Injury, repair and reconstruction of peripheral nerves in the upper limb. Unravelling the socioeconomic tapestry and patient reported outcomes, reviewing new treatment options and peering into proteomics

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LUND
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Abstract:

The aim of this thesis is to delve into the multifaceted landscape of peripheral nerve injuries, exploring the intricate interplay between different surgical interventions, the patient reported outcomes, the often-overlooked, influence of socioeconomic factors and cold sensitivity but also the complicated proteomic perspective of these injuries. From the common digital nerve injury to the more complex transection and laceration injuries of a major nerve trunk in the forearm, the spectrum of impairments encompasses mild discomfort to severe, lifelong challenges.

In Papers I-III, the thesis retrospectively maps the surgically treated peripheral nerve injuries, encompassing digital nerve injuries, as well as median, ulnar, and radial nerve injuries, utilizing prospectively collected data from the HAKIR registry in Sweden. In paper I, the objective was to investigate the impact of socioeconomic factors on outcome for individuals suffering from peripheral nerve injury in the upper extremity. The study revealed that individuals with major nerve trunk injuries were associated with poorer patient reported outcome scores and lower income compared to the individual with digital nerve injuries. Outcome was also influenced by factors, such as immigration status, sick leave, and education level, emphasizing the impact of non-biological factors on the outcome of nerve surgery. In papers II-III the patient-reported outcome shed light on the often-overlooked symptom of cold sensitivity, emerging as a significant factor impacting recovery after both digital nerve and major nerve trunk injuries. An ulnar nerve injury had the worst outcome of the three major nerve trunk injuries.

In Paper IV, a comprehensive review on the use of processed nerve allografts (PNAs) for peripheral nerve injuries, where nerve graft reconstruction is needed, was conducted aiming to clarify advantages or disadvantages of the use of PNAs compared to nerve autografts. Despite a substantial body of literature, the dearth of controlled studies limited conclusive insights into the clinical efficacy of PNAs.

In Papers V-VI, adding another layer of understanding of peripheral nerve injuries, mass spectrometry explored proteomic patterns of injured peripheral nerve endings. An optimal method for protein extraction from peripheral nerves was established. Dynamic cellular responses aimed at promoting tissue degeneration and restoration were observed, while suppressing non-essential processes when comparing the proximal and distal ends of a human injured digital nerve within two days after injury.

A peripheral nerve injury and outcome after surgery is a clinical challenge due to the suboptimal outcome in many cases. In conclusion, this thesis calls for a holistic approach to peripheral nerve injuries—one that recognizes the intricate web connecting surgical interventions, patient outcomes, and socioeconomic influences. The systematic exploration of processed nerve allografts and proteomic patterns adds depth to our understanding, paving the way for improved treatment strategies and, ultimately, enhanced outcomes in the realm of peripheral nerve injuries.

Key words: Peripheral nerve injury, Digital nerve injury, Major nerve trunk injury, Nerve repair, Nerve reconstruction, Socioeconomic factors, Patient reported outcome, Cold sensitivity, Processed nerve allograft, Proteomics, Mass spectrometry,

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To the extraordinary people who form the very fabric
*of **my** world*

Table of Contents

List of Papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Socioeconomic factors and outcome after repair and reconstruction of digital and major nerve trunk injuries in the upper limb.
Scientific Reports. 2024 Mar 27;14(1):7242. doi: 10.1038/s41598-024-57757-w

Drifa Frostadottir, Raquel Perez, Lars B. Dahlin

II. Cold sensitivity, functional disability and predicting factors after a repaired digital nerve injury. A national registry-based cohort study.
Scientific Reports. 2022 Mar 22;12(1):4847. doi: 10.1038/s41598-022-08926-2.

Drifa Frostadottir, Linnéa Ekman, Malin Zimmerman, Stina Andersson, Marianne Arner, Elisabeth Brogren, Lars B. Dahlin

III. Cold sensitivity and its association to functional disability following a major nerve trunk injury in the upper extremity – a national registry-based study.
PLoSOne.2022Jul12;17(7):e0270059.doi:10.1371/journal.pone.0270059. eCollection 2022.

Drifa Frostadottir, Linnea Ekman, Malin Zimmerman, Lars B. Dahlin

IV. Evaluation of processed nerve allograft in peripheral nerve surgery – a systematic review and critical appraisal
Plastic and Reconstructive Surgery Global Open. 2023 Jun 27;11(6): e5088. doi: 10.1097 /GOX. 0000000000005088. eCollection 2023 Jun.

Drifa Frostadottir, Anette Chemnitz, Linn J. Johansson, Jan Holst, Lars B. Dahlin

V. Quantitative mass spectrometry analysis of fresh frozen human sural nerve: optimizing methods for enhanced nerve regeneration research.
Submitted to Journal of Proteomic Research, February 2024

Drifa Frostadottir, Charlotte Welinder, Raquel Perez, Lars B. Dahlin

VI. Quantitative mass spectrometry analysis of the injured proximal and distal human digital nerve ends
Submitted to Frontiers in Molecular Neuroscience April 2024.

Drifa Frostadottir, Charlotte Welinder, Raquel Perez, Lars B. Dahlin

Abbreviations and definitions

ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
AUC	Area under the curve
BDNF	Brain-derived neurotrophic factor
BMI	Body Mass Index
BORCS7	BLOCK-1 Related Complex Subunit 7
CGRP	Calcitonin gene-related peptide
CI	Confidence Interval
CTS	Carpal Tunnel Syndrome
DA	Discriminatory Accuracy
DDA	Data-dependent acquisition
DIA	Data-independent acquisition
DTI	Diffusion tensor imaging
ECM	Extracellular matrix
EGFL8	Epidermal growth factor-like protein 8
EHR	Electronic Health Record
FAM3C	Protein FAM3C
GBA1	Glucosidase Beta Acid 1
GDNF	Glial cell-line derived neurotrophic factor
GDPR	General Data Protection Regulation
GPLD1	Glycosylphosphatidylinositol Specific Phospholipase D1
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAKIR	Swedish National Quality Registry for Hand Surgery

HAVS	Hand-arm vibration syndrome
HMGB3	High mobility group protein 3
HSBP1	Heat Shock factor binding protein
HSPA2	Heat shock-related 70 kDA protein 2
HSP27	Heat shock protein 27
HQ-8	Eight specific questions in HAKIR
ICAM-1	Intracellular adhesion molecule-1
IQR	Interquartile Range
IR	Immunoreactivity
ITGA2	Integrin alpha 2
JIP	JNK interacting protein
LC-MS	Liquid chromatography - mass spectrometry
LC-MS/MS	Liquid chromatography - tandem mass spectrometry
NDR	National Diabetes Register
NGF	Nerve growth factor
NCS	Nerve conduction studies
MALDI	Matrix-assisted laser desorption/ionization
MAN	Molecular Anatomy
MAP1LC3A	Microtubule Associated Protein 1 Light Chain 3 Alpha
MCP-1	Monocyte chemoattractant protein-1
MEKK1	Mitogen activated kinase kinases 1
MRI	Magnetic Resonance
MS	Mass Spectrometry
MS	Multiple sclerosis
OCTR	Open carpal tunnel release
OECD	The Organization for Economic Co-operation and Development
PICO	Patient, Intervention, Comparison, Outcome
PNA	Processed Nerve Allograft
PR	Prevalence Ratios

PROMs	Patient Reported Outcome Measures
PTM	Post-translational modification
QuickDASH	Disabilities of Arm Shoulder and Hand
RBM12	RNA-binding protein 12
RCT	Randomized controlled trials
RHOC	Ras Homolog Family Member C
ROB	Risk of Bias
SC	Schwann cell
SCB	Statistics Sweden
SD	Standard Deviation
SELDI	Surface-enhanced laser desorption/ionization
SNAP25	Synaptosome Associated Protein 25
SNAP91	Clathrin coat assembly protein AP180
TM	Thrombomodulin
TNNI1	Troponin 1
TSPAN6	Tetraspanin-6
TWF1	Twinfilin 1
UBA5	Ubiquitin Like Modifier Activating Enzyme 5
UFL1	E3 UFM1-protein ligase 1
UNE	Ulnar nerve entrapment
US	Ultrasonography
WHO	World Health Organization
2-DE	Two-dimensional gel electrophoresis
2PD	Two-Point Discrimination

Thesis at a glance

I. Socioeconomic factors and outcome after repair and reconstruction of digital and major nerve trunk injuries in the upper limb.

Objective: Investigate the impact of socioeconomic factors on outcome of upper limb nerve injury.
Methods: Retrospective study, 670 cases, Swedish National Quality Registry for Hand Surgery linked to Statistics Sweden.
Findings: Major nerve trunk injuries are associated with worse QuickDASH scores and lower income among patients. Immigration, sick leave, and education level affected outcome negatively.
Conclusion: Recognizing non-biological factors (immigration, sick leave, education) is vital for improving nerve surgery outcome.

II. Cold sensitivity, functional disability and predicting factors after a repaired digital nerve injury.

Objective: Examine the role of cold sensitivity in functional disability after digital nerve repair.
Methods: Cohort study, 3204 cases, Swedish national quality registry.
Findings: Cold sensitivity is common after digital nerve injuries; concomitant flexor tendon injuries, hand fractures, and multiple injuries predict worsened cold sensitivity.
Conclusion: Cold sensitivity impacts self-reported disability; concomitant injuries predict postoperative cold sensitivity.

III. Cold sensitivity and its association to functional disability following a major nerve trunk injury in the upper extremity – a national registry-based study.

Objective: Investigate cold sensitivity and functional disability after a major nerve trunk injury in the upper limb.
Methods: Cohort study, 735 cases, Swedish national quality registry.
Findings: Cold sensitivity is common after nerve trunk injuries; ulnar nerve injuries result in the most severe symptoms. Severe cold sensitivity can lead to disability and decreased ability to perform daily activities.

Conclusion: Severe cold sensitivity affects daily activities; ulnar nerve injury may have the worst outcome of the three major nerve trunk injuries.

IV. Evaluation of processed nerve allograft in peripheral nerve surgery – a systematic review and critical appraisal.

Objective: Systematic review of processed nerve allograft (PNA) use in nerve reconstruction.
Method: Literature review, PICO, Grade.
Findings: No conclusions could be drawn concerning differences in outcome of nerve reconstruction using PNAs compared to use of nerve autografts or conduits.
Conclusion: Properly conducted randomized controlled trials are needed to establish PNA recommendations.

V. Quantitative mass spectrometry analysis of fresh frozen human sural nerve: optimizing methods for enhanced nerve regeneration research.

Objective: Determine a reliable method for protein extraction from freshly frozen human peripheral nerves.
Methods: Utilized freshly frozen human sural nerve tissues; evaluated different buffers and minimum amount for reliable results from quantitative mass spectrometry.
Findings: Ripa buffer, in combination with 8 M Urea, and the Bullet Blender is a reliable method for protein extraction from fresh frozen human nerve tissue weighing ≥ 0.12 mg.
Conclusion: The varying extraction of proteins, based on buffer choice, homogenization method, and sample weight, collectively provides a reliable protein extraction method for fresh frozen human peripheral nerve tissue.

VI. Quantitative mass spectrometry analysis of the injured proximal and distal human digital nerve ends.

Objective: Investigation of early protein expression differences in injured digital nerve ends with mass spectrometry analysis.
Methods: Utilized fresh frozen injured human digital nerves; comparing protein abundances in distal nerve end to proximal end of injured digital nerves.
Findings: In distal end, downregulated proteins are associated with synaptic transmission, autophagy, neurotransmitter regulation, cell adhesion and migration. Upregulated proteins are implicated in cellular stress response, neuromuscular junction stability, muscle contraction, neuronal excitability and neurotransmitter release, synaptic vesicle recycling, axon guidance and angiogenesis.
Conclusion: Dynamic cellular responses aimed at promoting tissue degeneration and restoration were revealed, while non-essential processes were suppressed.

Summary in Swedish

Populärvetenskaplig sammanfattning

Det perifera nervsystemet är ett komplicerat nätverk av nervtrådar, som förbinder hjärnan och ryggmärgen, det centrala nervsystemet, med kroppens olika delar. Beröringssinnet i handen spelar en avgörande roll för den mänskliga handens rörelse och känsel och för vår interaktion med omvärlden. En nervskada kan innebära en komplex utmaning för den drabbade individen. Skador på perifera nerver kan manifestera sig från enbart milt obehag till djupa funktionsnedsättningar med nedsatt eller bortfallen känsel- och muskelfunktion samt ibland ihållande smärta.

Skador på fingrarnas känselnerver, digitalnerverna, avfärdas ofta som mindre betydelsefulla, men är till antalet den vanligaste typen av perifer nervskada, med en förekomst, s.k. incidens, av 6.2 skador per 100 000 invånare årligen. Män verkar drabbas oftare av digitalnervskador, vilket kastar ljus över den intressanta könsfördelningen vid perifera nervskador.

Längre upp på armen hittar vi större nervstammar, tex medianus- och ulnarisnerverna, som i handen delar upp sig i digitalnerver till de enskilda fingrarna. De större nervstammarna innehåller både motoriska (impulser till muskler) och sensoriska (förmedlar känselimpulser) nervtrådar, och innerverar fler delar av handen jämfört med digitalnerverna. Vid en skärskada i underarmen, med skada på medianus- eller ulnarisnerverna, blir konsekvenserna ofta svåra med nedsatt känsel i handen, minskad motorisk funktion och ibland en ihållande och kvarstående smärta. Den kirurgiska behandlingen vid nervskador innebär en noggrann balansakt, där valet mellan en direkt nervsutur (dvs. sy ihop de skadade nervändarna med fina trådar) eller, i mer komplexa fall, användningen av ett nervgraft (en reservdel som används för att överbrygga gapet mellan de skadade nervändarna om dessa inte kan sys ihop direkt) kan vara avgörande för återhämtningen.

Bortom operationsrummet börjar dessa patienter en långvarig rehabiliteringsresa. Hur socioekonomiska faktorer, dvs, utbildningsnivå, civilstånd, typ av arbete, sjukskrivning, invandrarstatus och inkomst, påverkar återhämtningen har hittills inte klarlagts tillräckligt. Individernas sociala interaktioner kan förändras, fysisk närhet och förmågan till intima förbindelser kan bli svåra. I grund och botten sträcker sig följderna av perifera nervskador i hand och underarm långt bortom

kliniska mätvärden och understryker vardagens komplexiteter, såsom ekonomiska svårigheter, arbete- och sysselsättningsutmaningar och social isolering.

Syftet med denna avhandling har varit att överbrygga avståndet mellan kliniska bedömningar och den nyanserade verklighet som nervskadade individer rapporterar samt att försöka förstå reparationsmekanismer och förändringar i proteinmönstret (äggviteämnen) i cellerna i de skadade nervändarna efter en nervskada.

Avhandlingen inkluderar en noggrann retrospektiv kartläggning av kirurgiskt behandlade perifera nervskador. Genom att använda den nationella HAKIR-databasen i Sverige syftade forskningen till att identifiera patientgrupper mer mottagliga för dessa skador och att analysera en mångfald av socioekonomiska faktorer. Undersökningen sträckte sig in i det subjektiva området med undersökning av patientupplevelser efter skadan.

Dessutom genomfördes en systematisk kunskapsgenomgång och kritisk utvärdering av tidigare publicerade originalarbeten som beskrivit användningen av bearbetade nervgrafter (Processed nerve allograft; en slags konstgjorda reservdelar av nerver som används för att överbrygga gap mellan skadade nervändar), vilket är kemiskt behandlade nerver från döda donatorer och som inte ger någon avstötningseffekt, vid perifera nervskador hos människa. Detta innefattade en noggrann granskning av fördelarna och nackdelarna av denna metod och bidrog med värdefulla insikter för evidensbaserat beslutsfattande inom klinisk praxis. Trots en betydande mängd litteratur begränsade bristen på kontrollerade vetenskapliga studier avgörande insikter om den kliniska effekten av bearbetade nervgrafter.

Avhandlingen sträcker sig också till det molekylära området, där Liquid Chromatography-Mass Spectrometry (LC-MS) användes för att noggrant kartlägga eventuella förändringar i de proteomiska (dvs. äggviteämnen) mönstren i skadade perifera nervändar. Studien syftade till att undersöka skillnader mellan proteinuttryck i nervändarna på varsin sida om skadan. Denna kunskap skulle kunna bidra till en vidare förståelse av nervläkningsprocesser samt till att förutsäga resultat efter behandling. Dynamiska cellulära svar som syftar till att främja både vävnadsnedbrytning (degeneration) och uppbyggnad funktion avslöjades i undersökningarna, samtidigt som fingrarnas känselnerver undertryckte icke-essentiella processer i samband med skada.

Perifer nervskada och utfall efter operation är en klinisk utmaning på grund av det i många fall suboptimala resultatet. Sammanfattningsvis efterlyser denna avhandling ett holistiskt förhållningssätt till perifera nervskador – som väver samman kirurgiska ingrepp, patientresultat och socioekonomiska influenser. Den systematiska kunskapsgenomgången av bearbetade nervgrafter och analysen av det komplicerade proteomiska mönstret ger djupare inblick i nervskador, insyn som kan bana vägar i framtiden för förbättrade behandlingsstrategier och, i slutändan, förbättrade resultat för patienter som drabbas av perifera nervskador.

Summary in Icelandic

Almenn vísindaleg samantekt

Úttaugakerfið er flókið net taugaþráða sem tengja heilann, miðtaugakerfið, við hina ýmsu hluta líkamans. Snertiskyn handarinnar gegnir mikilvægu hlutverki við hreyfingu og skyn og í samskiptum okkar við umheiminn. Taugaáverkar geta verið flókin áskorun fyrir viðkomandi einstakling. Skaðar á úttaugum geta komið fram á breiðu rófi einkenna, allt frá vægum óþægindum til mikils og viðvarandi sársauka og fötlunar.

Skaðar á skyntaugum fingranna, eru oft taldar minni háttar og eru tölfræðilega algengasta tegund úttaugaskaða, með tíðni 6,2 á hverja 100,000 íbúa árlega. Karlar verða fyrir skyntaugaskaða sem varpar ljósi á áhugaverða kynjadreifingu hvað varðar taugaskaða.

