M, et al. What Are the Patient-reported Outcomes of Trapeziectomy and Tendon Suspension at Long-term Follow-up? *Clin Orthop Relat Res* 2021;479(9):2009-18.
134. Brand RA. Ernest Amory Codman, MD, 1869–1940. *Clinical Orthopaedics and Related Research*® 2009;467(11):2763-65.
135. Hicks CW, Makary MA. A prophet to modern medicine: Ernest Amory Codman. *BMJ : British Medical Journal* 2013;347:f7368.
136. Forsberg U. Kvalitetsregistrens historia (Swedish) The Swedish Association of Local Authorities and Regions; 2022 [accessed 20230301.
137. Emilsson L, Lindahl B, Köster M, et al. Review of 103 Swedish Healthcare Quality Registries. *Journal of Internal Medicine* 2015;277(1):94-136.
138. Statistics_Sweden. Background Facts – Population and Welfare Statistics 2016:1 - Personal identity number. 2016
139. Socialstyrelsen. Kvalitet och innehåll i patientregistret (Swedish), 2009:2009-125-15
140. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450-50.
141. Meyer AC, Hedström M, Modig K. The Swedish Hip Fracture Register and National Patient Register were valuable for research on hip fractures: comparison of two registers. *J Clin Epidemiol* 2020;125:91-99.
142. Bergdahl C, Nilsson F, Wennergren D, et al. Completeness in the Swedish Fracture Register and the Swedish National Patient Register: An Assessment of Humeral Fracture Registrations. *Clinical Epidemiology* 2021;13:325-33.
143. Löfvendahl S, Schelin MEC, Jöud A. The value of the Skåne Health-care Register: Prospectively collected individual-level data for population-based studies. *Scand J Public Health* 2020;48(1):56-63.
144. World Health O. ICD-10 : international statistical classification of diseases and related health problems : tenth revision. 2nd ed. Geneva: World Health Organization, 2004.
145. Löfvendahl S, Theander E, Svensson Å, et al. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden--a population-based register study. *PLoS One* 2014;9(5):e98024.

146. Piwernetz K, Home PD, Snorgaard O, et al. Monitoring the targets of the St Vincent Declaration and the implementation of quality management in diabetes care: the DIABCARE initiative. The DIABCARE Monitoring Group of the St Vincent Declaration Steering Committee. *Diabetic medicine : a journal of the British Diabetic Association* 1993;10(4):371-7.
147. Svensson A-M. The Swedish National Diabetes Register (NDR) 20 years: Centre of Registers, Region Västra Götaland; 2016 [Available from: https://www.ndr.nu/pdfs/20%20years%20of%20successful%20improvements_lowres_singelpage.pdf.
148. Rawshani A, Landin-Olsson M, Svensson A-M, et al. The incidence of diabetes among 0–34 year olds in Sweden: new data and better methods. *Diabetologia* 2014;57(7):1375-81.
149. The Swedish National Diabetes Register (Nationella Diabetesregistret). Annual report 2021 (In Swedish) [20230203]. Available from: https://www.ndr.nu/pdfs/Arsrapport_NDR_2021.pdf accessed 20230203.
150. Arner M. Developing a national quality registry for hand surgery: challenges and opportunities. *EFORT Open Rev* 2017;1(4):100-06.
151. Beaton DE, Wright JG, Katz JN, et al. Development of the QuickDASH: Comparison of Three Item-Reduction Approaches. *JBJS* 2005;87(5)
152. Carlsson IK, Ekstrand E, Åström M, et al. Construct validity, floor and ceiling effects, data completeness and magnitude of change for the eight-item HAKIR questionnaire: a patient-reported outcome in the Swedish National Healthcare Quality Registry for hand surgery. *Hand Therapy* 2020;26(1):3-16.
153. Berglund G, Elmstahl S, Janzon L, et al. The Malmo Diet and Cancer Study. Design and feasibility. *J Intern Med* 1993;233(1):45-51.
154. Manjer J, Carlsson S, Elmståhl S, et al. The Malmö diet and cancer study: representativity, cancer incidence and mortality in participants and non-participants. *European Journal of Cancer Prevention* 2001;10(6):489-99.
155. Manjer J, Elmståhl S, Janzon L, et al. Invitation to a population-based cohort study: differences between subjects recruited using various strategies. *Scand J Public Health* 2002;30(2):103-12.
156. Enhorning S, Wang TJ, Nilsson PM, et al. Plasma copeptin and the risk of diabetes mellitus. *Circulation* 2010;121(19):2102-8.
157. Melander O, Maisel AS, Almgren P, et al. Plasma proneurotensin and incidence of diabetes, cardiovascular disease, breast cancer, and mortality. *Jama* 2012;308(14):1469-75.
158. Drake I, Sonestedt E, Gullberg B, et al. Dietary intakes of carbohydrates in relation to prostate cancer risk: a prospective study in the Malmö Diet and Cancer cohort. *The American Journal of Clinical Nutrition* 2012;96(6):1409-18.
159. Härstedt M, Holmberg A, Rogmark C, et al. Cardiovascular biomarkers and risk of low-energy fractures among middle-aged men and women-A population-based study. *PLoS One* 2018;13(9):e0203692.