Ofar i grimlimnum finnum við stærri taugastofna, svokallaða mið- og ulnartaug. Þessar taugar innihalda bæði hreyfi- og skyntaugaþræði en deila sé síðar neðan við úlnlið og verða að skyntaugum fingranna. Við skaða á mið- eða ulnartaug, eru afleiðingarnar oft alvarlegri með skertri tilfinningu og hreyfivirkni í hendi, og jafnvel þrálátum verkjum. Skurðaðgerð við slíkum áverkum felur oft í sér flókið ferli þar sem val á milli beins taugasaums eða í vissum tilfellum, notkun taugaígræðslu getur ráðið úrslitum um bata.

Eftir skurðaðgerð hefja þessir sjúklingar langvinnt endurhæfingarferli. Hvernig félagslegir þættir hafa áhrif á bata hefur ekki verið rannsakað að fullu til þessa. Félagsleg samskipti einstaklinga geta breyst svo sem líkamleg nálægð sem oft getur orðið erfið. Í grundvallaratriðum ná afleiðingar úttaugaskaða í hendi og framhandlegg langt út fyrir klínískar mælingar og undirstrika mikilvægi þeirra í margbreytileika daglegs lífs.

Tilgangur þessarar ritgerðar er að brúa bilið milli klínísks mats og þess veruleika sem einstaklingar með úttaugaskaða upplifa

Ritgerðin felur í sér afturskyggna rannsókn á árangri skurðaðgerða sem gerðar voru á úttaugaáverkum. Byggt var á sænska gagnagrunninum HAKIR. Rannsóknin miðaði að því að greina sjúklingahópa sem eru sérstaklega útsettir fyrir þessum meiðslum sem og margvíslegra félagsþátti. Rannsóknin skoðaði einnig eigin upplifun sjúklinga eftir áverka.

Þá var og lagt gagnrýnt mat á árangur við notkun á sérmeðhöndluðum taugaígræðslum (Processessed nerve allograft) við úttaugaskaða. Þetta fól í sér vandlega endurskoðun á kostum og göllum þessarar aðferðar, hugsað sem framlagt til aðstoðar við faglega ákvarðanatöku í klínískri meðferð í framtíðinni. Þrátt fyrir umtalsvert magn af rannsóknum, takmarkaði skortur á tvíblindum samanburðarrannsóknum rannsóknum innsýn í klíníska árangur sérmeðhöndlaðra taugaígræðsla.

Ritgerðin nær einnig til sameindasviðsins, þar sem Mass Spectormetry greiningartækni var notuð til að kryfja próteinmynstur skaðaðra úttaugaenda. Markmiðið var að sýna fram á breytingar í próteinmynstri sem gæti verið lykillinn að því að spá fyrir um árangur eftir meðferð við taugaskaða og stuðla að frekari skilningi á taugaheilunarferlum. Upp- og niðurstýring einstakra próteina leiddi í ljós flóknar sameindabreytingar í nær- og fjarlægum taugaendum eftir áverka.

Úttaugaskaðar og útkoma eftir aðgerð er klínísk áskorun vegna óásættanlegrar útkomu í mörgum tilfellum. Niðurstöður þessarar ritgerðar kalla á heildræna nálgun við meðferð á útlægum taugaskaða. Rannsóknin sýnir fram á flókið samspil þar sem val á meðferð og félagslegir þættir hafa áhrif á hvernig sjuklingum reiðir af bæði líkamlega og félagslega. Kerfisbundin rannsókn sem gerð var á sérmeðhöndluðum taugaígræðslum og hinu flókna próteinmynstri úttauga hefur einnig aukið skilning okkar og getur orðið vegvísir aðbetri aðferðum við meðferð og þar með bætt árangur á meðhöndlun úttaugaskaða.

Introduction

The complex network of peripheral nerves within the upper limb plays a role in sensory and motor functions, including feedback systems, as well as pain function. However, when subjected to a nerve injury, alterations in these delicate neural pathways present complex challenges, ranging from discomfort to profound disabilities and even persistent pain.

Digital nerves, often perceived as insignificant, are particularly vulnerable to injury, with an incidence rate for a partial and total transection injury of 6.2 per 100,000 inhabitants every year, with a notable preference for men[1]. Transection injuries to the median and ulnar nerves in the forearm carry significant consequences, such as impaired hand sensibility, diminished motor function, and sometimes persistent pain. Surgical interventions for nerve injuries require precise decision-making, which may involve direct nerve repair with sutures, or in cases where there is a nerve defect, nerve reconstruction through grafts, or employing increasingly prevalent nerve transfers[2,3]. Additionally, while new interventions like processed nerve allografts (PNA) are becoming more common, the lingering uncertainties regarding their efficacy complicate treatment decisions.

Postoperative rehabilitation for individuals undergoing nerve surgery is comprehensive, but the impact of socioeconomic factors on recovery remains inadequately understood. Peripheral nerve injuries not only affect clinical outcomes but also disrupt social interactions, challenging physical proximity, and intimate connections, compounded by the loss of motor and sensory function in the upper extremity.

While the measurable outcomes of surgically treated peripheral nerve injuries are well-documented, understanding the subjective experiences of individuals within broader populations remains a challenge. This thesis aims to fill this gap by retrospectively mapping surgically treated peripheral nerve injuries in the upper limb. By leveraging Sweden's national HAKIR database, with linking to other registers, like Statistics Sweden (scb.se), the research seeks to identify patient groups more susceptible to these injuries as well as their impact on outcome, considering a diverse range of socioeconomic factors.

Furthermore, the thesis includes a systematic review of original research articles evaluating the use of processed nerve allografts (PNAs) in peripheral nerve surgery. This involves an examination of the advantages and disadvantages of PNA,

contributing to insights into evidence-based decision-making in future clinical practice.

The exploration of the thesis extends to the molecular level, employing mass spectrometry techniques to dissect alterations in the proteomic patterns of injured digital nerve endings. This molecular-level scrutiny aims to uncover differences that could serve as keys to a better understanding of the nerve healing processes, including perspectives on the timing of surgery.

In conclusion, this doctoral thesis seeks to comprehensively elucidate the intricacies of surgically treated peripheral nerve injuries in the upper limb. Beyond clinical metrics, the research amplifies the multifaceted nature of these injuries and provides insights that might guide future treatment strategies, ultimately enhancing the holistic care of individuals grappling with the functional loss of peripheral nerve injury.

"Mostly it is loss which teaches us about the worth of things"
Arthur Schopenhauer

Background

The peripheral nerve

The peripheral nerve, a fundamental component of the nervous system, consists of intricate structures designed for efficient communication between the brain, the spinal cord and various body parts[4]. The structures known as fascicles are comprised of bundles of nerve fibers with their protective layer called the perineurium which ensures the structural integrity of the clusters of axons, and their surrounding Schwann cells (SC). In addition, the axons are surrounded by a basal membrane, collagen fibers and other cells, like resident macrophages, mast cells and fibroblasts, comprising the endoneurium. Further safeguarding the entire nerve is the epineurium, a loose connective tissue layer that acts as a sheath connecting the fascicles, which vary among nerves (Figure 1).

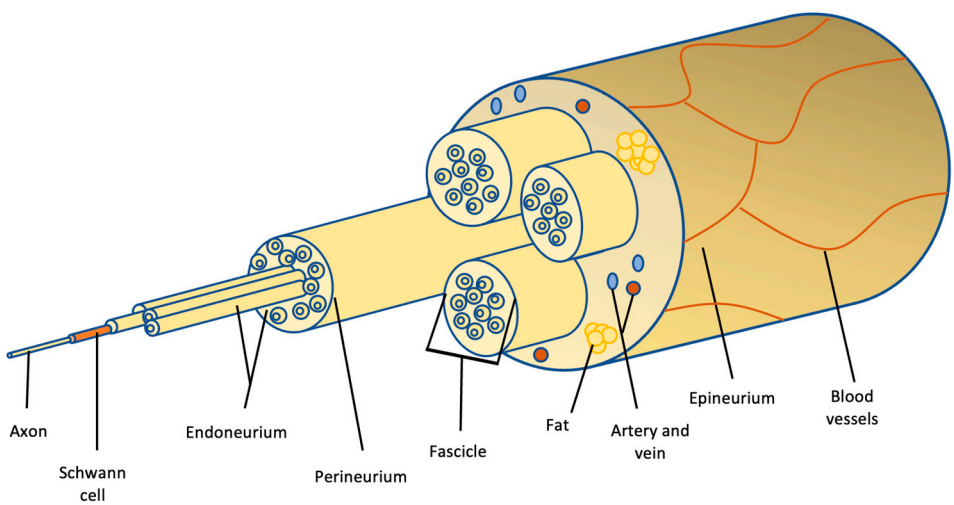

Figure 1. Schematic drawing of the peripheral nerve

Crucially contributing to nerve function are the SC, specialized cells that wrap around axons to form myelin, a fatty substance optimizing the speed of electrical impulses along the myelinated nerve fibers[4]. This myelination process enhances the precision and rapidity of signal transmission between the nodes of Ranvier. In the case of unmyelinated fibers, several axons are often enclosed within troughs or invaginations of a single SC. These troughs are called "Remak bundles" or "Remak fibers," named after the German anatomist Robert Remak who first described them. Remak bundles are typically found in peripheral nerves and are more prevalent in smaller-diameter nerve fibers[5] (Figure 2).

Peripheral nerves house axons from sensory neurons, where the nerve cell bodies predominantly are situated in the dorsal root ganglia adjacent to the spinal cord. These sensory neurons function as channels tasked with receiving signals from cutaneous mechanoreceptors and other receptors to enable the perception of external and internal stimuli. Conversely, motor units, comprising motor neurons, with their nerve cell bodies in ventral horn of the spinal cord, their axonal projections, and the associated muscle fibers, execute motor commands emanating from the central nervous system, showcasing the intricate functionality inherent in peripheral nerves. In addition to its structural complexity, peripheral nerves are highly vascularized, both on their surface and internally. This extensive vascular network ensures the efficient delivery of oxygen and nutrients to the nerve tissue, supporting its metabolic demands.

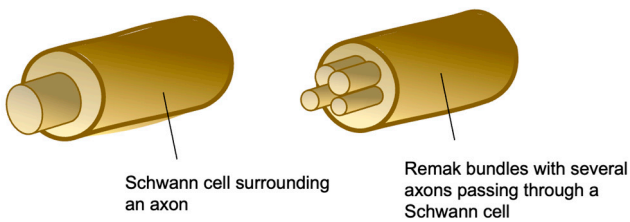

Figure 2. Myelinated fibers and unmyelinated fibers

Peripheral nerve injury

A peripheral nerve injury refers to the impairment or dysfunction of a peripheral nerve. These nerves play a pivotal role in motor function, sensory perception, and the regulation of various physiological functions, including perception of cold, heat and pain[6]. In 1943, Seddon introduced a comprehensive classification system for nerve injuries, categorizing them into three main types based on the nature of nerve fiber injuries and the presence or absence of nerve continuity. Neurapraxia denotes a disruption in the conduction of electrical signals, while leaving the axons intact,

often leading to recovery without surgical intervention. Axonotmesis, on the other hand, entails disrupted axons, while preserving the integrity of the epi- and perineurium, often facilitating natural recovery without surgical intervention. The most severe type, Neurotmesis, involves complete nerve transection, demanding surgical intervention for restoration[6].

Subsequently, in 1951, Sunderland expanded Seddon's classification to include five degrees of peripheral nerve injury, primarily distinguishable through histological examination[7]. A later addition by Susan Mackinnon introduced a sixth-degree injury, describing nerve injuries encompassing a combination of two or more of the degree I-V[8] (Figure 3).

Following a peripheral nerve injury of sufficient severity, the affected nerve fibers undergo Wallerian degeneration, a process involving the removal of myelin debris and the disintegration of axons in the damaged nerve distal to the site of injury. Consequently, the normal transmission of information along the nerve pathway is disrupted, leading to functional impairment in the corresponding muscles and skin areas supplied by the affected nerve. This prompts an immediate inflammatory response with the recruitment of immune cells, such as M1 and M2 macrophages, which have several functions, such as cleaning up the debris as well as stimulating the nerve regeneration process[9]. Proximal to the injury site, neurons initiate an axonal regrowth program, with elongation of the axons into the distal nerve end guided by dedifferentiated SC that are activated and proliferate, forming structures known as bands of Büngner[10]. SC transition from a myelinating state, also including the SC related to unmyelinated axons, to a growth-supportive state, marked by the upregulation of numerous genes associated with regeneration[11]. Simultaneously, various signaling pathways are activated in both neurons and SC, essential for the regenerative response, involving a spectrum of proteins[9,12-14]. These include the well-known neurotrophic factors, like nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which activate intracellular signaling cascades, including pathways regulating cell survival, proliferation, and differentiation[15,16]. Additionally, extracellular matrix (ECM) molecules, such as laminin, fibronectin, and collagen, provide structural support and guidance cues for regenerating axons[17]. The interplay between ECM molecules and cell surface receptors, notably integrins, regulate cellular responses to promote axonal outgrowth[18]. Furthermore, cell-cell interactions involving neurons, SC, and immune cells within the injured nerve microenvironment play a role in regulating the regenerative process through paracrine signaling and the release of cytokine[16].

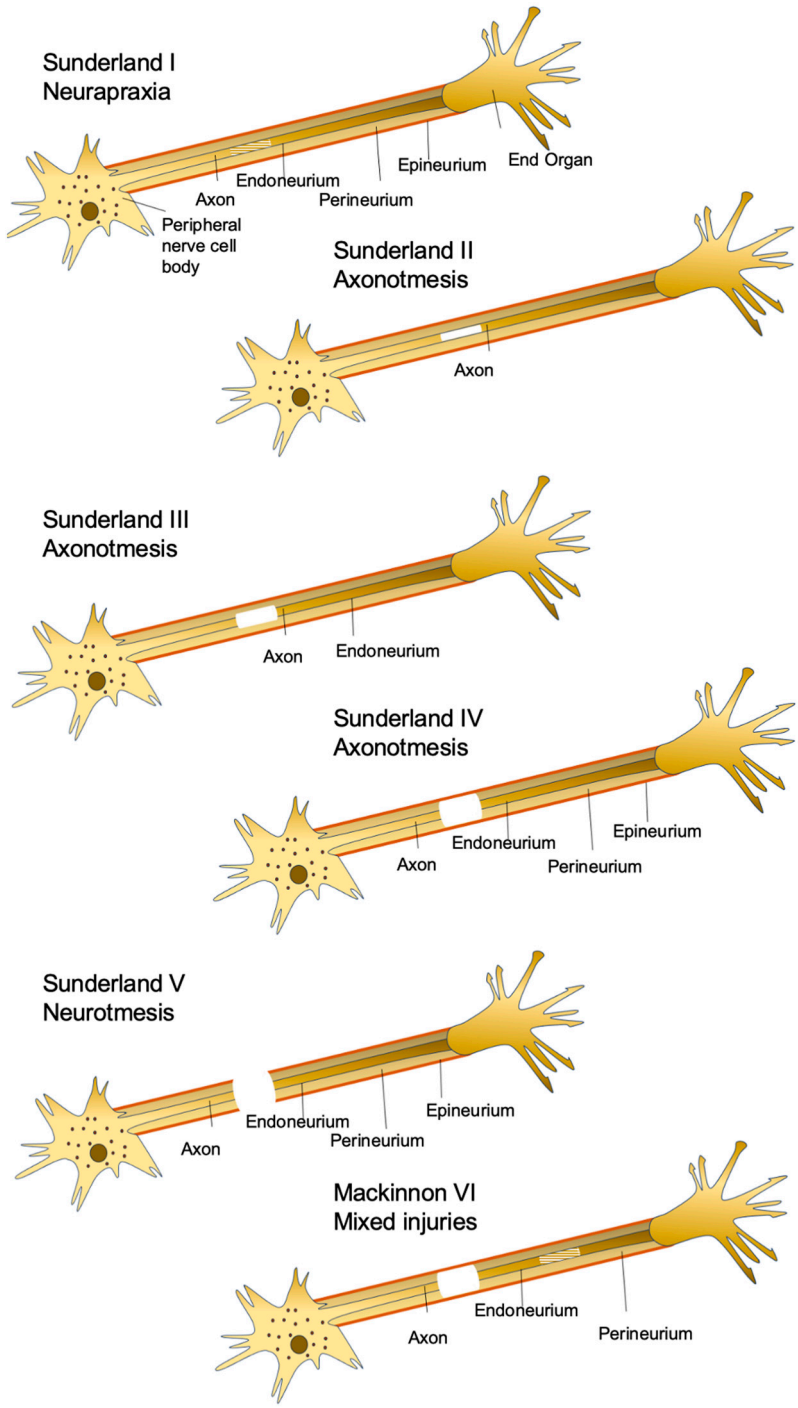

Figure 3. Schematic drawing of the six injury degrees for peripheral nerve injury.

Over time, regenerating axons may re-establish connections with their target tissues, leading to functional recovery, although this process can span from months to years [19,20], and at that time the "cell machinery" returns to "maintenance" from a "production machinery" during regeneration, probably with subsequent changes in the proteomic pattern. As these regenerating axons traverse the injury site, their entry into the endoneurial tubes of the distal end - the protective tunnels encasing individual nerve fibers within the peripheral nerve - plays a crucial role in directing them back to their original target organs, specifically, the receptors in the skin and muscles. However, it is common for regenerating axons to become misdirected after a complete nerve injury [19,21] significantly impacting the outcome following a nerve injury (Figure 4).

At last, the rate of axonal outgrowth in humans is relatively slow, at approximately 1-2 mm per day[19]. Consequently, the level and location of the nerve injury play a pivotal role in determining the distance and time required for axons to re-establish connections with their target organs. Proximal injuries, occurring closer to the nerve cell bodies or central nervous system, often pose more serious and troublesome challenges for nerve regeneration compared to distal injuries located further along the nerve pathway due to the risk of neuronal cell death as well as the long regeneration distance. Additionally, variations between nerves have been shown to exist were nerves that contain mixed motor and sensory fibers may present with more complex challenges for regeneration and functional recovery compared to those with predominantly motor or sensory functions[22,23].

Our understanding of peripheral nerve injury has been greatly enhanced through extensive research. However there remains a crucial gap in our knowledge concerning the intricate proteomic profiles at the proximal and distal ends of peripheral nerves in humans where previous studies have predominantly relied on animal models. Furthering the comprehensive understanding of the peripheral nerve injury processes is vital for developing effective strategies in nerve injury treatment and rehabilitation for optimal recovery.