160. Pearce N. Effect measures in prevalence studies. *Environ Health Perspect* 2004;112(10):1047-50.
161. Clark TG, Bradburn MJ, Love SB, et al. Survival analysis part I: basic concepts and first analyses. *British journal of cancer* 2003;89(2):232-8.
162. Bradburn MJ, Clark TG, Love SB, et al. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. *British journal of cancer* 2003;89(3):431-6.
163. Jager KJ, van Dijk PC, Zoccali C, et al. The analysis of survival data: the Kaplan–Meier method. *Kidney International* 2008;74(5):560-65.
164. van Dijk PC, Jager KJ, Zwinderman AH, et al. The analysis of survival data in nephrology: basic concepts and methods of Cox regression. *Kidney International* 2008;74(6):705-09.
165. Nick TG, Campbell KM. Logistic Regression. In: Ambrosius WT, ed. Topics in Biostatistics. Totowa, NJ: Humana Press 2007:273-301.
166. DeVore GR. Computing the Z Score and Centiles for Cross-sectional Analysis: A Practical Approach. *J Ultrasound Med* 2017;36(3):459-73.
167. National Institute for Health and Care Excellence: Clinical Guidelines. Type 1 diabetes in adults: diagnosis and management. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2021. 2021.
168. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2021. *Diabetes Care* 2020;44(Supplement_1):S73-S84.
169. Brown H, Prescott R. Applied Mixed Models in Medicine: Wiley 2006.
170. Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. *Jama* 2016;315(4):407-08.
171. Varkey B. Principles of Clinical Ethics and Their Application to Practice. *Med Princ Pract* 2021;30(1):17-28.
172. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;24(11):659-67.
173. Ludvigsson JF, Håberg SE, Knudsen GP, et al. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol* 2015;7:491-508.
174. Johnsson L, Hansson MG, Eriksson S, et al. Patients' refusal to consent to storage and use of samples in Swedish biobanks: cross sectional study. *Bmj* 2008;337:a345.
175. Papanas N, Stamatiou I, Papachristou S. Carpal Tunnel Syndrome in Diabetes Mellitus. *Current Diabetes Reviews* 2022;18(4):16-19.
176. Rota E, Morelli N. Entrapment neuropathies in diabetes mellitus. *World J Diabetes* 2016;7(17):342-53.
177. Rota E, Zavaroni D, Parietti L, et al. Ulnar entrapment neuropathy in patients with type 2 diabetes mellitus: An electrodiagnostic study. *Diabetes Research and Clinical Practice* 2014;104(1):73-78.
178. Zhang D, Earp BE, Homer SH, et al. Factors Associated With Severity of Cubital Tunnel Syndrome at Presentation. *Hand (New York, NY)* 2021:15589447211058821.

179. Gunduz A, Candan F, Asan F, et al. Ulnar Neuropathy at Elbow in Patients with Type 2 Diabetes Mellitus. *Journal of Clinical Neurophysiology* 2020;37(3):220-24.
180. Brownlee M. The Pathobiology of Diabetic Complications. *Diabetes* 2005;54(6):1615.
181. Sessions J, Nickerson DS. Biologic Basis of Nerve Decompression Surgery for Focal Entrapments in Diabetic Peripheral Neuropathy. *J Diabetes Sci Technol* 2014;8(2):412-18.
182. Tomlinson DR, Gardiner NJ. Glucose neurotoxicity. *Nat Rev Neurosci* 2008;9(1):36-45.
183. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers* 2019;5(1):41.
184. Fang C, Bourdette D, Banker G. Oxidative stress inhibits axonal transport: implications for neurodegenerative diseases. *Molecular Neurodegeneration* 2012;7(1):29.
185. Sleigh JN, Rossor AM, Fellows AD, et al. Axonal transport and neurological disease. *Nat Rev Neurol* 2019;15(12):691-703.
186. Baptista FI, Pinheiro H, Gomes CA, et al. Impairment of Axonal Transport in Diabetes: Focus on the Putative Mechanisms Underlying Peripheral and Central Neuropathies. *Molecular Neurobiology* 2019;56(3):2202-10.
187. Dahlin LB, Meiri KF, McLean WG, et al. Effects of nerve compression on fast axonal transport in streptozotocin-induced diabetes mellitus. *Diabetologia* 1986;29(3):181-85.
188. Gonçalves NP, Vægter CB, Andersen H, et al. Schwann cell interactions with axons and microvessels in diabetic neuropathy. *Nature Reviews Neurology* 2017;13(3):135-47.
189. Østergaard L, Finnerup NB, Terkelsen AJ, et al. The effects of capillary dysfunction on oxygen and glucose extraction in diabetic neuropathy. *Diabetologia* 2015;58(4):666-77.
190. Tan JKS, Wei X, Wong PA, et al. Altered red blood cell deformability—A novel hypothesis for retinal microangiopathy in diabetic retinopathy. *Microcirculation* 2020;27(7):e12649.
191. Ducic I, Yoon J, Buncke G. Chronic postoperative complications and donor site morbidity after sural nerve autograft harvest or biopsy. *Microsurgery* 2020;40(6):710-16.
192. Thomsen NO, Mojaddidi M, Malik RA, et al. Reduced myelinated nerve fibre and endoneurial capillary densities in the forearm of diabetic and non-diabetic patients with carpal tunnel syndrome. *Acta Neuropathol* 2009;118(6):785-91.
193. Mojaddidi MA, Ahmed MS, Ali R, et al. Molecular and pathological studies in the posterior interosseous nerve of diabetic and non-diabetic patients with carpal tunnel syndrome. *Diabetologia* 2014;57(8):1711-9.
194. Lee SK, Hwang SY, An YS, et al. The Influence of Transverse Carpal Ligament Thickness on Treatment Decisions for Idiopathic Mild to Moderate Carpal Tunnel Syndrome. *Ann Plast Surg* 2020;85(2):127-34.