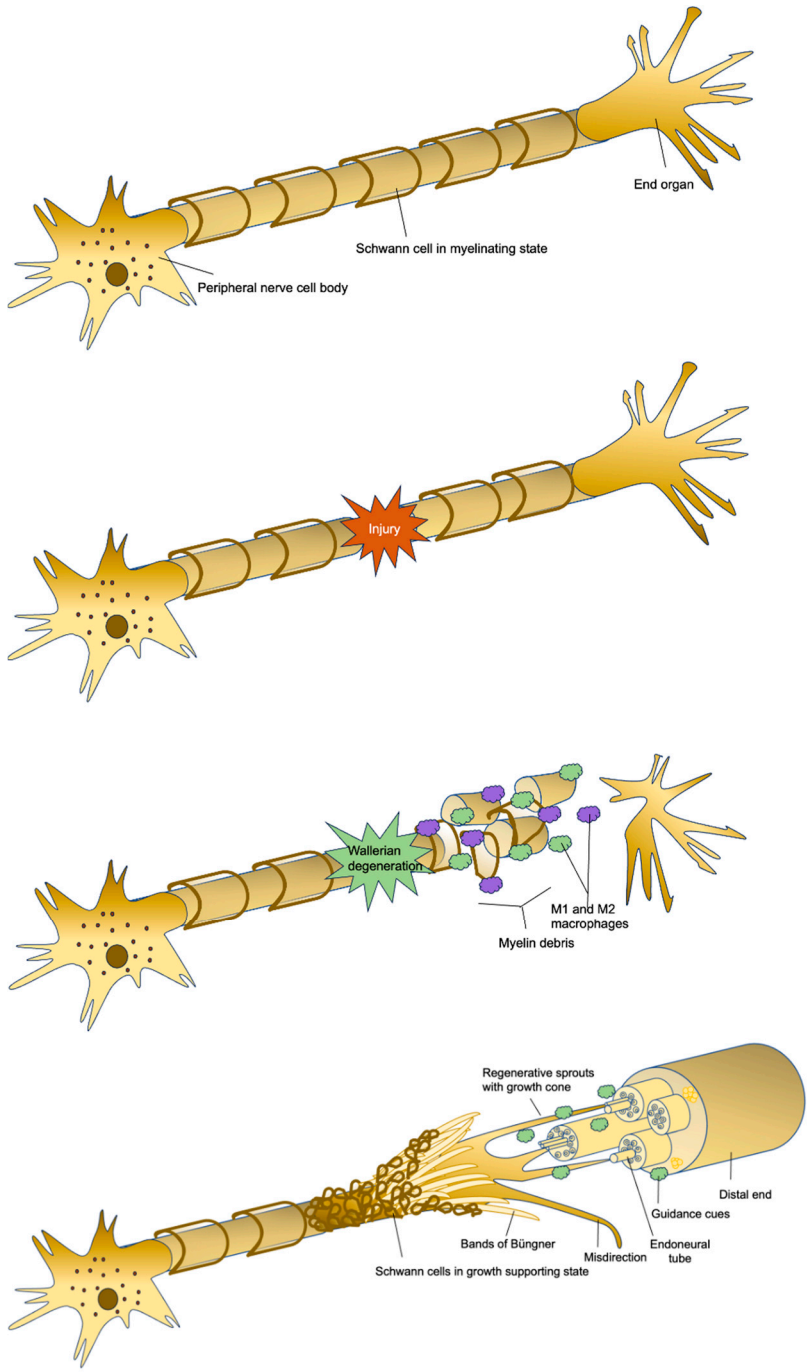

Figure 4. The process of Wallerian degeneration and regeneration after peripheral nerve injury.

Outcome measures for peripheral nerve injury

Outcome measures for peripheral nerve injuries typically encompass a variety of physical, functional, and subjective assessments to evaluate the extent of injury and monitor recovery progress. These assessments measure different aspects of nerve function and recovery, each with its advantages and limitations. Therefore, a comprehensive approach that combines multiple tests is often necessary in both clinical practice and research settings to provide a more thorough evaluation and better understand the nuances of nerve injury and recovery.

Sensory and motor function assessment

Evaluation of sensory perception involves various tests, including two-point discrimination (2PD), light touch, proprioception, shape and texture identification vibrometry, and temperature threshold tests[24]. These tests aim to assess the patient's ability to discern between two separate points, perceive light touch sensations, maintain joint position sense, identify small “items”, detect vibratory stimuli, and the perception of heat and cold, respectively. Conversely, motor function assessment entails evaluating individual muscle strength, grip strength, and pinch grip, which offer insights into motor nerve integrity and function[25]. Impairment of sensory function, resulting from a peripheral nerve injury, can affect motor strength via a feedback mechanism. Diminished sensory input may lead to reduced motor output, impacting muscle activation and coordination[26]. These evaluations are important for understanding the extent and severity of peripheral nerve injury, guiding treatment decisions, and monitoring patient progress over time.
For the advantages and limitations of each assessment test, the reader is referred to Table 1.

Two-point discrimination (2PD)

The 2PD is designed to test the ability to distinguish between the touch of one or two points. The distance between the points ranges from 2-15 mm and stimulates the skin through pressure. A m2PD (moving 2PD) is performed instead by dragging the two points along the fingertip. The American Society for Surgery of the Hand classifies 2PD as follows: <6 mm=normal, 6-10 mm=good, 11–15 mm=poor. Thresholds are lower for m2PD[25]. The 2PD was included as an outcome measure in the PICO framework for Paper IV.

Semmes-Weinstein Monofilament Test (SWMT)

Semmes-Weinstein Monofilament Test (SWMT) is a reliable and validated instrument that measures different thresholds between light touch and deep pressure. The SWMT is usually in clinical praxis divided according to a 5-point scale for functional sensation, where 1 (6.65) = the perception of deep pressure, 2 (4.56) =

loss of protective sensation, 3 (4.31) = decreased protective sensation, 4 (3.61) = decreased perception of light touch and 5 (2.83) = normal perception of touch and pressure[27]. A more extensive kit of filaments is also available consisting of 20 different monofilaments. The SWMT was included as an outcome measure in the PICO framework for Paper IV.

Ten test (TT)

Ten Test" (TT) serves as a practical bedside tool for evaluating discriminative sensation, particularly the magnitude of abnormal sensation in comparison to an area with normal sensation. During the test, a gentle touch is applied to the region experiencing abnormal sensation and the patient assesses its magnitude using an 11-point Likert scale, ranging from 0 (indicating abnormal sensation) to 10 (representing the most severe abnormal sensation)[28]. The TT offers simplicity in execution and yields a quantitative measure of abnormal sensation, potentially capturing changes in sensation over time, thereby aiding in the assessment of treatment efficacy. However, like other subjective assessments, the TT relies on the patient's perception and interpretation of abnormal sensations which may vary among individuals. Although the TT test was not used in any of the papers included in the thesis it is presented here for informational purposes.

Vibrometry and temperature thresholds

Vibrometry uses controlled vibrations to assess the patient's ability to perceive sensations. It measures the minimum amplitude of vibration the patient can detect, indicating nerve or mechanoreceptor dysfunction. This test aids in diagnosing and monitoring conditions, like neuropathies and carpal tunnel syndrome. Similarly, temperature threshold testing assesses the patient's ability to detect temperature changes, helping identify abnormalities in nerve function. In clinical practice, vibrometry and temperature threshold testing are typically performed as part of a comprehensive sensory examination, along with other tests, such as light touch, two-point discrimination, and proprioception assessments. Both tests provide quantitative data on sensory function and aid in treatment monitoring[25]. While vibrometry and temperature threshold testing provide additional measures of sensory function, they may not be routinely employed in clinical settings for peripheral nerve injury follow-up. While the vibrometry and temperature threshold testing were not used in any of the papers included in the thesis they are presented here for informational purposes.

The Shape texture identification test (STI)

The original shape-texture-identification (STI) test, presented in 1998, is a common assessment tool for tactile gnosis. The STI assesses the ability of an individual to discriminate between different shapes and textures using tactile sensation alone. It is commonly used in clinical settings to evaluate sensory

function, including in individuals with a peripheral nerve injury. A new version of the STI test—STI_2—has recently been introduced and validated[29]. The test was not used in any of the papers included in the thesis but is presented here for informational purposes.

Manual muscle testing

Manual muscle testing, using the Medical Research Council (MRC) grading system, assesses the strength of individual muscles or muscle groups affected by the nerve injury. This scale provides a systematic way to quantify muscle weakness from M0-M5 and monitor changes in strength over time.

M0 – No contraction: The muscle is completely flaccid and unable to produce any contraction, even with maximal effort.

M1 – Trace contraction: A trace contraction or "flicker of movement" is observed, indicating minimal muscle activity that is usually palpable but not visible or measurable as a joint movement.

M2 – Active movement with gravity eliminated: The muscle can move actively when gravity is eliminated, such as in a supine position or with the limb supported against gravity.

M3 – Active movement against gravity: The muscle can move actively against gravity, but not against resistance applied by the examiner.

M4 – Active movement against some resistance: The muscle can move actively against resistance applied by the examiner, but not against strong resistance.

M5 – Normal strength: The muscle can move actively against strong resistance and maintain a normal range of motion.

During muscle strength testing, the examiner evaluates the patient's ability to perform specific movements or resist applied force while assessing the level of muscle contraction. Each muscle or muscle group is graded individually based on the observed strength. The MRC scale allows for consistent and objective assessment of muscle strength across different patients and clinicians[25,30]. The manual muscle testing was included as an outcome measure in the PICO framework for Paper IV.

Grip strength and pinch grip

Dynamometers or handheld pinch grip gauge meters, such as the Jamar hand dynamometer, are used to quantify grip and pinch strength, which is particularly relevant for nerve injuries affecting the hand and forearm. Comparing strength between the affected and unaffected sides provides valuable information about motor deficits[25,30]. The grip strength and pinch grip tests were included as an outcome measure in the PICO framework for Paper IV.

Table 1. Advantages and limitations of different sensory and motor function assessment tools

Measure	Advantages	Limitations
2PD	- Tests ability to distinguish between touch sensations - Provides quantifiable results for assessing sensory function	- Requires specialized equipment and training
SWMT	- Reliable and validated instrument for measuring sensory thresholds - Divides sensory perception into different functional categories	- Requires a set of specific monofilaments for testing - May be time-consuming to administer and interpret
TT	- Practical bedside tool for evaluating discriminative sensation - Provides quantitative measure of abnormal sensation	- Relies on subjective assessment by the patient - Interpretation may vary between individuals
Vibrometry and temperature threshold	- Assess patient's ability to perceive vibrations and temperature changes - Provides quantitative data on sensory function	- Not routinely employed in clinical settings for peripheral nerve injury follow-up - Requires specialized equipment and expertise
STI	- Assesses ability to discriminate between shapes and textures using tactile sensation alone - Commonly used in clinical settings to evaluate sensory function	- May not fully capture sensory function related to nerve injuries - Interpretation may be subjective
Manual muscle testing	- Systematic way to quantify muscle weakness and monitor changes over time - Provides objective assessment of muscle strength	- Requires familiarity with the MRC grading system - Muscle testing may not fully capture motor deficits related to nerve injuries
Grip strength and pinch grip	- Quantifies grip and pinch strength, relevant for nerve injuries affecting the hand and forearm - Provides valuable information about motor deficits	- Comparing strength between affected and unaffected sides may be influenced by other factors - Impaired sensory function may impact strength measurement

2PD-Two-point discrimination, SWMT-Semmes-Weinstein Monofilament, TT-Ten test, STI-The Shape texture identification test

Cold sensitivity

Cold sensitivity presents as a significant and disabling symptom following various hand conditions and injuries, particularly those involving the digital and major nerves in the upper extremity[31,32]. Cold sensitivity is defined by four types of symptoms on exposure to cold: 1) pain/discomfort, 2) stiffness, 3) altered sensibility, and 4) color change; all of which may occur in isolation or any combination and severity[33]. The onset of symptoms varies widely, ranging from immediately to months after the injury. However, in the majority of cases, symptoms typically manifest within the initial six months following injury and may persist for several years[31,32,34], with the risk of becoming permanent[35]. The mechanism(s) of cold sensitivity remain(s) largely unknown, and the understanding of this phenomenon is still incomplete. The previously reported prevalence varies and is reported to be 38% to 83%[36]. Nerve entrapment syndromes appear to have an overall lower prevalence compared with traumatic peripheral nerve injuries, where surgical treatment appears to reduce the prevalence and severity of cold sensitivity[37]. Research into the underlying causes and pathways contributing to cold sensitivity after peripheral nerve injury is ongoing, but many aspects have not been fully investigated or understood. Additionally, there is limited knowledge regarding the impact of cold sensitivity on daily life.

Cold sensitivity in the HAKIR questionnaire

The HAKIR questionnaire (HQ-8)[38,39] is a newly developed, and validated PROM available in both Swedish and English versions, It includes questions on seven hand symptoms and one question on hand function, where all questions are scored zero to 100 numerical scale (0 = no symptoms; 100 = worst outcome). One question regards cold sensitivity, which allows for a deeper investigation of the connection of such a symptom to a nerve injury (Appendix 1). The HAKIR questionnaire including the question on cold sensitivity was used as a outcome measure for Papers II-III. For details concerning the HAKIR registry, the reader is referred to the Methods section.

The Cold Sensitivity Severity Scale (CSS)

The rating scale is used to evaluate cold sensitivity during daily life activities. Patients are asked to mark on a line the severity of cold sensitivity during certain activities and the score is summarized[25]. The CSS was not used as an outcome measure in this thesis. It is presented here for informational purposes.

Cold intolerance symptom severity (CISS)

Consists of 6 questions that highlight the impact of cold intolerance on daily life. The threshold value for pathological cold intolerance of 30 and 50 for a population with a Scandinavian climate[25]. The CISS was not utilized in this thesis but presented to provide informational clarity.

Pain assessment

Assessing pain accurately is crucial in the management of peripheral nerve injuries. Typically, pain intensity and characteristics of peripheral nerve injury are evaluated using standardized pain scales, such as the Visual Analog Scale (VAS) or NRS scale[24]. These scales provide clinicians with a quantitative measure of the pain severity reported by patients, which assists in devising treatment plans and monitoring the effectiveness of pain management strategies[24]. Moreover, individuals with peripheral nerve injuries might encounter heightened sensitivity to pain, a condition known as allodynia, where ordinarily non-painful stimuli of the skin can trigger discomfort or pain sensations. It is imperative to address allodynia alongside other pain symptoms for comprehensive pain management in these scenarios. Nonetheless, the intricate nature of pain perception and the diversity of individual experiences highlight the ongoing need for research to refine pain assessment techniques and enhance patient outcomes. Further, an exploration into the mechanisms underlying pain generation and modulation in the context of peripheral nerve injuries is warranted to deepen our understanding and improve pain management strategies for affected individuals. For the advantages and limitations of each assessment test, the reader is referred to Table 2.

Visual Analog Scale (VAS)

VAS is a simple tool used to employed to assess subjective experiences, such as pain. It comprises a horizontal line 10 centimeters in length, delineated with one end denoting "no pain" and the opposite end representing the "worst possible pain." Participants mark this line to indicate the intensity of their pain and the distance from the "no pain" end is measured to provide a quantitative score ranging from 0 to 100[40]. The VAS scale was used included as an outcome measure in the PICO framework for Paper IV.

Numerical Rating Scale (NRS)

The pain rating box scale is commonly used for assessing pain intensity. It utilizes a unidimensional scale where individuals rate their perceived pain level intensity on a scale from 0-100. On this scale, 0 denotes “no pain” while 100 signifies “pain as bad as it could be”[24]. The NRS has demonstrated superior compliance rates, responsiveness, and ease of use compared to the VAS, with a robust correlation established between the two[41]. The NRS scale was considered an outcome measure in the PICO framework for Paper IV.

McGill pain Questionnaire

Designed to provide quantitative evaluations of clinical pain, the McGill Pain Questionnaire offers a thorough examination of pain intensity, quality, and affective elements. It comprises a set of inquiries and descriptors enabling individuals to articulate and delineate their pain experience in depth[42]. Although not utilized in the papers for this thesis, it is presented here for informational purposes.

Eight specific questions in HAKIR (HQ-8)

The questionnaire presented as a box scale from 0 to 100 contains among others, three questions specifically designed to assess pain, including the questions “pain on load”, “pain on motion without load” and “pain at rest”. By including these questions, the questionnaire aims to provide a comprehensive assessment of pain across different contexts and activities, allowing for a more detailed understanding of the nature and impact of pain experienced by the individual[43] (Appendix 1). The HQ-8 was used as an outcome measure for Papers II-III. For details concerning the HAKIR registry, the reader is referred to the Methods section.

Central neuropathic pain

Unlike nociceptive pain, which is caused by the activation of pain receptors in response to tissue damage or inflammation, central neuropathic pain is characterized by abnormal processing of pain signals within the central nervous system (CNS). After a peripheral nerve injury, pain can occur because of changes in the way pain signals are transmitted and processed by the CNS. Injury to the peripheral nerves can lead to altered sensory processing, hyperexcitability of neurons, and abnormal

pain perception. This can result in chronic, persistent pain[44]. To assess central neuropathic pain, clinicians may use a combination of self-reported pain scales, such as the NRS or McGill pain Questionnaire, sensory testing, neurological examinations, and psychosocial assessments[24].

Table 2. Advantages and limitations of different pain assessment tools

Measure	Advantages	Limitations
VAS	- Easy to use - Provides visual representation of pain - Quantitative scoring for tracking changes over time	- Only measures pain intensity - Interpretation varies between individuals - Doesn't capture pain quality or affect
NRS	- Simple numerical assessment of pain intensity - Offers a wide range of scores for nuanced assessments	- Interpretation depends on individual perception - May not detect subtle changes in pain perception
McGill Pain Questionnaire	- Comprehensive evaluation of pain - Provides detailed insights into various aspects of pain	- Lengthy questionnaire may be time-consuming - Scoring range may limit nuanced assessment
HAKIR (HQ-8)	- Includes specific questions for pain assessment - Aims for comprehensive understanding of pain nature	- Limited scoring range may lack nuance - May lack specificity for nerve injury assessment

VAS Visual Analog Scale, NRS Numerical Rating Scale, HAKIR Swedish National Quality Registry for Hand Surgery

Electrophysiological studies

Nerve conduction studies (NCS) and electromyography (EMG) serve as indispensable diagnostic instruments for evaluating nerve function and identifying abnormalities in nerve conduction and muscle activity[25]. NCS evaluates the velocity and amplitude of electrical signals as they propagate along peripheral nerves, while EMG gauges the electrical activity produced by muscles during both contraction and relaxation. These diagnostic procedures are widely employed globally as part of the initial assessment and ongoing monitoring of peripheral nerve injuries. By furnishing objective insights into nerve and muscle functionality, NCS and EMG aid clinicians in rendering precise diagnoses, formulating tailored treatment plans, and tracking the progression of nerve regeneration and recovery over time. Furthermore, NCS and EMG play a pivotal role in evaluating the efficacy of interventions, such as surgical nerve repair, nerve reconstruction with grafts, or rehabilitative therapies, in enhancing nerve function and reinstating muscle strength[45]. While electrophysiological studies were not included in the papers for

this thesis, the studies are presented here for informational purposes. For the advantages and limitations of each assessment test, the reader is referred to Table 3.

Nerve conduction studies (NCS)

During NCS, electrodes are placed on the skin overlying specific nerves, and small electrical pulses are delivered to stimulate the nerves. The response of the nerves to these stimuli is recorded, allowing clinicians to assess parameters, such as conduction velocity, latency, and amplitude. Conduction velocity reflects the speed at which nerve impulses travel along the nerve fibers, while latency measures the time it takes for a nerve impulse to reach a specific point along the nerve pathway. Amplitude represents the strength or intensity of the nerve signal. Abnormalities in nerve conduction parameters observed during NCS can provide valuable information about the location, severity, and pathophysiology of lesions affecting the peripheral nerve. For example, a reduction in conduction velocity indicates demyelination or the effects of remyelination after an injury or after nerve regeneration, with or without a surgical procedure. A lower amplitude indicates axonal degeneration or an impaired regeneration of nerve fibers after an injury, with or without a surgical procedure. Impaired nerve conduction velocity and a lower amplitude may both be present after nerve injuries, such as nerve compression or entrapment disorders, and particularly after nerve repair or nerve reconstruction[30].

Electromyography (EMG)

EMG involves the insertion of small needle electrodes into muscles to record their electrical activity. By assessing the pattern and amplitude of muscle responses to nerve stimulation, such as during voluntary activation by the patient, EMG can help to identify abnormalities in muscle function, such as denervation, reinnervation, or neuromuscular disorders[30].

Table 3. Advantages and limitations of electrophysiological studies in peripheral nerve injury

Measure	Advantages	Limitations
NCS	- Objectively assesses nerve function - Helps identify nerve signal characteristics like speed and strength - Aids in locating and understanding nerve lesions - Differentiates between types of nerve damage, aiding diagnosis	- May cause discomfort during electrode placement and stimulation - Requires specialized equipment and trained staff - Results interpretation can be complex - Results may be influenced by factors like temperature or limb position
EMG	- Evaluates muscle function and detects issues - Detects denervation, reinnervation, and neuromuscular disorders - Guides diagnosis and treatment planning - Part of a comprehensive nerve injury evaluation	- Involves needle insertion into muscles, which can be uncomfortable - Potential for minor bleeding or bruising at needle insertion sites - Results interpretation may require expertise - May not detect deficits that only occur during specific movements or activities

NCS-Nerve conduction studies, EMG-Electromyography

Patient reported outcome measures (PROMs)

PROMs offer valuable insights into patients' symptoms, functional limitations, satisfaction with treatment, and overall perception of recovery in peripheral nerve injuries. While they contribute to a comprehensive understanding of patient recovery, PROMs are primarily utilized in research settings and large-scale studies to measure outcomes across diverse patient populations. They help researchers evaluate the effectiveness of treatments and interventions, providing essential data for refining therapeutic approaches and improving patient carer[46]. The QuickDASH was used as a PROM and presented in Papers I-III. For informational purposes several common PROMs are also presented below. For the advantages and limitations of each outcome measure the reader is referred to Table 4.

Disabilities of the Arm, Shoulder, and Hand (DASH) and the short version (QuickDASH)

The assessment of upper extremity disabilities is facilitated by tools like the DASH questionnaire and its abbreviated version, QuickDASH. These instruments offer insights into the impact of injuries or conditions on various aspects of life quality, encompassing physical function, emotional well-being, and social interactions. With DASH consisting of 30 questions, patients rate their perceived ability to perform daily activities on a 5-point scale, resulting in scores ranging from 0 (no disability) to 100 (highest disability). The DASH and the QuickDASH featuring 11 questions, have undergone reliability and validity testing. The

minimum clinically relevant difference for DASH is 10.83–15 points and for QuickDASH 15.91–20[25,47] (Appendix 1).

Michigan Hand Outcome Questionnaire (MHQ)

The MHQ available both in Swedish and English is a reliable and valid instrument for measuring hand outcomes. The questionnaire consists of 37 questions assessing disability from different domains, including overall hand function, activities of daily living (ADL), pain, work performance, aesthetics, and patient satisfaction with hand function[46,48].

International Consortium for Health Outcomes Measurement (ICHOM)

The ICHOM has developed a standardized set of metrics for assessing hand and wrist conditions, aiming to cover a wide spectrum of disorders, including those potentially involving peripheral nerve injuries[49]. While the standard set may not specifically focus on peripheral nerve injuries as a distinct category, it does include measures that can be applicable to assess outcomes related to nerve injuries affecting the hand and wrist[50]. For example, assessments of pain intensity, functionality, and quality of life included in the standard set can be relevant for individuals with peripheral nerve injuries involving the hand and wrist. These measures can help to evaluate the impact of nerve injuries on pain levels, hand function, and overall well-being, providing valuable information for treatment planning and monitoring. Additionally, complications related to peripheral nerve injuries, such as nerve entrapment syndromes or neuropathic pain, may be considered within the standard set's framework for monitoring postoperative complications and adverse events.

Impact of a Hand Nerve Disorders (I-HaND)©

The I-HaND scale is a reliable and validated tool specifically crafted to evaluate the influence of peripheral nerve disorders on hand function. Patients engage with a set of inquiries addressing diverse questions of hand functionality, encompassing sensation, strength, dexterity, pain, and overall functional impairment. Each item is rated on a Likert-type scale. The I-HaND can be used in clinical practice to monitor changes in hand function over time, to evaluate the effectiveness of treatment interventions, and to guide rehabilitation strategies[51].

Table 4. Advantages and limitations of different patient reported outcome measures.

Measure	Advantages	Limitations
DASH / QuickDASH	- Comprehensive assessment of quality of life - Reliability and validity tested	- The longer questionnaire may be time-consuming - Limited scoring range may lack nuance
MHQ	- Reliable and valid tool for measuring hand outcomes - Assesses disability across various domains	- Lengthy questionnaire may be time-consuming - Limited scoring range may lack nuance
ICHOM	- Captures outcomes relevant to hand and wrist disorders - Includes measures applicable to nerve injuries affecting the hand	- Doesn't specifically address peripheral nerve injuries - May lack specificity for nerve injury assessment
I-HaND©	- Tailored for assessing impact of peripheral nerve disorders on hand function - Validated patient-reported outcome measure - Useful in clinical practice for monitoring hand function changes	- Limited to assessing hand function, may miss broader issues - Scoring range may lack nuance - May not fully capture all aspects of peripheral nerve disorder-related disability

DASH Disabilities of the Arm, Shoulder, and Hand, MHQ Michigan Hand outcome questionnaire, ICHOM International Consortium for Health Outcomes Measurement, I-HaND© Impact of a Hand Nerve Disorders

Imaging Studies

Imaging methods, such as Magnetic Resonance Imaging (MRI) or ultrasonography (US), offer valuable insights into nerve anatomy, enabling the identification of structural abnormalities associated with degeneration and regeneration[52]. While not applied in the papers for this thesis, imaging studies are presented for informational purposes in relation to peripheral nerve injuries. For the advantages and limitations of each imaging modality, the reader is referred to Table 5.

Magnetic Resonance Imaging (MRI)

MRI offers detailed imaging of soft tissues, providing valuable insights into nerve structures and potential injuries. It enables non-invasive multiplanar imaging, allowing comprehensive assessment of nerve anatomy and s surrounding structures, like muscles, blood vessels, and bone. However, MRI scans can be expensive and may not be universally accessible in all healthcare settings. Moreover, they can be time-consuming, and their sensitivity for detecting certain types of nerve injuries may be limited[30].

Diffusion tensor imaging (DT

DTI is an advanced MRI technique. It analyses the diffusion of water molecules in biological tissues. Having emerged as a possible technique for evaluating peripheral nerve injuries, its ability to analyze nerve integrity, predict outcomes

based on lesion localization, and monitor possible regeneration, makes it a promising complement to conventional imaging modalities and a possible tool in the management of these injuries[53,54].

Ultrasonography

Ultrasonography provides real-time imaging of nerve structures, allowing for dynamic assessment of nerve mobility and function during movement. It is portable, cost-effective, and does not involve ionizing radiation. Ultrasonography offers high spatial resolution for superficial nerves and is convenient for bedside use. However, it is operator-dependent, and imaging quality may vary. Ultrasonography, however, has limited penetration through bone and air, which may hinder visualization of deeper nerves. It also has a smaller field of view compared to MRI and may have difficulty identifying subtle abnormalities[30]. However, recently it has been used to visualize hour-like changes in peripheral nerves after acute not traumatic mononeuropathies/plexopathies[55].

Table 5. Advantages and limitations of different imaging studies in peripheral nerve injury

Measure	Advantages	Limitations
MRI	- Provides detailed images of soft tissues, including nerves - Non-invasive and offers multiplanar imaging - Helps visualize nerve structures and potential injuries - Can assess surrounding structures like muscles and blood vessels	- Can be costly and not available in all healthcare settings - Time-consuming procedure - Limited sensitivity for certain types of nerve injuries
DTI	- Quantifies nerve integrity and aids in lesion localization - Predicts outcomes and monitors nerve regeneration	- Availability may be limited - Interpretation requires expertise
US	- Real-time imaging of nerve structures - Allows dynamic assessment of nerve mobility and function during movement - Portable, cost-effective, and does not involve ionizing radiation	- Operator-dependent - Limited penetration through bone and air - Imaging quality may vary

MRI Magnetic Resonance, DTI Diffusion tensor imaging, US Ultrasonography

Biomarkers in peripheral nerve injuries

A biomarker is a measurable characteristic that provides insight into biological processes, disease progression, or response to treatment. In the context of peripheral nerve injury research, biomarkers offer valuable information about the severity, prognosis, and underlying mechanisms of nerve damage. They can be detected in bodily fluids or tissues and are studied to enhance diagnosis, monitoring, and

treatment strategies. Biomarkers have emerged as possible tools in the field of peripheral nerve injury, offering insights into pathophysiology, severity, and prognosis. Although not yet widely adopted, scientists have made significant efforts to apply biomarker research to peripheral nerves, based on knowledge from experimental studies on different nerve injuries and repair and reconstruction procedures. Among the most studied biomarkers in this context are neurofilament proteins[56]. Neurofilaments, which are structural proteins found predominantly in axons, are released into the extracellular space and bloodstream following axonal damage during nerve injury. This release has been implicated in various neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)[56,57] as well as in metabolic diseases, such as diabetes[58]. However, further research is needed to explore the utility of these biomarkers in the context of traumatic peripheral nerve injury that can be used in certain injuries to evaluate severity and prognosis. Apart from neurofilament proteins, S-100 protein has emerged as a potential biomarker for peripheral nerve injury. These proteins, primarily found in glial cells, like SC, exhibit elevated levels in the blood or cerebrospinal fluid after nerve injury suggesting their role as markers for SC activation, proliferation, and apoptosis as well as other aspects of the regeneration process[59]. However, further research is still required to fully understand their clinical implications. Studies have also shown elevated levels of biomarkers associated with injuries to endothelial cells or dysfunction of such cells, an inflammatory response, and apoptosis in different cells in patients with conditions, like hand-arm vibration syndrome (HAVS)[60]. These biomarkers comprise the intercellular adhesion molecule-1 (ICAM-1), the monocyte chemoattractant protein-1 (MCP-1), thrombomodulin (TM), heat shock protein 27 (HSP27), von Willebrand factor, calcitonin gene-related peptide (CGRP), and caspase-3[60]; some of them also involved in traumatic nerve injuries in experimental models in healthy and diabetic rat sciatic nerves[61]. Importantly, exploring the role of these biomarkers from human nerve biopsies is scarce in the context of peripheral nerve injury and could provide insights into mechanisms of nerve degeneration after the injury, and the regeneration processes after nerve repair or reconstruction; particularly to what is known as from both animal and human experimental studies of nerve injuries[12,62-67]. Biomarkers hold promise for enhancing the diagnosis, monitoring, and treatment of peripheral nerve injuries. Further research is still needed for the identification and validation of biomarkers specific to peripheral nerve injury, particularly to confirm or refute findings observed in experimental models when translated to human subjects.

Treatment for peripheral nerve injury

The origins of peripheral nerve repair or reconstruction can be traced back to antiquity, with mentions as early as Hippocrates' era, although the exact details remain uncertain. In the 7th century, Paulus Aeginatus (626-696 AD) proposed the restoration of severed nerves, and the modern concept of suturing injured nerves was articulated by Gabriele Ferrara (1543-1627) in Italy[68]. Jan Forssman conducted in 1898 at the University of Lund, Sweden, research with animal nerves introduced into tubes and chambers made of straw, demonstrating that axons organized themselves into well-differentiated nerve structures within these spaces, showing a clear attraction towards the distal end[69]. This concept was further demonstrated in subsequent experimental models utilizing mesothelial chambers or silicone tubes- an innovation later translated into clinical practice[70-74]. The research paved the way for novel approaches, leading to the development and implementation of various conduits and alternative methods in clinical practice[75].

Over the last decades, advancements in specialized instruments, delicate suture materials, and the introduction of operative magnification have significantly enhanced the surgical technique for nerve repair and reconstruction, including nerve transfers, but the outcome of treatment is still not optimal.

Nerve repair with sutures

Restoration of function of the injured nerve can be performed by different surgical techniques[76,77] (Figure 5), where the primary end-to-end nerve suture, possible to perform in about 80% of the cases[78,79], is the most common choice of method. Additionally, repair performed with either loupe or operating microscope magnification by skilled hand surgeons can yield comparable outcomes, particularly in digital nerve repairs[80]. It is imperative to minimize tension during nerve repair, as excessive tension can compromise the nerve's blood supply, potentially leading to adverse effects on SC, including increased apoptosis and reduced activation[78,81-83]. Timing has emerged as a critical factor, emphasizing the importance of initiating primary sutures under appropriate conditions as soon as possible for neurobiological reasons[81]. Delayed nerve repair may result in greater nerve cell loss and poorer regrowth and remyelination of nerve fibres[84].

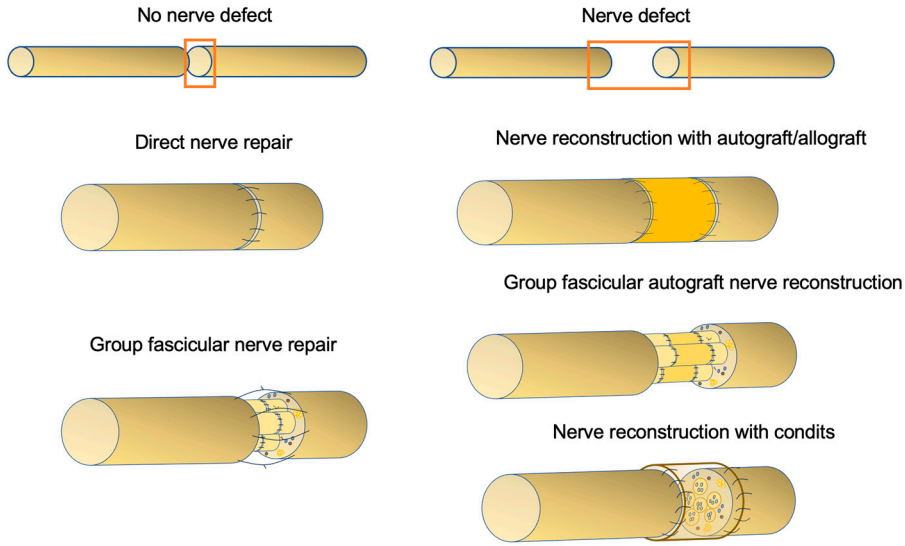

Figure 5. Schematic drawing of different surgical techniques for peripheral nerve injuries

Neuroma

In cases of a peripheral nerve injury, where repair or reconstruction is neglected or ineffective, the consequence can be the formation of a painful neuroma that may occur as an end neuroma, a neuroma-in-continuity or even a neuroma due to a surrounding scar or tethering of the nerve[85]. Neuromas are abnormal growths of the nerve fibers that develop at the site of the injury, often characterized by intense and persistent pain. These painful nodules arise due to the body's attempt to regenerate the damaged nerve fibers, leading to disorganized nerve endings that become hypersensitive to stimuli. PROMs have shown that neuromas not only cause physical discomfort but can also significantly impair daily activities and quality of life for affected individuals[78,86]. Proper management of peripheral nerve injuries is therefore crucial to mitigate the risk of neuroma formation, emphasizing the importance of timely and effective nerve repair strategies to promote optimal recovery and prevent debilitating sequelae[87], since residual problems remain despite surgery[86,88].

Nerve reconstruction with nerve autografts

In complex injuries, with an extensive nerve defect or when the nerve repair is delayed, different techniques are used to bridge the defect (Figure 5). Bridging a nerve defect with nerve autografts, such as the sural nerve, the terminal branch of the posterior interosseous nerve, or other alternatives, is well established and considered to be the gold standard[89-94]. Professor Hanno Millesi, along with his colleagues, modernized and highlighted the need for nerve reconstruction and

presented principles of the technique in the 1960s. His key contribution lies in perfecting microsurgical techniques, emphasizing precision and minimal trauma to the peripheral nerve. Millesi prioritized selecting suitable donor nerves and enhancing regeneration in the nerve grafts[92,95]. However, the use of nerve autografts in nerve reconstruction has several possible disadvantages, which mainly may be related to potential residual problems from donor site[96-98] with risks of neuroma formation and subsequent symptoms[99,100] as well as risk for infections and scar formation. Harvesting a nerve autograft prolongs the surgical procedure, implicating an increased need for resources. Lastly, a miss-match in the size of the nerve autograft with the size of the injured nerve may occur as well as a lack of enough graft material.