195. Tekin F, Sürmeli M, Şimşek H, et al. Comparison of the histopathological findings of patients with diabetic and idiopathic carpal tunnel syndrome. *International Orthopaedics* 2015;39(12):2395-401.
196. Watanabe T, Ito H, Morita A, et al. Sonographic evaluation of the median nerve in diabetic patients: comparison with nerve conduction studies. *J Ultrasound Med* 2009;28(6):727-34.
197. Lakshminarayanan K, Shah R. Median nerve and carpal arch morphology changes in women with type 2 diabetes: a case–control study. *Journal of Ultrasound* 2022;25(3):469-74.
198. Kerrigan JJ, Bertoni JM, Jaeger SH. Ganglion cysts and carpal tunnel syndrome. *The Journal of hand surgery* 1988;13(5):763-65.
199. Granger A, Sardi JP, Iwanaga J, et al. Osborne's Ligament: A Review of its History, Anatomy, and Surgical Importance. *Cureus* 2017;9(3):e1080.
200. Reddy YM, Murthy JMK, Suresh L, et al. Diagnosis and Severity Evaluation of Ulnar Neuropathy at the Elbow by Ultrasonography: A Case-Control Study. *J Med Ultrasound* 2022;30(3):189-95.
201. Volpe A, Rossato G, Bottanelli M, et al. Ultrasound evaluation of ulnar neuropathy at the elbow: correlation with electrophysiological studies. *Rheumatology (Oxford)* 2009;48(9):1098-101.
202. Kerasnoudis A, Tsivgoulis G. Nerve Ultrasound in Peripheral Neuropathies: A Review. *Journal of Neuroimaging* 2015;25(4):528-38.
203. Chen J, Wang CL, Wu S, et al. The feasibility of using high-resolution ultrasonography to assess ulnar nerve in patients with diabetes mellitus. *J Ultrason* 2017;17(70):160-66.
204. Broekstra DC, Groen H, Molenkamp S, et al. A Systematic Review and Meta-Analysis on the Strength and Consistency of the Associations between Dupuytren Disease and Diabetes Mellitus, Liver Disease, and Epilepsy. *Plast Reconstr Surg* 2018;141(3):367e-79e.
205. Alser OH, Kuo RYL, Furniss D. Nongenetic Factors Associated with Dupuytren's Disease: A Systematic Review. *Plast Reconstr Surg* 2020;146(4):799-807.
206. Hacquebord JH, Chiu VY, Harness NG. The Risk of Dupuytren Diagnosis in Obese Individuals. *The Journal of hand surgery* 2017;42(3):149-55.
207. Gudmundsson KG, Arngrímsson R, Sigfússon N, et al. Epidemiology of Dupuytren's disease: Clinical, serological, and social assessment. The Reykjavik Study. *Journal of Clinical Epidemiology* 2000;53(3):291-96.
208. Majeed M, Wiberg A, Ng M, et al. The relationship between body mass index and the risk of development of Dupuytren's disease: a Mendelian randomization study. *Journal of Hand Surgery (European Volume)* 2020:1753193420958553.
209. Pagnotta A, Specchia N, Greco F. Androgen receptors in Dupuytren's contracture. *J Orthop Res* 2002;20(1):163-8.
210. Pagnotta A, Specchia N, Soccetti A, et al. Responsiveness of Dupuytren's disease fibroblasts to 5 alpha-dihydrotestosterone. *The Journal of hand surgery* 2003;28(6):1029-34.

211. Derby CA, Zilber S, Brambilla D, et al. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clin Endocrinol (Oxf)* 2006;65(1):125-31.
212. Eriksson J, Haring R, Grarup N, et al. Causal relationship between obesity and serum testosterone status in men: A bi-directional mendelian randomization analysis. *PLoS One* 2017;12(4):e0176277.
213. Blyth MJG, Ross DJ. Diabetes and Trigger Finger. *Journal of Hand Surgery* 1996;21(2):244-45.
214. Fedak KM, Bernal A, Capshaw ZA, et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging Themes in Epidemiology* 2015;12(1):14.
215. Luther GA, Murthy P, Blazar PE. Cost of Immediate Surgery Versus Non-operative Treatment for Trigger Finger in Diabetic Patients. *The Journal of hand surgery* 2016;41(11):1056-63.
216. Stirling PHC, Jenkins PJ, Duckworth AD, et al. Functional outcomes of trigger finger release in non-diabetic and diabetic patients. *J of Hand Surg* 2020;45(10):1078-82.
217. Ashour A, Alfattni A, Hamdi A. Functional outcome of open surgical A1 pulley release in diabetic and nondiabetic patients. *J Orthop Surg (Hong Kong)* 2018;26(1):2309499018758069.
218. Goh S-Y, Cooper ME. The Role of Advanced Glycation End Products in Progression and Complications of Diabetes. *The Journal of Clinical Endocrinology & Metabolism* 2008;93(4):1143-52.
219. Kuzan A. Toxicity of advanced glycation end products (Review). *Biomed Rep* 2021;14(5):46.
220. Kyung SY, Byun KH, Yoon JY, et al. Advanced glycation end-products and receptor for advanced glycation end-products expression in patients with idiopathic pulmonary fibrosis and NSIP. *Int J Clin Exp Pathol* 2013;7(1):221-28.
221. Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: role in pathology of diabetic cardiomyopathy. *Heart Failure Reviews* 2014;19(1):49-63.
222. Hwang KR, Murrell GAC, Millar NL, et al. Advanced glycation end products in idiopathic frozen shoulders. *Journal of Shoulder and Elbow Surgery* 2016;25(6):981-88.
223. Takase F, Mifune Y, Inui A, et al. Association of advanced glycation end products in Dupuytren disease. *J Orthop Surg Res* 2018;13(1):143.
224. Tripoli M, Cordova A, Moschella F. Update on the role of molecular factors and fibroblasts in the pathogenesis of Dupuytren's disease. *J Cell Commun Signal* 2016;10(4):315-30.
225. Verhoekx JSN, Verjee LS, Izadi D, et al. Isometric Contraction of Dupuytren's Myofibroblasts Is Inhibited by Blocking Intercellular Junctions. *Journal of Investigative Dermatology* 2013;133(12):2664-71.