Nerve reconstruction with nerve conduits

An alternative in the absence of nerve tissue is the utilization of commercially available nerve conduits (Figure 5), constructed from materials, such as collagen or polymers[79]. These conduits offer a promising avenue for nerve regeneration, particularly in cases where traditional nerve tissue is not readily available. The damaged nerve ends are inserted into the conduit, facilitating the overgrowth of new nerve fibers towards the distal part of the nerve. Professor Göran Lundborg and his team pioneered experimental silicone tubes for nerve regeneration across very short nerve gaps, i.e., more than an alternative to nerve repair with sutures, in humans, paving the way for advancements in the field[74]. In recent years, nerve conduits have emerged as a promising alternative but probably only when the defect is less than 3 cm[101-104].

Nerve reconstruction with processed nerve allograft (PNA)

In recent years, a prospective innovation has emerged in the field of nerve regeneration, a so-called processed nerve allograft (PNA), which is a commercially available product manufactured and marketed as Avance® Nerve Graft by Axogen Corporation (https://axogeninc.eu/avance-nerve-graft/). PNA is a human nerve graft that has undergone a thorough sterilization and processing procedure to remove cellular components while preserving the structural integrity and nerve guidance properties[105-109]. PNA offers several possible advantages over traditional treatment options, including reduced surgical complexity with shorter operating time and decreased donor site morbidity. While previously published meta-analysis has shown promising results, defined as “meaningful recovery” rates for autograft (82%) and for allograft (87%)[75], especially when compared to conduits[110], studies have emerged in recent years showing suboptimal results after PNA treatment[111-114] when compared to autograft, contributing to doubts in its suitability for treatment of all kinds of nerve defects, including the type of nerve, where higher risk of failure may be present when used in larger nerve trunk injuries[115]. However, the absence of systematic studies on PNA efficacy underscores the pressing need for

comprehensive research to elucidate its effectiveness across various patient populations and nerve injury types, potentially guiding its optimization and clinical application, including considerations of its cost-effectiveness. In particular, there is a lack of studies evaluating the economic ramifications of PNA compared to traditional methods, especially within the context of healthcare systems in Sweden and Europe, in contrast to the healthcare system in the USA.

Nerve transfers in peripheral nerve injury

Nerve transfers in peripheral nerve injury involve surgically redirecting a healthy, expendable nerve to restore function in a paralyzed or injured nerve. This innovative technique bypasses the damaged area by transferring neural input from a nearby functioning nerve. It has gained popularity for its potential to offer quicker recovery and improved functional outcomes compared to traditional nerve repair or reconstruction methods[116]. Nerve transfers are particularly useful in cases where conventional techniques, like nerve grafting, are not feasible.
Nerve transfers may include shorter recovery times, enhanced functional outcomes, and reduced risk of donor site morbidity. Additionally, they may provide better muscle reinnervation and functional recovery compared to traditional methods. However, nerve transfers also have limitations. They require precise surgical skills and may not be suitable for all patients or all types of nerve injuries. Furthermore, nerve transfers involve sacrificing a functioning nerve, which could potentially lead to loss of function in the donor area. Critical factors influencing the success of nerve transfers include patient selection, surgical technique, such as how the donor nerve is attached to the injured nerve (for example, through epineurial or perineurial window techniques), and postoperative rehabilitation. Furthermore, while nerve transfers represent a promising advancement in peripheral nerve injury management, their superiority over traditional methods requires empirical evidence from comparative studies, including randomized controlled trials, that consider both clinical outcomes and the natural progression of nerve injury recovery.

Factors influencing outcome after peripheral nerve injury

Surgical intervention

The surgical technique employed in peripheral nerve repair or reconstruction plays a pivotal role in determining the ultimate outcome of the procedure. Precision and adherence to established principles significantly influence the success of nerve regeneration. Careful handling of nerve tissue during dissection, alignment of nerve ends, and minimizing tension at the repair site are critical considerations[78,81-83]. Tension-free coaptation is essential for optimal axonal regrowth and preventing

complications, like neuroma formation[87]. However, determining the optimal timing for surgery remains a challenge. While early repair under appropriate conditions[2] are generally favored to promote axonal regrowth, the precise window for intervention to balance functional recovery and minimize complications is still under investigation[117]. This aspect poses an intriguing question, particularly concerning the proteomic patterns at the nerve ends of the injured nerve.

Type and level of injury

The mechanism(s) of nerve injury significantly impacts the outcome. In cases of neurapraxia or axonotmesis, where continuity remains in the injured nerve, guiding regenerating axons back to their peripheral target organs is more feasible, usually not requiring any surgical treatment. However, in more severe injuries involving nerve discontinuity or significant defects, surgical interventions such as nerve repair with direct suturing, nerve grafting, or nerve transfer may be necessary to restore function. Additionally, the level of the nerve injury is believed to influence the outcome, as injuries at higher levels necessitate longer distances and time for axons to reach their target organs, thereby placing greater demand on SC which regulate growth factors for a limited time[19]. The farther the distance, the more fatigued the SC become distally, increasing the risk of cell death in cases of proximal injury, and potentially leading to misdirection of regenerating axons. Further research is needed to address this obstacle in nerve injury, repair or regeneration, and regeneration. Notably, the type of nerve injury also carries weight, with reported superior functional outcomes following median nerve injuries compared to ulnar nerve injuries[22,23,118], potentially attributed to the important motor function of the ulnar nerve driven by the intrinsic muscles of the hand and possibly the large effect of misdirection of regenerating axons in the mixed sensory and motor ulnar nerve[119-121].

Age

Age is considered a pivotal factor influencing the outcome of peripheral nerve injuries, with various studies confirming superior results in children[122]. However, it remains unclear whether the enhanced outcome in children following a peripheral nerve injury can be attributed to changes in the peripheral nerve itself or to alterations in the brain. The prevailing belief is that the youthful brain exhibits greater plasticity, characterized by an increased capacity to adapt, and interpret modified signals from the peripheral nerve[123,124].

Nerve regeneration and healing

In 1898, John Forssman observed that axons emerging from injured nerves showed a tendency to align towards the distal nerve end. This directional growth persisted even when the distal nerve end was misaligned. Further investigations into nerve regeneration have unveiled additional complexities[69]. Axonal growth not only

targets the distal nerve end but also displays specificity, where axons preferentially grow towards components of the same nerve type but also regarding the topographic components of the nerve[10]. This has been seen in that the peroneal nerve axons tend to favor distal peroneal nerve components over distal tibial nerve components[10]. This specificity underscores the influence exerted by the distal nerve end on axonal growth and directionality, even in the absence of physical attachment between proximal and distal nerve ends. In ongoing proteomic research, scientists are working hard to understand the molecular mechanisms behind nerve regeneration. However, the intricate interplay of signaling pathways and molecular factors guiding axonal growth toward the distal end remains elusive.

Peripheral nerve tissue healing is thought to present distinct differences compared to the healing processes of other human body tissues, such as skin and bone. Generally, injury to a human organ generates a wound and is normally followed by a spontaneous healing process at the end of which the wound is closed with a scar formation[125], or a glial scar in the case of the CNS[126]. This process involves specialized cellular interactions and molecular signaling pathways unique in the case of the peripheral nervous system.

The process of peripheral nerve tissue regeneration shares some similarities with the remarkable regenerative abilities observed in diverse animals, including certain amphibians like salamanders, fish species, like zebrafish, and invertebrates, such as planarians. These animals possess extraordinary regenerative capacities, able to fully regenerate complex tissues and organs[126-128]. Recent comparative studies exploring the immune response following injury and its role in tissue regeneration show regenerative animals exhibit finely tuned immune responses that promote tissue repair while minimizing inflammation and scarring, characterized by the timely resolution of inflammation and the promotion of tissue repair processes including ECM remodeling[128].

Schwann cells are primarily associated with nerve tissue in both salamanders and mammals. However, in the context of regeneration, SC in salamanders demonstrate remarkable plasticity and can also contribute to tissue repair in non-neural tissues. During limb regeneration in salamanders, SC not only aid in the regeneration of nerve fibers but also participate in the formation of the regeneration blastema, a mass of undifferentiated cells at the site of injury that gives rise to new tissues, including muscle, bone, and cartilage[126]. This highlights the versatile nature of SC in salamanders, where they contribute to both neural and non-neural tissue regeneration. This raises the question of why human peripheral nerve tissue does not regenerate with the same functional capacity as seen in salamanders. In the process of human peripheral nerve regeneration, the presence of scar tissue surrounding the regenerating nerve may potentially influence the outcome. Recent research has introduced a deformation field theory of scar formation in nerve wounds, shedding light on the mechanical processes that influence the healing outcome. The theory proposes that contractile mechanical forces exerted by myofibroblasts around the regenerating nerve act similarly to a pressure cuff applied

to a person's arm for measuring blood pressure. This "pressure cuff" theory suggests that the compression exerted by myofibroblasts leads to shrinkage of the regenerating nerve tissue, impeding its regeneration and resulting in poor functional properties[125].

Patient engagement and socioeconomic considerations

Patient motivation and adherence to treatment and rehabilitation play pivotal roles in determining outcomes following peripheral nerve injuries[129]. Active participation in rehabilitation programs, including physical therapy and occupational therapy, is crucial for maximizing functional recovery. However, challenges may arise in maintaining patient compliance, emphasizing the need for tailored support and education throughout the recovery process. Despite the acknowledged impact of socioeconomic status on healthcare outcomes, there remains a significant gap in understanding how socioeconomic status specifically influences the management and outcome of peripheral nerve injuries. Considering the patients´ background and socioeconomic status may contribute to understanding their motivation levels and tailoring intervention and follow-up accordingly. In Sweden, with its social welfare model, everyone has the right to healthcare, sick leave, and social benefits, contributing to a unique context for patient care. Hence, the generalizability of results from other nations, such as the USA, to Sweden might be restricted owing to differences in healthcare systems and social policies. Evaluating PROMs and quality of life measures can provide insights into the overall impact of peripheral nerve injuries on the patient's well-being. For a detailed description of the different national registers, the reader is referred to the Methods section.

Prevention and management of pain and cold sensitivity

Pain management is a critical aspect of peripheral nerve injury care, as neuropathic pain can significantly impact patients' quality of life. Multimodal pain management approaches, including pharmacotherapy, nerve blocks, physical therapy, and psychological interventions, aim to alleviate pain and improve functional outcomes. However, achieving effective pain control can be challenging due to the complex nature of neuropathic pain and individual variability in treatment responses. Further research is needed to develop targeted interventions for preventing and managing pain following peripheral nerve injury. Cold sensitivity, which some patients experience as very painful, is a common symptom described by individuals recovering from peripheral nerve injuries[32]. Despite its perceived significant impact on patient well-being, there remains a notable gap in understanding this symptom and the optimal management strategies for addressing it effectively. Limited research has been conducted to identify the effect cold sensitivity has on individuals and its role in functional disability after a peripheral nerve injury. Whether individuals recovering from digital nerve injuries experience different degrees and presentation of cold sensitivity, compared to those with

injuries to the larger nerves such as the median, radial, and ulnar nerves has not been established. Optimal management strategies for addressing cold sensitivity effectively are lacking, highlighting the need for further investigation into its mechanisms and potential therapeutic interventions.

Concomitant diseases and factors as an obstacle for regeneration

Certain underlying health conditions can significantly influence outcomes following peripheral nerve injury and repair. Individuals with diabetes may experience delayed healing and are at a higher risk of complications following nerve injuries. This delay can be attributed to slower nerve regeneration, observed in both the large myelinated and the small non-myelinated nerve fibers, particularly in individuals with diabetes, a notion supported by experimental models using rats with diabetes[130-133]. Peripheral neuropathy associated with diabetes can further complicate the recovery process, but in subjects with particularly type 1 diabetes there is an ongoing nerve degeneration and regeneration process as a part of diabetic neuropathy[12,134] It is essential to delineate this subgroup of individuals within clinical study populations to enable comparative measures and mitigate the risk of skewed effects on outcome of Thus further emphasizing the importance to define this group of individuals within the study group for comparative measures and minimize risk of confounding effect on outcome. Smoking has also been linked to impaired wound healing and reduced blood flow. Individuals who smoke may experience slower recovery and increased complications after nerve repair surgery[135]. Further research, including at the molecular level is warranted to enhance our understanding of these processes.

Aims

The common objective across the thesis is the investigation of surgically treated peripheral nerve injuries in the upper limb. The thesis aims to map out various types of nerve injuries, analyze patient-reported outcomes in relation to socioeconomic status and cold sensitivity, predict functional outcomes, assess the utility of processed nerve allografts, and delineate the proteomic patterns post-injury in humans, where each study shares a central focus on advancing our understanding of peripheral nerve injuries in the upper limb. The overarching aim is to provide valuable insights that can advance diagnostic and surgical practices, improve patient outcomes, and deepen the overall comprehension of the complexities involved in peripheral nerve injuries, encompassing perspectives spanning from the patient´s lived experience to the researcher's domain.

The specific aims for the papers included in the thesis were as follows:

Paper I To study the impact of socioeconomic factors on outcome after repaired or reconstructed digital or major nerve trunk injuries in the upper limb.

Paper II To investigate self-reported cold sensitivity and functional disability after a repaired digital nerve injury.

Paper III To investigate self-reported cold sensitivity and functional disability after a repaired major nerve trunk injury in the upper extremity.

Paper IV To systematically review if processed nerve allograft (PNA) is justified in reconstruction of a nerve defect in patients after a posttraumatic or iatrogenic peripheral nerve injury and to compare PNA with other established methods.

Paper V To establish an effective method for protein extraction from fresh frozen human peripheral nerves and to determine the minimum amount required for consistent protein extraction outcomes.

Paper VI To investigate the molecular patterns underlying a digital nerve injury, concentrating on differences in protein expression between the proximal and distal nerve ends.

Methods

The thesis is based on three types of studies, three observational studies (Papers I-III), a systematic review (Paper IV), and two exploratory studies (Papers V-VI). The methods for each study type will be presented separately.

The Observational Studies (Papers I-III)

Participants

During the study period, 5142 individuals with surgical repair of digital nerve and major nerve trunk injuries (4372 and 770 individuals, respectively) were identified in the Swedish National Quality Registry for hand surgery (HAKIR) 2010-2018. An overview of the participants, exclusion criteria, and data sources are shown in Table 6.

Table 6. Overview of participants, exclusion criteria and data sources of the three observational studies

	Paper I	Paper II	Paper III
Participants	- Total 670 - 573 with digital nerve injury - 97 with major nerve trunk injury - Age <20-64>	- Total 1553 with digital nerve injury - Age <16	- Total 281 with major nerve trunk injury upper limb - Age <18
Exclusion criteria	- Nerve biopsy - Combined injuries (digital and major nerve trunk)	- Nerve biopsy - Combined injuries (digital and major nerve trunk) - Nerve graft	- Nerve biopsy - Combined injuries (digital and major nerve trunk)
Data sources	- HAKIR - NDR - SCB	- HAKIR - NDR	- HAKIR - NDR

HAKIR-Swedish National Quality Registry for Hand Surgery, NDR-National Diabetes Register, SCB-Statistics Sweden.

Data sources and outcome measures

Statistics Sweden (SCB) (Paper I)

Statistics Sweden (SCB) has a rich history rooted in its establishment in 1858, making it one of the world's oldest national statistical offices. Initially known as the Central Statistical Bureau of Sweden, its primary objective was to collect and disseminate vital statistics for governmental and administrative purposes. Over the years, SCB evolved to meet the changing needs of society, expanding its scope to include a wide array of statistical data beyond vital statistics. Throughout the 20th century, SCB played a crucial role in shaping Sweden's economic and social policies, providing policymakers, researchers, and the public with reliable and comprehensive statistical information[136]. In recent decades, SCB has embraced technological advancements, transitioning to digital data collection and analysis methods to ensure the timeliness and accuracy of its statistics. Statistics Sweden (SCB) served as a crucial resource for this thesis, offering a comprehensive collection of statistical data that spanned various aspects of Swedish society. When conjoined with data from the Hand Surgery Quality Registry (HAKIR) for Paper I, an invaluable synergy emerged for the socioeconomic aspect of peripheral nerve injuries. This included exploring associations between patient outcomes in HAKIR and variables, such as cohabiting, income, education level, employment (manual/non-manual), sick leave, and immigration status. Data was available from 2009-2017 and variables were documented in the year preceding surgery. Due to the limited availability of socioeconomic data for the age groups <20 and >64 years from the Swedish statistical agency, an exclusion was set for individuals outside of this range.

Swedish National Quality Registry for Hand Surgery (HAKIR) (Papers I-III)

Established in 2010 by the Swedish Society for Hand Surgery, the Swedish National Quality Registry for Hand Surgery (HAKIR) has expanded to include all seven university hospitals in Sweden and several private hand surgery units, demonstrating its dedication to improving healthcare quality and promoting research initiatives for improved treatment methods[39].

Individuals included in the HAKIR registry following a peripheral nerve injury in the upper limb are asked to complete two Patient-Reported Outcome Measures (PROMs). The first questionnaire, a Swedish version of QuickDASH, which evaluates disability via an 11-item questionnaire. The scores fall between 0 and 100, with higher scores indicating more pronounced functional impairment. The QuickDASH, a condensed version of the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, focuses on assessing upper extremity function and the patient's ability to perform daily tasks[137,138]. The second questionnaire, HQ-8, exclusive to HAKIR, comprises eight validated Likert-scale questions assessing symptoms (i.e., pain on load, pain on motion without load, pain at rest, stiffness, weakness, numbness/tingling, cold sensitivity and ability to perform daily

activities)[38]. Each symptom is graded by the individual from 0-100, with a higher score representing more severe problems[38]. The HQ-8 questionnaire is not a disease-specific outcome instrument, but it complements other PROMs, such as the QuickDASH questionnaire, with symptom-related questions and shares some features with the validated Cold Intolerance Symptom Scale (CISS). Yet, the HQ-8 questionnaire is considered somewhat simpler, making it easier to use in routine clinical practice and to engage a larger population to partake[139,140]. Both questionnaires are available in Appendix 1.

An individual with a QuickDASH score below 15 has previously been described as having "no problem," whereas a score falling within the range of 40-69 indicated "significant difficulties and inability to work"[141]. For Paper I, we used QuickDASH scores of 40 or higher for individuals with digital and major nerve trunk injuries postoperatively to investigate the relationship between socioeconomic status and outcome.

For Paper II, the QuickDASH and HQ-8 scores were compared to baseline at three and 12 months postoperatively. The individuals were also classified into three categories according to the results from answers to the question on cold severity in the HQ-8 questionnaire agreeing to a previously published study[142]. Mild cold sensitivity was defined as an HQ-8 score of ≤30, moderate cold severity as a score of 30-70, and severe cold severity as a score of >70. Data regarding both isolated and multiple concomitant injuries, such as flexor tendon injuries, fractures in the hand (e.g., phalangeal, metacarpal, or carpal fractures), joint/ligament injuries, and vascular injuries (at the hand or wrist level), was gathered from the HAKIR database. Multiple injuries encompassed combinations of flexor tendon injuries, hand fractures, vascular injuries, and/or joint/ligament injuries. Individuals ages 16 and above were included in the study.

For Paper III, the QuickDASH and HQ-8 scores were examined at three and 12 months postoperatively. The included individuals were divided into three groups according to the involved nerve in the upper extremity – the median, ulnar, or radial nerve trunks. Data on any concomitant injury, such as flexor tendon injury, extensor tendon injury, fracture in the upper extremity, joint/ligament injury, and vascular injury, was also retrieved from the HAKIR database. Isolated and multiple concomitant injuries were analyzed and presented together. Cold sensitivity was classified into three categories according to severity at 12 months postoperatively for each of the three nerve groups, as previously done. Individuals included in the database, eligible for the study were all age >18 years.

National Diabetes Register (NDR) (Papers I-III)

Launched in 1996, in alignment with the St. Vincent Declaration's objectives, the National Diabetes Register (NDR) is dedicated to enhancing diabetes care throughout Sweden, employing evidence-based approaches to care development[143]. The initiative aims to elevate the quality of care in participating units, including both

primary care and hospital-based clinics, by providing valuable feedback to both patients and individual units.

The NDR collects a diverse set of data, encompassing diabetes type, date of diagnosis, disease duration, medication details, laboratory results (HbA1c, blood lipids, fasting glucose), anthropometric measurements (BMI), lifestyle variables (smoking, physical activity), and information on complications (stroke, retinopathy, albuminuria). Achieving an impressive coverage rate of approximately 85-90% of diabetes patients in Sweden, the NDR ensures that all individuals provide informed consent before registration in the database. The HAKIR database was linked to The Swedish National Diabetes Register (NDR) (http://www.ndr.se) through personal identifying numbers and data on the individuals' diabetic status in Papers I-III was retrieved.

The Systematic Review (Paper IV)

The systematic review for this thesis employs a comprehensive methodological approach to evaluate the efficacy of Processed Nerve Allografts (PNAs) in the treatment of peripheral nerve injuries. The validity of a study may be viewed from two perspectives. The first perspective is whether the study addresses the appropriate research question (external validity) and is closely linked to the transferability of a study's findings. The second perspective is whether it answers its research question correctly, and is free of bias (internal validity)[144]. The inclusion criteria in our review were defined in advance of data abstraction using the Patient, Intervention, Comparison, and Outcome (PICO) framework[145] followed by risk of bias (ROB) evaluation. The certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluations (GRADE)[146].

Patients, Intervention, Comparison and Outcome (PICO)

The PICO framework guided the selection of studies for inclusion in the systematic review. **Patients** encompassed those with posttraumatic or iatrogenic peripheral nerve injuries, with the **intervention** involving surgery utilizing a processed allograft (PNA). **Comparative** analyses included standard treatments in peripheral nerve surgery, such as direct suture, reconstruction with nerve autografts, and nerve conduits, while **outcomes** considered in the analysis spanned postoperative measures of motor and sensory function, pain, cold sensitivity, side effects, rehabilitation evaluations and health-related quality of life. The PICO is summarized in Figure 6.

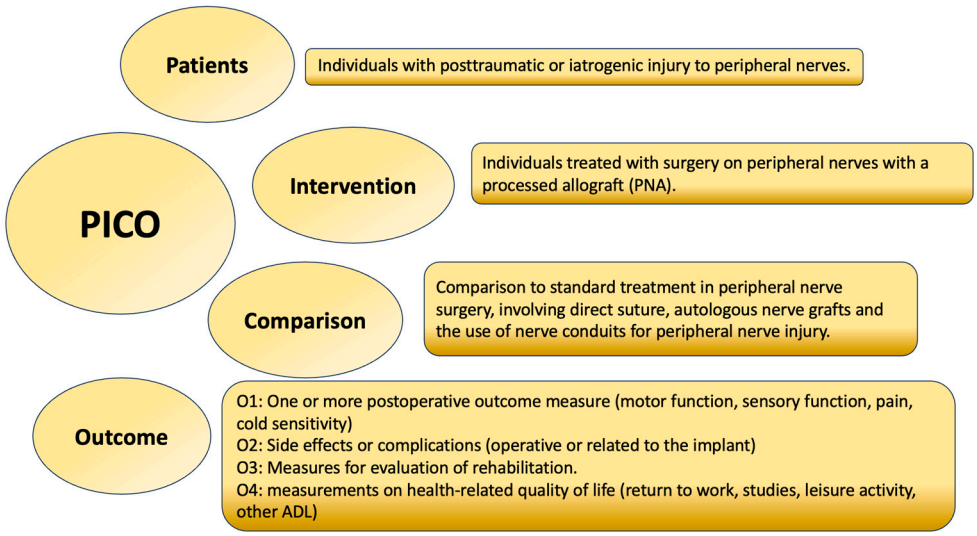

Figure 6. PICO framework for selection of studies included in the systematic review concerinng the processed nerve allografts (PNAs).

Risk of bias (ROB)

Relevant publications were evaluated for risk of bias (ROB). The different types of bias evaluated help interpret study findings accurately.

Selection bias

Selection bias occurs when there is a systematic error in how participants are selected for inclusion in a study, leading to a sample that does not accurately represent the target population. This bias can skew study results if certain groups are overrepresented or underrepresented, affecting the generalizability of findings[144].

Treatment bias

Treatment bias, also referred to as allocation bias, arises when there is a systematic variance in the care or treatment administered to participants across various study groups. This bias may occur if researchers or healthcare providers possess knowledge of the treatment assignments and inadvertently influence treatment decisions or outcome assessments based on this knowledge[144].

Assessment bias

Assessment bias, also known as measurement bias, occurs when there is a systematic error in how outcomes are measured or assessed, leading to inaccurate

or biased results. This bias can arise if outcome assessors are not blinded to the treatment group assignments, leading to differential detection or reporting of outcomes[144].

Attrition bias

Attrition bias occurs when there is a systematic difference in the loss of participants or incomplete follow-up between study groups, leading to biased estimates of treatment effects. This bias can occur if dropout rates differ between intervention and control groups, leading to differential loss of participants and potential bias in outcome assessments[144].

Reporting bias

Reporting bias, also known as publication bias, occurs when the dissemination of study results is influenced by the nature or direction of the findings. This bias can arise if studies with positive results are more likely to be published or if certain outcomes within studies are selectively reported, leading to an incomplete or biased representation of the evidence[144].

Conflict of interest bias

Conflict of interest bias occurs when individuals involved in the research process have financial, professional, or personal interests that may unduly influence study design, conduct, analysis, interpretation, or reporting. This bias can lead to distorted or biased study findings that favor the interests of those with conflicts of interest[147].

Each assessment was made by at least two individuals from the project's expert group and a HTA supervisor, independently of each other. An example of ROB evaluation is presented in Table 7.

Table 7. Compilation of the risk of bias for the RCT identified in accordance with PICO

Bias	Means et al 2016
Selection bias	Low
Treatment bias	Medium
Assessment bias	Low
Attrition bias	High
Reporting bias	Medium
Conflict of intrest bias	Medium
Overall bias assessment	**Medium**

Grading of Recommendations Assessment, Development and Evaluations (GRADE)

The GRADE framework was applied to assess the quality of evidence and strength of recommendations (Table 8). The systematic review utilized GRADE to critically appraise the outcomes of studies included in the analysis, considering factors such as study design, consistency, and directness. This methodological approach contributed to a comprehensive understanding of the effectiveness and limitations of PNA in peripheral nerve injury treatment.

Table 8. Certainty of the evidence assessed using methods of the GRADE[146]

GRADE	
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	Any estimate of effect is very uncertain.

Literature search and selection process

The systematic exploration of databases yielded a comprehensive collection of 8695 articles. Following screening and final exclusion by the project group, 5 studies were included in the synthesis. For a PRISMA flowchart of the search results and articles retrieved the reader is referred to Paper IV.

The Exploratory Studies (Papers V-VI)

Proteomics stands at the forefront of molecular biology, representing an innovative domain that delves into the exhaustive examination of proteins within biological systems. Proteins, crucial entities in living organisms, assume multifaceted roles as

enzymes, structural components, signaling molecules, and more. Unraveling the intricacies of life's complex mechanisms hinges on a profound understanding of the proteome, a comprehensive assembly of proteins expressed by an organism, tissue, or cell at a given moment. The landscape of proteomics has undergone substantial transformations in recent decades, propelled by advancements in technology and analytical methodologies. Proteomics with its capability to analyze a wide range of proteins even from small tissue samples, particularly through techniques like mass spectrometry, holds great promise for studying complex biological samples like nerve tissue, where limited sample size is often a challenge.

The history of proteomics

The narrative of proteomics unfolds as a captivating exploration marked by groundbreaking discoveries and technological strides. Despite the official coinage of the term "proteomics" in 1997, the origins of this field trace back to the mid-20th century. In the early 1960s, Norman G. Anderson laid the foundation for the Molecular Anatomy (MAN) program, envisioning a comprehensive cataloging of the human proteome[148]. However, technological constraints, financial limitations, and the predominant focus on the Human Genome Project delayed the realization of Anderson's ambitious goals for several decades.

A pivotal juncture emerged in the mid-1970s with the introduction of two-dimensional gel electrophoresis (2-DE) by Patrick O'Farrell[149]. This revolutionary technique enabled simultaneous separation and visualization of thousands of proteins based on their molecular weight and chemical properties. By the late 1970s, 2-DE underwent refinement and standardization, providing a platform aligned with the earlier concepts of the MAN project[150]. Despite being hailed as the "rebellious child of proteomics," 2-DE became a cornerstone in the field[148]. O'Farrell's work showcased its capacity to resolve up to 5000 proteins, establishing the groundwork for large-scale protein analysis[149]. However, 2-DE faced limitations, particularly in detecting low-abundance proteins and ensuring reproducibility[151].

The 1990s witnessed a transformative shift with the emergence of mass spectrometry (MS) techniques in proteomics. Surface-enhanced laser desorption/ionization (SELDI) and matrix-assisted laser desorption/ionization (MALDI) emerged as potent tools for protein identification and quantification, offering alternatives to gel-based approaches and addressing the shortcomings of 2-DE[152]. As proteomic methods rapidly evolved, advanced technologies such as liquid chromatography-mass spectrometry (LC-MS) and high-throughput mass spectrometry came to the forefront[153]. This historical trajectory underscores the continuous innovation within proteomics, transforming it into a dynamic and indispensable field for comprehending the intricate realm of proteins in biological systems. It has also paved the way for a unique opportunity: the development of a universally standardized method tailored for optimized protein extraction from peripheral nerve tissue, specifically crafted for investigation using LC-MS.

Mass Spectrometry

At the core of proteomics lies mass spectrometry (MS), a powerful analytical method that has revolutionized the field by facilitating precise measurements of protein mass and structure. Operating on the principle of ionizing molecules and sorting them based on their mass-to-charge ratio, MS is integral to the identification and quantification of proteins, characterization of post-translational modifications (PTMs), and exploration of protein-protein interactions[154].

MS's efficacy in proteomics is underscored by its ability to handle complex protein mixtures. In contemporary proteomics, liquid chromatography-mass spectrometry (LC-MS) has emerged as a leading technique. This approach allows the separation of peptides, generated through enzymatic protein digestion, followed by precise mass determination and sequencing. By aligning acquired mass spectra with protein databases, researchers can achieve accurate identification and quantification of proteins in biological samples[153,155]. Additionally, mass spectrometry is instrumental in investigating PTMs, including phosphorylation, glycosylation, and acetylation—essential for protein function and cellular signaling. This capability provides valuable insights into the regulatory mechanisms governing protein activities within the cell[156].

Protein extraction method development for peripheral nerve tissue

Our understanding of the proteomic changes occurring in human nerve tissue after injury is limited[63]. Injured peripheral nerves may exhibit changes in protein expression and composition, impacting the processes of inflammation, regeneration, extracellular matrix (ECM) remodeling, oxidative stress, neurotrophic support, myelin integrity, pain signaling, and cell signaling pathways[157,158].

For further investigation of the changes occurring in the human peripheral nerve five protein extraction methods, specific for peripheral nerve tissue were developed in Paper V (Figure 7). The full technical description of sample preparation, liquid chromatography-mass spectrometry (LC-MS) analysis and subsequent data analysis can be found in Paper V and VI.

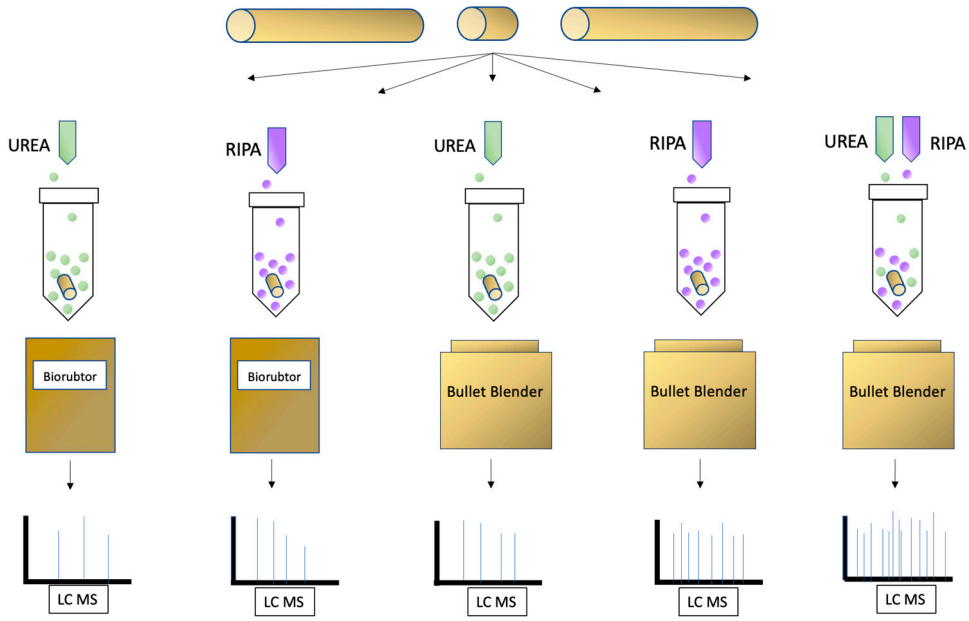

Figure 7. The five protein extraction methods developed using a fresh frozen sural nerve.

Participants

Nerve tissue samples were obtained from a donor for Paper V during a scheduled surgical procedure in which the sural nerve was harvested in connection with a nerve reconstruction procedure. The remaining portions of the harvested sural nerve, not needed for the nerve reconstruction procedure, were collected.

For Paper VI the nerve tissue samples were obtained from donors during an acute surgical procedure. A segment of the proximal and distal end to an injured digital nerve in the hand was removed as a part of preparing the digital nerve for a direct nerve repair with sutures or a reconstruction procedure with a nerve graft at the Department of Hand Surgery in Malmö, Sweden (Figure 8). The pieces were collected, and promptly placed in a freezer and stored at a -80 °C. Prior to surgery informed consent was retrieved from the donors. For Paper VI, 19 individuals with 26 digital nerve injuries, each containing a proximal and distal end were included subsequently leading to the analysis of 52 nerve ends. The workflow of the final method used in Paper VI is presented in Figure 9.

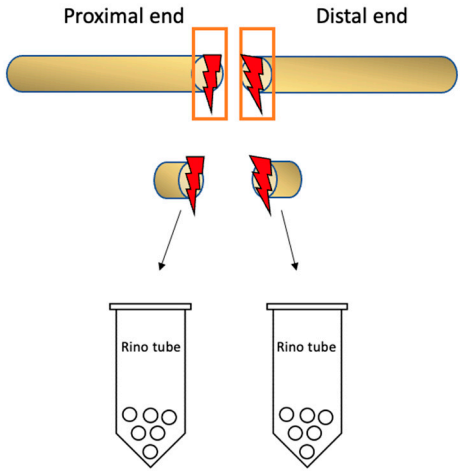

Figure 8. A segment of the proximal and distal end of an injured digital nerve was removed as a part of preparing the digital nerve for a direct nerve repair with sutures or a reconstruction procedure with a nerve graft.

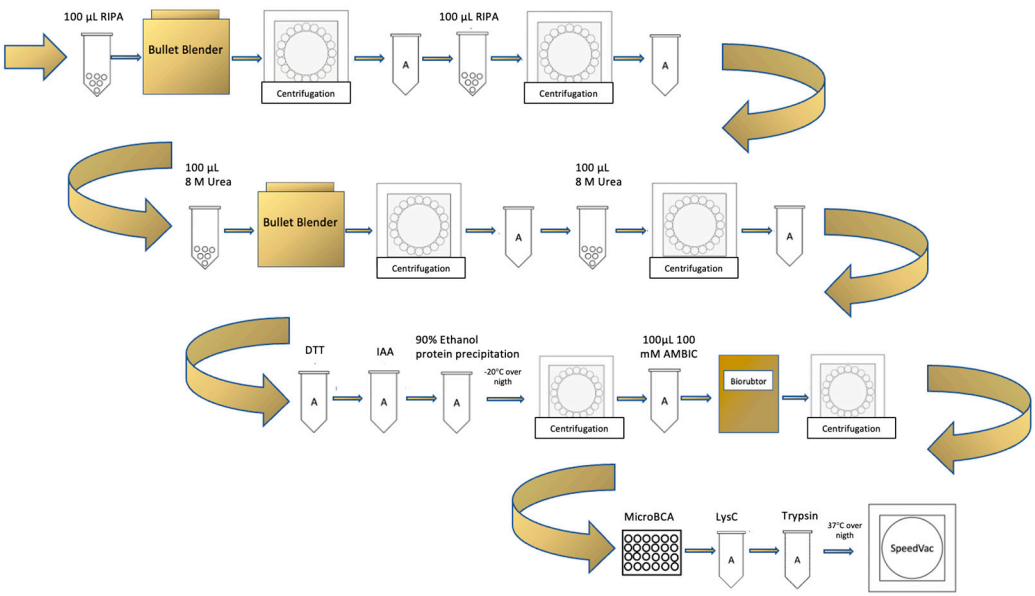

Figure 9. Workflow of sample preparation. Nerve tissues were homogenized using a Bullet Blender Storm Pro, first with Ripa buffer, followed by 8 M Urea. Enzyme digestion was performed by LysC for 3 hours followed by trypsination overnight.