226. Zhang AY, Fong KD, Pham H, et al. Gene expression analysis of Dupuytren's disease: the role of TGF-beta2. *J Hand Surg Eur Vol* 2008;33(6):783-90.
227. Lambi AG, Popoff SN, Benhaim P, et al. Pharmacotherapies in Dupuytren Disease: Current and Novel Strategies. *The Journal of hand surgery* 2023
228. Sato J, Ishii Y, Noguchi H, et al. Sonographic Appearance of the Flexor Tendon, Volar Plate, and A1 Pulley With Respect to the Severity of Trigger Finger. *The Journal of hand surgery* 2012;37(10):2012-20.
229. Kim SJ, Lee CH, Choi WS, et al. The thickness of the A2 pulley and the flexor tendon are related to the severity of trigger finger: results of a prospective study using high-resolution ultrasonography. *J Hand Surg Eur Vol* 2016;41(2):204-11.
230. Lundin AC, Eliasson P, Aspenberg P. Trigger finger and tendinosis. *J Hand Surg Eur Vol* 2012;37(3):233-6.
231. Alp NB, Akdağ G, Karduz G, et al. Biochemical markers decrease and increase disproportionally in A1 pulley tissue of type 2 diabetic trigger finger patients. *Eklem Hastalik Cerrahisi* 2019;30(2):117-23.
232. Kameyama M, Chen K-R, Mukai K, et al. Histopathological Characteristics of Stenosing Flexor Tenosynovitis in Diabetic Patients and Possible Associations With Diabetes-Related Variables. *The Journal of hand surgery* 2013;38(7):1331-39.
233. Ranger TA, Wong AMY, Cook JL, et al. Is there an association between tendinopathy and diabetes mellitus? A systematic review with meta-analysis. *British Journal of Sports Medicine* 2016;50(16):982-89.
234. Abate M, Schiavone C, Salini V, et al. Occurrence of tendon pathologies in metabolic disorders. *Rheumatology* 2013;52(4):599-608.
235. Cannata F, Vadalà G, Ambrosio L, et al. The impact of type 2 diabetes on the development of tendinopathy. *Diabetes/Metabolism Research and Reviews* 2021;37(6)
236. Kolhe R, Ghilzai U, Mondal AK, et al. Nanostring-Based Identification of the Gene Expression Profile in Trigger Finger Samples. *Healthcare (Basel)* 2021;9(11):1592.
237. Bianchi E, Taurone S, Leopizzi M, et al. Immunohistochemical Profile of VEGF, PGE2 and TGF-β in Inflammatory Tenosynovitis of Carpal Tunnel Syndrome. *European Journal of Inflammation* 2012;10(3):491-99.
238. Gingery A, Yang T-H, Passe SM, et al. TGF-β signaling regulates fibrotic expression and activity in carpal tunnel syndrome. *Journal of Orthopaedic Research* 2014;32(11):1444-50.
239. Hernandez DM, Kang J-H, Choudhury M, et al. IPF pathogenesis is dependent upon TGFβ induction of IGF-1. *FASEB J* 2020;34(4):5363-88.
240. Marshall M, Peat G, Nicholls E, et al. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. *Osteoarthritis Cartilage* 2013;21(11):1674-84.