Ethical considerations

Papers I-III

As quality registers have grown in scope and significance, ethical considerations and data privacy have come to the forefront. Striking a balance between data utility for research and the protection of patient privacy has been a continuous challenge. Regulatory frameworks, such as the General Data Protection Regulation (GDPR) in Europe, have been enacted to safeguard patient data while promoting research.
In my study on peripheral nerve injuries, ethical considerations played a pivotal role, requiring a delicate balance between scientific rigor and participant respect. Obtaining informed consent and safeguarding privacy, guided by regulations like GDPR, is paramount. Ensuring data accuracy involves transparent reporting of limitations and biases. Analyzing socioeconomic factors demands sensitivity to avoid reinforcing inequalities. Patient-reported outcomes, such as QuickDASH and HQ-8, add a subjective dimension, necessitating careful interpretation to respect participants' experiences. In essence, adherence to transparent and responsible research practices is paramount, ensuring a meaningful contribution to peripheral nerve injury research, while upholding fundamental ethical principles in scientific inquiry.
The studies were approved by the Regional Ethical Review Board in Stockholm, Sweden, and the national Ethical Review Board (2017/2023:31; 2017/3:11; 2018/1106-32; 2019-00880; 2021-0418 and 2021-00902). The research was conducted by the principles of the Helsinki Declaration. Individuals provided informed written consent before inclusion in HAKIR and NDR.

Paper IV

The clinical evidence for the use of nerve allograft is insufficient, which certainly is not unique to nerve allografts but occurs in virtually all medical specialties. What is statistically assured at the group level often does not apply at the individual level where specific needs or conditions might steer the decision of what type of treatment is recommended.
The benefit and risk paradigm can be directly traced to Hippocrates' first rule; “primum non nocere” (first, do no harm). When a treatment that has not been proven clinically beneficial to standard treatment is available as an alternative, the doctor may find himself in a reversed position in the patient meeting. The individual in question can legally request such a treatment though he cannot demand treatment. Because the nerve allograft is a commercial product, it is subject to specific product costs, where there is no direct corresponding cost when using a nerve autograft. The above may come to the fore in cases where you do not have the same treatment policy that is applied nationally, with the consequent risk of unequal care. It can

follow that such an increased cost for the product can lead to an economically based crowding-out effect for another patient category with a healthcare need at a comparable level of difficulty. Theoretically, such a displacement could, in this case, be balanced by a shorter time of operation, whereby the operative space could thus be used for another patient. For a patient who has been reconstructed with a nerve allograft, there is also a theoretically lower risk of complications as he only has one area of surgery, thus, a lower risk of getting a postoperative infection and development of neuroma.

The integrity of the individual also needs to be considered in this context as the treatment is a form of transplantation, with its inherent potential invasion of privacy. Unlike some other transplant therapies such as, for example, heart and kidney transplants, nerve allografts are not directly lifesaving, which is why the grading of a perceived invasion of privacy can be experienced or tolerated differently. However, nerve allograft patients do not need to be treated with immunosuppressive drugs as is the case with heart and kidney transplants. Thus, these patients would experience a lesser invasion of privacy than other transplant recipients.

Finally, it is essential to address the broader ethical implications, especially within the context of Sweden's healthcare system, which relies on taxpayer funds to ensure universal access to care. Prioritizing evidence-based interventions not only safeguards patient well-being but also upholds the principles of equity and efficiency inherent in the Swedish welfare model. Allocating resources towards non-evidence-based treatments risks compromising the integrity of the system and undermines public trust.

As a systematic review does not involve the collection of new data and solely synthesizes existing information, ethical consent was not required for the study, given the absence of original data or direct involvement with human subjects.

Papers V-VI

Conducting a proteomic investigation on injured peripheral nerves through mass spectrometry raised intricate ethical considerations, especially regarding informed consent before nerve repair surgery. The study involved prioritizing autonomy, ensuring data privacy, minimizing harm, upholding scientific rigor, and transparently reporting findings.

Informed consent was paramount, requiring individuals to be fully informed about the research's purpose, risks, and benefits, and ensuring voluntary participation. Rigorous data protection measures, such as anonymization, were made sure to safeguard participant privacy.

Scientific rigor was crucial in the preparation of the nerve tissue and during the mass spectrometry investigations. Adherence to standards, technique validation, and transparent reporting was maintained throughout the project.

Considering the long-term impact on injured peripheral nerves is also essential to the equation of ethics. It is also an ethical obligation to assess the clinical relevance

and translational implications of the study, which I considered to ultimately benefit patients with nerve injuries.
These studies were approved by the Regional Ethical Review Board in Lund, Sweden (no 311/2016). All study participants provided informed written consent. All procedures were carried out in line with relevant current guidelines and regulations.

Statistical analysis

The statistical analyses employed in the Papers comprising the thesis were tailored to address distinct research questions and data attributes with statistical significance set at a p-value of <0.05.

In Paper I, the data was presented as mean ± SD, prevalence ratio (PR) along with its corresponding 95% confidence interval (CI), or as numbers and percentages. Continuous variables such as age and QuickDASH score were analyzed using t-tests, while categorical variables were assessed using the Chi-Square test. Analysis of variance (ANOVA) with Bonferroni comparison and Tukey test were employed to evaluate mean differences among multiple groups. The decision to use prevalence ratios (PRs) in Paper I, instead of odds ratios, offered a more intuitive interpretation of the relationship between exposure and outcome for peripheral nerve injuries, particularly since there was a high prevalence of outcomes[159]. Additionally, the choice of Cox proportional hazards regression with a constant follow-up time ensured standardized assessments of the impact of socioeconomic factors on the occurrence of upper limb peripheral nerve injuries, enhancing the comparability and reliability of the results. To evaluate the discriminatory accuracy (DA) of each model, we utilized the area under the receiver operating characteristic curve (AUC) and its corresponding 95% confidence intervals (CI). AUC values range from 0.5, indicating no predictive accuracy[160] to 1 (representing perfect discrimination). to 1, representing perfect discrimination. The DA was categorized according to criteria outlined by Hosmer and Lemeshow[161].

In Papers II and III, the data were presented as median [interquartile range, IQR] or numbers (%). Categorical variables were assessed using the Chi-Square test. The Kruskal-Wallis test was used for significance testing for continuous variables, with the Mann-Whitney U-test as the post-hoc test. Mann-Whitney U-test was also used for sex, age, and seasonal comparisons. The application of multiple linear regression analysis allowed for the prediction of cold sensitivity outcomes while adjusting for relevant confounding factors. Furthermore, the use of univariate general linear analysis and the Spearman rank test (Paper II) facilitated comprehensive

assessments of associations and correlations between cold sensitivity, functional disability, and other variables of interest.

In Paper V and VI, the data are presented as numbers. Categorical variables were assessed using the Chi-Square test. The Student's t-test in Paper VI enabled comparisons between different digital nerve end groups, thereby identifying significant differences and trends in protein expression patterns and other variables of interest.

Results

The main findings in each paper are presented in Table 9 and are briefly summarized below. The reader is referred to the individual papers for details.

Table 9. Major findings for each Paper and influencing factors

Study	Main Findings	Influencing factors
Study I	Major nerve trunk injuries linked to higher QuickDASH scores and lower income.	• Immigration background • History of sick leave • Lower education level
Study II	Cold sensitivity prominent in digital nerve injuries.	• Flexor tendon injury • Hand fracture • Injury to multiple structures
Study III	Cold sensitivity prominent in median and ulnar nerve injuries.	• Nerve type • Cold sensitivity severity • Stiffness, weakness, daily activities
Study IV	No significant differences in outcome between PNA and nerve autograft/conduits.	• Lack of control groups • Financial disclosures
Study V	Protein extraction methods yield varying identification rates.	• Sample amount • Combination of extraction methods
Study VI	Proteomic differences between proximal and distal nerve ends.	• Promotion of tissue degeneration and restoration • Suppression of non-essential processes

Paper I

Individuals suffering a **major nerve trunk injury** were more likely to have **higher QuickDASH scores** and **lower income** compared with those with digital nerve injuries.

Individual **QuickDASH scores** were significantly **higher** for individuals that had a background of **immigration** to Sweden (adjusted PR= 2.0, 95% CI 1.2-3.2), had a history of more than 4 weeks of **sick leave** the year before surgery (adjusted PR=

1.8, 95% CI 1.1-3.1) or had an **education level lower than tertiary** (adjusted PR= 2.8, 95% CI 1.7-4.7).

Paper II

Cold sensitivity (scored 0-100) was the **most prominent symptom** among 1553 included individuals (998 men, 555 women; median age 41 [IQR 27-54] years) suffering digital nerve injury.

In the regression analysis, concomitant **flexor tendon injury**, **hand fracture,** and **injury to multiple structures** predicted **worse cold sensitivity** (6.9, 15.5, and 25.0 points; p=0.005, 0.046, and <0.001) at 12 months.

Individuals with **moderate** (30-70) and **severe** (>70) **cold sensitivity** had **higher QuickDASH scores** at three and 12 months postoperatively than individuals with mild cold sensitivity (6.0 and 5.5; 19.8 and 21.0 points; p=0.001).

Flexor tendon injury, **injuries to multiple structures,** and **diabetes** had **significant effects on QuickDASH scores** at three, but not at 12, months postoperatively.

Paper III

Cold sensitivity emerged as the **most significant symptom** 12 months following repair or reconstruction of the injured **median** (p<0.001) or **ulnar** (p<0.001) nerves, whereas individuals with radial nerve injury displayed milder symptoms.

Concomitant injuries had no discernible impact on cold sensitivity scores.

Individuals with **ulnar nerve injuries** demonstrated higher scores in **stiffness** (p=0.019), **weakness** (p<0.001), and **ability to perform daily activities** (p=0.003) compared to those with median nerve injuries at 12 months postoperatively.

Furthermore, individuals suffering a median, ulnar, or radial nerve injurie experiencing **severe cold sensitivity** (>70) had **QuickDASH scores that were** 25, 37, and 30 points **higher**, respectively (p<0.001), at 12 months postoperatively than those with mild cold sensitivity (<30).

No disparities in QuickDASH scores or cold sensitivity scores at 12 months postoperatively were observed between direct nerve repair or nerve reconstruction with nerve autografts. Additionally, neither age nor sex affected QuickDASH for the same period.

Paper IV

No conclusions, concerning differences in outcome of nerve reconstruction using PNA compared to the use of nerve autograft or conduits, could be drawn.

The **level of certainty** for all evaluated outcomes was **very low** (⨁◯◯◯).

Most published studies lack a control group for patients treated with PNA; being only descriptive, making it difficult to properly compare PNA with nerve autograft or conduits without substantial risk of bias (ROB).

For studies including a control group, the **scientific evidence** was of **very low certainty**, due to a low number of included patients, and a large and undefined loss of patients during follow-up, rendering a high ROB.

Finally, the **authors** often had **financial disclosures**.

Paper V

Out of the total **2619 identified proteins**, protein extraction using **Ripa buffer** combined with either Bioruptor or the **Bullet Blender** resulted in the identification of 1582 (60%) and **1615 (62%) proteins**, respectively. In contrast, using **8 M Urea** and Bioruptor for protein extraction resulted in 1022 proteins (39%), whereas employing the **Bullet Blender** yielded **1446 (55%) proteins**.

Sample amounts, ranging from 0.6 to 10 mg, were prepared with **consistent protein extraction outcomes** obtained for **samples ≥ 1.2 mg**.

Combining **Ripa and 8M Urea with Bullet Blender** increased protein identification to **2126 (81%)** from the total proteins found**.**

Proteins were **classified** by their **cell components, molecular functions**, and **biological processes**. Furthermore, a **subclassification** of proteins involved in the **extracellular matrix (ECM)** was introduced.

Paper VI

A total of **3914 proteins** were identified, with **127 proteins** showing **significant differences** in abundance between the **proximal and the distal nerve ends**.

The **downregulation** of proteins in the **distal nerve end** was associated with **synaptic transmission, autophagy, neurotransmitter regulation, cell adhesion,** and **migration**.

Conversely, proteins **upregulated** in the **distal nerve end** were implicated in **cellular stress response, neuromuscular junction stability and muscle contraction, neuronal excitability and neurotransmitter release, synaptic vesicle recycling, axon guidance, and angiogenesis.**

Discussion

The thesis can be divided into three parts, consisting of observational studies, with a focus on socioeconomic status and outcome measures including cold sensitivity (Papers I-III), a systematic review analyzing the use of processed nerve allograft (PNA) in nerve reconstruction (Paper IV) and finally the exploratory part with a focus on the use of proteomic to analyze early events in the proximal and distal nerve ends in injured human peripheral nerves (Papers V-VI).

The Observational Studies (Papers I-III)

Socioeconomic factors and outcome after peripheral nerve injury

Exploring the impact of socioeconomic factors on outcomes following peripheral nerve injuries represents a novel aspect of medical research. This thesis delves into uncharted territory by examining how variables, like income, education level, and employment status, influence postoperative recovery after peripheral nerve injury. These findings illuminate the broader socioeconomic implications for health outcomes, underscoring the significance of factors that extend beyond the surgical intervention. The impact of socioeconomics extends far beyond the operating room, influencing the trajectory of recovery and overall well-being for individuals navigating the challenges of peripheral nerve injury rehabilitation. While research has shown the effect of socioeconomic factors on nerve entrapment syndromes[162,163], direct comparisons cannot be made. Nerve entrapments often develop over time, and individuals may learn to cope with the effects, potentially delaying seeking medical help, especially among those facing financial or educational challenges. In contrast, peripheral nerve injuries typically involve sudden accidents prompting immediate healthcare intervention or seeking help within the healthcare system, potentially mitigating the influence of socioeconomics at the time of injury. However, postoperatively, socioeconomic factors may significantly impact the rehabilitation process, giving us a clearer picture of the postoperative outcome effect of socioeconomic disparities. Thus, there is a pressing need for targeted interventions aimed at mitigating these disparities and ensuring equitable access to comprehensive care for all patients, irrespective of their socioeconomic backgrounds.

Income disparities and education level

A noteworthy finding in Paper I is the association between low income and worse QuickDASH scores, particularly among women with major nerve trunk injuries. This aligns with the broader literature on socioeconomic influences on health outcomes[164]. This relationship may arise from several factors, including restricted access to healthcare services leading to delays in diagnosis or treatment, physically demanding occupations, psychosocial stressors associated with socioeconomic deprivation, and lifestyle choices, such as diet and exercise habits. Further, educational disparities can lead to more significant bodily pain, partly attributed to health literacy[165].

Occupation and sick leave

Occupational factors, such as manual labor and prolonged sick leave, were identified as predictors of poorer outcomes. Men engaged in manual labor have consistently been shown to be more susceptible to digital nerve injuries compared to women[166]. Moreover, findings from Paper III indicate that men, who are often engaged in manual work and possess lower education levels, exhibit higher QuickDASH scores, especially in cases of major nerve trunk injuries. This highlights the complex interplay of socioeconomic factors on health outcomes, encompassing psychosocial elements that may significantly affect recovery and return-to-work rates.

Immigration Status

Disparities among immigrants, characterized by higher QuickDASH scores, underscore the importance of considering cultural and linguistic factors in the delivery of healthcare services. Immigrants may encounter language barriers, cultural differences, and limited access to culturally competent care, which can impede effective communication, treatment adherence, and health outcomes[167]. Moreover, immigrants may experience social isolation, economic insecurity, and discrimination, further compounding the challenges they face in accessing and navigating the healthcare system. Culturally sensitive preoperative and postoperative education, interpreter services, and community-based support programs can help address the unique needs of immigrant populations and promote equitable healthcare delivery[168]. Understanding these disparities is crucial for tailoring interventions and support systems.

Cold sensitivity's influence on outcome

Acknowledging the broad spectrum of symptoms and disabilities that may ensue following treated nerve injuries, historically, medical focus has been predominantly centered around assessing sensibility and muscle strength. However, contemporary methodologies have brought to light the significance of utilizing modern

approaches, which involve employing national registries encompassing large patient cohorts and integrating PROMs, such as QuickDASH and HQ-8[43]. These approaches offer a holistic understanding of patient experiences beyond conventional clinical evaluations. Despite the advancements in assessment techniques, follow-up for individuals with a peripheral nerve injury presents challenges due to the multifaceted nature of their conditions, necessitating an inclusive approach that considers various facets of their well-being.

Cold sensitivity emerges as a notable and persistent symptom among individuals with repaired or reconstructed digital and major nerve trunk injuries, which has previously been described in individuals with nerve entrapment disorders, such as CTS[142]. Beyond its immediate impact on daily activities, long-term consequences of cold sensitivity were observed, as evidenced in Papers II and III, where it correlated with higher QuickDASH scores at 12 months postoperatively. This underscores the necessity for targeted interventions aimed at managing and alleviating cold sensitivity in individuals undergoing recovery after a nerve injury.

A digital nerve injury sparks an ongoing debate regarding the necessity of nerve repair[169,170]. However, there remains insufficient evidence, particularly from randomized clinical trials addressing ethical considerations, to advocate for alternative methods over surgical repair[1,169,170]. Recent attention has emphasized the outcome of repaired digital nerve injuries and its significance for sensory re-innervation[169,170], particularly regarding the presence of cold sensitivity observed in individuals presenting with neuroma formation after injury[88]. Consequently, individuals experiencing poor recovery of sensation following a nerve injury may face an elevated risk of cold sensitivity and associated neuropathic pain[171].