241. Dahaghin S, Bierma-Zeinstra SMA, Koes BW, et al. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. *Annals of the rheumatic diseases* 2007;66(7):916-20.
242. Frey N, Hügle T, Jick SS, et al. Type II diabetes mellitus and incident osteoarthritis of the hand: a population-based case–control analysis. *Osteoarthritis and Cartilage* 2016;24(9):1535-40.
243. Khor A, Ma C-A, Hong C, et al. Diabetes mellitus is not a risk factor for osteoarthritis. *RMD Open* 2020;6(1):e001030.
244. Yusuf E, Nelissen RG, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Annals of the Rheumatic Diseases* 2010;69(4):761.
245. Jiang L, Xie X, Wang Y, et al. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. *Int J Rheum Dis* 2016;19(12):1244-54.
246. Wang T, He C. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. *Cytokine Growth Factor Rev* 2018;44:38-50.
247. Wolf JM, Scher DL, Etchill EW, et al. Relationship of relaxin hormone and thumb carpometacarpal joint arthritis. *Clin Orthop Relat Res* 2014;472(4):1130-37.
248. Lucas RM, McMichael AJ. Association or causation: evaluating links between "environment and disease". *Bull World Health Organ* 2005;83(10):792-5.
249. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proc R Soc Med* 1965;58(5):295-300.
250. Nowinski CJ, Bureau SC, Buckland ME, et al. Applying the Bradford Hill Criteria for Causation to Repetitive Head Impacts and Chronic Traumatic Encephalopathy. *Frontiers in Neurology* 2022;13
251. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018;362:k601.
252. Swerdlow DI. Mendelian Randomization and Type 2 Diabetes. *Cardiovasc Drugs Ther* 2016;30(1):51-7.
253. Ahmad OS, Morris JA, Mujammami M, et al. A Mendelian randomization study of the effect of type-2 diabetes on coronary heart disease. *Nat Commun* 2015;6:7060.
254. Mi J, Liu Z. Obesity, Type 2 Diabetes, and the Risk of Carpal Tunnel Syndrome: A Two-Sample Mendelian Randomization Study. *Frontiers in Genetics* 2021;12
255. Lesko CR, Buchanan AL, Westreich D, et al. Generalizing Study Results: A Potential Outcomes Perspective. *Epidemiology* 2017;28(4):553-61.
256. Bovbjerg M. Foundations of Epidemiology.: Oregon State University 2020.
257. Naimi TS, Stockwell T, Zhao J, et al. Selection biases in observational studies affect associations between 'moderate' alcohol consumption and mortality. *Addiction* 2017;112(2):207-14.
258. Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014;29(8):551-8.

259. Pham A, Cummings M, Lindeman C, et al. Recognizing misclassification bias in research and medical practice. *Family Practice* 2019;36(6):804-07.
260. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Sudbury, Mass: Jones and Bartlett 2018.
261. Rothman KJ. Epidemiology: An Introduction: Oxford University Press 2012.
262. Atroshi I, Gummesson C, Johnsson R, et al. Prevalence of carpal tunnel syndrome in a general population. *Jama* 1999;282(2):153-8.
263. Jager KJ, Tripepi G, Chesnaye NC, et al. Where to look for the most frequent biases? *Nephrology* 2020;25(6):435-41.
264. Malmö Stad. Demographics City of Malmö (in swedish): Malmö Stad; 2023 [updated 2023-01-01 20230310]. Available from: https://malmo.se/Fakta-och-statistik/Befolkning.html.
265. Wang K, Eftang CN, Jakobsen RB, et al. Review of response rates over time in registry-based studies using patient-reported outcome measures. *BMJ Open* 2020;10(8):e030808.
266. Stirling PHC, Jenkins PJ, Ng N, et al. Nonresponder bias in hand surgery: analysis of 1945 cases lost to follow-up over a 6-year period. *J of Hand Surg* 2021;47(2):197-205.
267. Ross LA, O'Rourke SC, Toland G, et al. Loss to patient-reported outcome measure follow-up after hip arthroplasty and knee arthroplasty : patient satisfaction, associations with non-response, and maximizing returns. *Bone Jt Open* 2022;3(4):275-83.
268. Choi SW, Bae JY, Shin YH, et al. Patient expectations and satisfaction in hand surgery: A new assessment approach through a valid and reliable survey questionnaire. *PLoS One* 2022;17(12):e0279341.
269. Harrison C, Clelland AD, Davis TRC, et al. A comparative analysis of multidimensional computerized adaptive testing for the DASH and QuickDASH scores in Dupuytren's disease. *Journal of Hand Surgery (European Volume)* 2022;47(7):750-54.
270. Whelton C, Peach CA. Review of diabetic frozen shoulder. *European Journal of Orthopaedic Surgery & Traumatology* 2018;28(3):363-71.
271. Kim SK, Khan C, Ladd AL, et al. A shared genetic architecture between adhesive capsulitis and Dupuytren disease. *Journal of Shoulder and Elbow Surgery* 2023;32(1):174-85.
272. Nelson JT, Gay SS, Diamond S, et al. Warning Signs: Occult Diabetes and Dysglycemia in the Hand Surgery Patient Population. *HAND* 2022:15589447221142893.

Appendix

The pre and postoperative patient questionnaire from HAKIR: (HQ-8) and QuickDASH

HAKIR
HANDKIRURGISKT
KVALITETSREGISTER

Date of birth (social security no) (yyyymmdd-nnnn): ☐☐☐☐☐☐☐☐-☐☐☐☐

Patient questionnaire HQ-8 (arm/hand)

Date (yyyy-mm-dd) ☐☐☐☐-☐☐-☐☐

I am (please indicate your writing hand): ☐ Left handed ☐ Right handed ☐ Ambidextrous

Arm/hand that was operated on: ☐ Left ☐ Right

This questionnaire reports on problems that you have had this past week in the hand/arm that was operated on. Please tick the alternative that best corresponds to any of your problems.

1. Pain on load

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

2. Pain on motion without load

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

3. Pain at rest

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

4. Stiffness

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

5. Weakness

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

6. Numbness / tingling in fingers

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

7. Cold Sensitivity (discomfort on exposure to cold)

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

8. Ability to perform daily activities

No problems	0	10	20	30	40	50	60	70	80	90	100	Worst problems imaginable
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Filled in by staff

HAKIR
Hand Surgery Quality Record

☐ **3 months** ☐ **12 months** ☐ **Other** (indicate no. of months) ☐☐

Patient's Personal Identity No. (12 digits) ☐☐ ☐☐☐☐☐☐-☐☐☐☐

Form filled in on (yyyy-mm-dd) ☐☐☐☐-☐☐-☐☐

QuickDASH (arm/shoulder/hand)

This form has to do with your symptoms and your ability to perform certain activities. Answer **each question**, on the basis of how you have been feeling **this last week**, by marking one of the alternatives for each question. If there is some activity that you have not done this past week, then mark the answer that you think **would be most correct** had you done the activity. It does not matter which arm or hand you use to perform the activity. The answer is based upon your ability regardless of how you do it.

	No difficulty	**Mild difficulty**	**Moderate difficulty**	**Severe difficulty**	**Unable**
1. Open a tight or new jar.	☐	☐	☐	☐	☐
2. Do heavy household chores (e.g., wash walls, floors).	☐	☐	☐	☐	☐
3. Carry a shopping bag or briefcase.	☐	☐	☐	☐	☐
4. Wash your back.	☐	☐	☐	☐	☐
5. Use a knife to cut food.	☐	☐	☐	☐	☐
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	☐	☐	☐	☐	☐

7. During **the past week**, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

8. During **the past week**, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?

☐ Not limited at all ☐ Slightly limited ☐ Moderately limited ☐ Very limited ☐ Unable

Please rate the severity of the following symptoms **in the last week**:

	None	**Mild**	**Moderate**	**Severe**	**Extreme**
9. Arm, shoulder or hand pain.	☐	☐	☐	☐	☐
10. Tingling (pins and needles) in your arm, shoulder or hand.	☐	☐	☐	☐	☐

11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand?

No difficulty Mild difficulty Moderate difficulty Severe difficulty So much difficulty that I can't sleep

Printed by Media-Tryck, Lund 2023 NORDIC SWAN ECOLABEL 3041 0903

The Diabetic Hand

"The Diabetic Hand" is a comprehensive thesis exploring the often overlooked and complex relationship between diabetes mellitus and hand function. Through extensive research and analysis of big data from Swedish national and regional registers and cohorts, this thesis sheds light on the epidemiology and pathophysiology of diabetic hand problems, their prevalence, incidence, and surgical outcome. The thesis offers valuable insights into the prevention, and management of diabetic hand diagnoses and provides a foundation for an evidence-based approach to detecting and treating diagnoses related to the diabetic hand.

Mattias Rydberg is a specialist in orthopaedic surgery and a resident in hand surgery at Skåne University Hospital, Malmö, Sweden. He currently resides in Lund with his family.

LUND UNIVERSITY

FACULTY OF MEDICINE

Hand Surgery, Malmö
Department of Translational Medicine

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2023:77
ISBN 978-91-8021-417-9
ISSN 1652-8220