Individuals with a digital nerve injury and severe cold sensitivity displayed QuickDASH scores approximately 20-21 points higher than those with mild cold sensitivity at 12 months postoperatively, indicating clinical relevance[172]. Similarly, individuals with a median nerve injury exhibited approximately 25 points higher scores, while the disparity was more pronounced for those with radial or ulnar nerve injuries and severe cold sensitivity, reporting approximately 30 and 37 points higher QuickDASH scores, respectively. These findings suggest the potential persistence of cold sensitivity beyond the initial 12-month period, aligning with results from smaller studies primarily focused on repaired digital nerves[35,173] as well as in cases with neuroma formation[88].

The presence of additional factors, such as a flexor tendon injury, fractures, or multiple injuries, intensified the severity of cold sensitivity in individuals with a digital nerve injury, highlighting the complex pathophysiology involved, but with the nerve injury considered as the pertinent origin of this symptom[174]. However, for major nerve trunk injuries, no significant difference was observed in cold sensitivity scores at 12 months, regardless of concomitant injuries, such as flexor tendon or vascular injuries, injuries that have long been associated with cold sensitivity[175,176]. This indicates that prolonged disability after repair or reconstruction of median or

ulnar nerve injuries at 12 months may be attributed to the presence of cold sensitivity rather than concomitant injuries.
Furthermore, seasonal variation did not affect cold sensitivity outcomes, as evidenced by similar results between individuals operated on during winter and summer periods. Despite potential regional differences in climate and temperatures, previous studies, and the findings from Papers II and III, suggest consistent cold sensitivity results across various regions[139,177,178]. The lack of sex-based differences in cold sensitivity outcomes adds nuance to our understanding, suggesting that this symptom affects both men and women similarly. Furthermore, it is important to recognize that individuals with peripheral nerve injuries resulting from work with hand-held vibrating tools may also experience cold sensitivity. Moreover, factors, such as a sense of coherence, have been found to impact recovery in individuals with peripheral nerve injuries[32,179].
Considering these findings, it becomes evident that evaluating cold sensitivity alongside sensibility is crucial in comprehensively assessing outcomes in individuals with repaired or reconstructed peripheral nerve injuries as well as in those patients with an unrepaired nerve injury or with a neuroma[86,88,170].

The peripheral nerve and impact on outcome

Different nerve- different impact

When comparing Papers I-III, it becomes evident that the type of nerve injury plays a crucial role in outcomes. Major nerve trunk injuries lead to higher QuickDASH scores, reflecting the broader impact on arm and hand function, while digital nerve injuries primarily affect finger sensation and fine motor skills. Understanding these nuances is pivotal for tailoring rehabilitation strategies.

The ulnar nerve stands out with distinct characteristics and often presents with poorer outcomes compared to other nerve injuries in the upper extremity, which also includes the outcome of surgery for ulnar nerve entrapment[180]. At 12 months postoperatively, individuals with an ulnar nerve injury exhibited heightened symptoms of stiffness, weakness, and difficulties in performing daily activities compared to those with a median nerve injury. This disparity underscores the critical motor function of the ulnar nerve, primarily governed by the intrinsic muscles of the hand[120,121]. The significant impact on daily activities may arise from the intricate nature of hand movements governed by the ulnar nerve. This complexity accentuates the challenges in restoring motor function effectively, a task often deemed more achievable with injuries to the median nerve, which have been linked to higher rates of motor recovery. In contrast, ulnar nerve injuries frequently encounter obstacles in achieving optimal functional restoration[23,74,181]. The complexity of ulnar nerve injuries extends to the regenerative process, where misdirection of regenerating axons may impede motor recovery[120,121]. Studies have demonstrated that individuals with an isolated ulnar nerve injury exhibit lower rates

of returning to work within one year compared to those with a median nerve injury, further emphasizing the disparity in recovery trajectories[22,182]. Further, individuals with an ulnar nerve injury report more severe cold sensitivity compared to individuals with a median nerve injury. Additionally, when contrasting postoperative recovery between individuals with UNS and CTS following decompression surgery, individuals with UNE demonstrate no clinically relevant recovery[47] in their QuickDASH scores compared to individuals operated for CTS[183]. This finding underscores the interplay between sensory and motor deficits in ulnar nerve injuries, highlighting the comprehensive impact on overall upper limb functionality[34].

Peripheral nerve injury and diabetes

In individuals with peripheral nerve injury and diabetes, the absence of a significant impact on cold sensitivity at 12 months postoperatively provides valuable insights. In cases of nerve compression syndromes, like carpal tunnel syndrome (CTS), previous research has indicated a higher prevalence of cold sensitivity among individuals with certain factors, including diabetes, BMI over 25, rheumatic diseases, and female gender[184,185]. However, studies have found that the scoring of cold sensitivity using QuickDASH also did not show significant differences between patients with and without diabetes[186]. Postoperative resolution of cold sensitivity is commonly observed after open carpal tunnel release (OCTR), although it may persist for a longer duration in patients with diabetes compared to those without[187]. However, the need for further research into the interplay between diabetes and cold sensitivity remains, considering the potential complexities associated with nerve regeneration and sensory recovery in this population.

The Systematic Review (Paper IV)

Critical evaluation of novel techniques for nerve reconstruction

PNAs have emerged as a promising innovation in the realm of peripheral nerve surgery, offering a potential solution for bridging nerve defects. This comes at a time when conventional conduits often have been associated with limiting effects, particularly in defects less than three centimeters in length[101-103]. The introduction of PNA as a new technique signifies a notable advancement, yet it necessitates a critical appraisal, considering the paucity of clear guidelines and the ambiguous benefits highlighted in the existing literature[105,188,189].

Deciding on the appropriate course of action for nerve injuries with a concurrent defect poses a considerable challenge for surgeons. Factors, such as nerve type, injury location, length of nerve defect, wound condition, and available graft material, must all be carefully considered[2]. While numerous studies have been

conducted on PNAs, some showing promising results[75,110,190], the systematic review of Paper IV, with an extensive literature search, shows that the existing literature lacks robust controlled studies with low risk of bias leaving the precise advantages of PNA and protocols for its implementation elusive. The heterogeneity among study groups further impedes meaningful meta-analyses, complicating the interpretation of results[191].

In light of these challenges, it is imperative to critically evaluate all novel techniques in peripheral nerve reconstruction, including PNAs. Despite the limited evidence, it is essential to acknowledge the value of having a diverse array of treatment options available for various clinical scenarios. While some uncontrolled studies suggest favorable outcomes with PNA, others report instances of failure[111-115], highlighting the need for cautious consideration[192]. Furthermore, comparisons with established techniques, like nerve autografts and conduits, are warranted to better understand the efficacy and safety profile of PNAs. Nerve conduits were established over 30 years ago and have been a used approach to reconstruct limited nerve defects as an alternative to nerve autograft for a substantially longer time than PNA. Several studies and well-conducted systematic reviews[103,193] indicate an acceptable outcome as to why comparisons to various nerve conduits are warranted. The results of the outcome parameter for PNA, though compared to a conduit, do not change, and can help to understand the meaningful recovery after such an intervention[79,110,194-198].

In conclusion, while PNAs represent a potentially valuable addition to the armamentarium of peripheral nerve surgeons, their efficacy and safety profile require further elucidation through rigorous research and controlled studies. Until clearer guidelines and evidence emerge, careful consideration of individual patient factors and available alternatives remains paramount in decision-making processes.

Costs affecting treatment choice

Another crucial consideration for healthcare providers involved in decision-making processes is comprehending the economic ramifications and cost-effectiveness of nerve reconstruction methodologies.

Access to comprehensive data on surgical expenses associated with peripheral nerve injury remains limited. A recent study shed light on the total costs incurred for inpatient and outpatient procedures involving nerve autografts ($25,950 and $10,178, respectively) versus PNA ($24,005 and $9,732, respectively)[199]. Similarly, Lans et al. conducted a comparable cost analysis, demonstrating lower expenses associated with PNA usage compared to nerve autografts, with inpatient costs of $25,751 and $29,560, respectively. The disparity in outpatient procedure costs was minimal[75]. Results from Ansaripour et al. suggest that nerve allografts have a high probability of being cost-saving ($12,677 vs. $14,023; saving $1346 with nerve allograft) and more effective over a lifetime horizon, from the perspective of US healthcare payers[200].

Considering the choice of nerve reconstruction necessitates a thorough examination of the organizational and health economic disparities between Europe and the USA. Variances in healthcare systems, spanning from the USA to Europe, including Sweden, reveal significant differences, particularly in coverage mechanisms. While Europe often embraces universal healthcare models funded through taxation, resulting in lower "out-of-pocket costs" for patients, the USA operates without universal coverage, relying on a mixture of private insurance, government programs, and direct patient payments. The notable disparity in healthcare expenditures between the USA and European nations profoundly impacts treatment decisions across both regions.

Moreover, recent research on the cost of utilizing PNA in Sweden sheds light on potential European cost-related realities. The findings indicate that PNA, priced at available unit rates, incurs approximately SEK 20,000 (roughly $1,870) more per patient than autografts in cases of digital nerve injury. However, the difference diminishes in the scenario of a major nerve trunk injury, with costs of PNA just above SEK 3,000 (approximately $280)[201] more per patient than autografts. This insight underscores the importance of considering regional cost dynamics when evaluating nerve reconstruction options.

The Exploratory Studies (Papers V-VI)

Novel aspects of peripheral nerve injuries in humans and protein composition

The foundation of Paper VI was laid through the establishment of a robust protein extraction method and the determination of the minimal tissue amount required for reliable results in Paper V. Thereby a solid framework for investigating proteomic changes in injured digital nerves within the crucial 48-hour window post-injury before surgical repair was established.

For Paper V, we chose the data-dependent acquisition (DDA) strategy since the main goal was to identify as many proteins as possible for each of the five different methods[202]. Conversely, for Paper VI we selected the data-independent acquisition (DIA) strategy. This decision was motivated by the need to compare the abundances of proteins across multiple samples. DIA is superior in yielding quantitative data for protein abundances, where the main goal was to compare the abundances of the proteins found in the injured proximal digital nerve end compared to the distal end[203].

Paper VI explored the complex molecular changes within the first 48 hours, a period often referred to as the initial degeneration phase[19]. By closely examining protein levels in injured proximal and distal digital nerve ends, a detailed understanding was gained of what is happening at the molecular level during this crucial time. The proteins identified in Paper VI are pivotal players in the degeneration phase, where axons disintegrate, myelin sheaths break down, and

cellular stress responses are activated. Through comparison of protein abundances between proximal and distal nerve ends, region-specific responses were revealed that shed light on the initial events following nerve injury.

Highlighted within Paper VI are proteins, such as HSBP1 and HSPA2 which spearhead cellular protection and survival mechanisms, crucial for mitigating the stress experienced by neurons and SC in the distal nerve end[12,204,205]. Further discussion on how proteins found up-regulated in the injured distal nerve end may contribute to the degenerative phase is presented in Table 10. Conversely, down-regulated proteins, like SNAP25 and TSPAN6, underscore the challenges in maintaining neurotransmitter balance and proper axonal guidance signals during this early phase, impeding effective axonal outgrowth and regeneration[206,207]. Further discussion on the down-regulated proteins in the distal end of the injured digital nerve is presented in Table 11.

Table 10. Up-regulated proteins in the injured distal nerve end

Proteins up-regulated in the injured distal nerve end	
Cellular stress response	Proteins involved in responding to cellular stressors such as heat shock proteins (e.g., HSPA2) and proteins involved in regulating protein turnover and quality control (e.g., UBA5 and HSBP1) contribute to the initial response to nerve injury.
Inflammation and immune response	Proteins associated with lipid metabolism regulation (e.g., GPLD1) and intracellular protein trafficking (e.g., BORCS7) may play roles in modulating the inflammatory responses observed during the early stages of Wallerian degeneration.
Axonal degeneration and synaptic dysfunction	Proteins involved in endocytosis and synaptic vesicle recycling (e.g., SNAP91) contribute to synaptic dysfunction and axonal degeneration, which are hallmark features of Wallerian degeneration
Cellular remodeling and adaptation	Proteins associated with muscle contraction regulation (e.g., TNNI1) and ECM protein regulation (e.g., EGFL8 and ITGA2) as well as intracellular signaling (e.g., FAM3C) are involved in cellular remodeling and adaptation processes during the later stages of Wallerian degeneration.

HSPA2-Heat shock-related 70 kDa protein 2[208], UBA5-Ubiquitin Like Modifier Activating Enzyme 5[209], HSBP1-Heat Shock Factor Binding Protein 1[204], GPLD1-Glycosylphosphatidylinositol Specific Phospholipase D1[209], BORCS7-BLOC-1 Related Complex Subunit 7[210], SNAP91-Clathrin coat assembly protein AP180[205], TNNI1 Troponin 1[211] EGFL8-Epidermal growth factor-like protein 8[212], ITGA2-Integrin alpha 2[213], FAM3C-Protein FAM3C[214]

Table 11. Down-regulated proteins in the injured distal nerve end

Proteins down-regulated in the injured distal nerve end	
RNA processing and gene regulation	Downregulation of RBM12 and HMGB3 may conserve energy resources and fine-tune cellular responses during the initial stages of degeneration. By moderating gene expression and mRNA stability, this may help orchestrate cellular activities necessary for tissue repair and regeneration, while minimizing excessive inflammation and tissue damage.
Cytoskeletal dynamics	Proteins regulating actin filament dynamics (e.g., TWF1 and RHOC) are downregulated, resulting in alterations in cytoskeletal organization. This may facilitate structural remodeling of the injured nerve by allowing for the reorganization of cellular architecture and clearance of cellular debris, essential steps prior to axonal regeneration and repair.
Cellular integrity and quality control	Downregulation of UFL1 and MAP1LC3A may serve to conserve energy and redirect resources towards essential repair processes. It may help modulate cellular responses to stress and injury, facilitating the orchestration of activities required for tissue repair and regeneration while minimizing excessive inflammation and tissue damage.
Membrane organization and neurotransmission	Downregulatation of proteins involved in axon membrane organization (e.g., TSPAN6), vesicle fusion (e.g., SNAP25), and lysosomal function (e.g., GBA1) may conserve energy and fine-tune neurotransmission processes. By reducing neurotransmitter release and modulating cellular membrane integrity, these changes help maintain cellular homeostasis during Wallerian degeneration.

RBM12-RNA-binding protein 12, HMGB3-High mobility group protein 3, TWF1-Twinfilin 1, RHOC-Ras Homolog Family Member C[215], UFL1-E3 UFM1-protein ligase 1,MAP1LC3A-Microtubule Associated Protein 1 Light Chain 3 Alpha[216], TSPAN6-Tetraspanin-6[207], SNAP25-Synaptosome Associated Protein 25 [217], GBA1- Glucosidase Beta Acid 1

By focusing on proteins intricately involved in the degeneration phase, Paper VI offers a unique insight into the early molecular events that set the stage for subsequent nerve regeneration processes. The study stands out as one of the largest investigations focused solely on digital nerves, all repaired within the crucial 48-hour window post-injury. Unlike previous studies often conducted on animal models, like rats, Paper VI offers insights directly relevant to human nerve injury. Extensive animal experiments on the rat sciatic nerve injury have revealed differences at 8 hours post-injury in immunoreactivity (IR) intensity in MEKK1, JIP, and c-Jun, presenting high on the distal side, while low proximally. These proteins were all found in the digital nerves in our data, yet no significant difference in abundance was found between the proximal and distal nerve ends. Additionally, considerable HSP27 IR intensity has been observed at 96 hours on the proximal side of a ligated sciatic rat nerve, whereas the IR on the distal side was faint. HSP27 was found in our data with no difference on the distal end compared to the proximal[218]. This discrepancy underscores the necessity for further studies focusing on human peripheral nerves, particularly regarding molecular events in the degeneration and regeneration phases after injury. Such studies are crucial for translating findings from animal models to clinical applications and improving treatment outcomes for patients with peripheral nerve injuries.

Methodological considerations and study strengths and limitations

The observational studies, as seen in Papers I-III, exhibit several methodological considerations essential for robust research outcomes. The sampling method involving the inclusion of participants from a national quality registry who have accepted to participate after experiencing a nerve injury ensured a thorough representation of individuals with digital nerve and major nerve trunk injuries in Sweden within a specific timeframe. Moreover, the studies included a substantial number of participants, providing adequate statistical power to detect meaningful differences and relationships, thereby enhancing the precision and reliability of the estimates derived from the data. However, it is important to acknowledge that this approach may introduce a selection bias, as those who choose to participate may differ from those who do not. Individuals with more severe injuries or those experiencing persistent symptoms may be more motivated to participate which may lead to an overrepresentation of certain symptoms, such as cold sensitivity. Additionally, the low rate of the same responders to all three questionnaires was a limitation and led to paired analyses not being applicable for significance testing over time for Papers II and III. Nevertheless, the response rate corresponds well to previously published studies[142], and the drop-out analysis showed no significant difference in the population of responders compared to the non-responders for Papers I-III.

Reliable and validated measurement tools, such as the QuickDASH and HQ-8 questionnaires, were utilized to assess disability, symptoms, and functional outcomes in individuals with peripheral nerve injuries. These tools have been previously validated and are widely accepted in clinical and research settings, ensuring the validity and reliability of the collected data[43]. Furthermore, potential confounding variables, such as socioeconomic factors and concomitant injuries, were identified and accounted for in the analyses, employing statistical techniques, such as multivariable regression, to control for their effects and minimize bias.

In the context of the Papers I-III, both external and internal validity are important considerations. External validity refers to the generalizability of the study findings to populations beyond those included in the study[219]. In the presented papers, the use of national quality registries allowed for the inclusion of a large and diverse sample of individuals with peripheral nerve injuries across Sweden. However, it's essential to consider whether the findings can be extrapolated to populations outside of Sweden or to individuals with different demographic characteristics. Factors, such as healthcare systems, cultural differences, and socioeconomic disparities, may influence the generalizability of the results to other settings.

Internal validity, on the other hand, pertains to the degree to which the study accurately measures the relationships between variables without interference from

confounding factors[219]. Steps were taken to enhance internal validity in these studies, such as using validated measurement tools and statistical techniques to control for potential confounders. However, factors, like selection bias, measurement error, and unmeasured confounding variables, could still impact the internal validity of the findings underscoring the importance of researchers understanding these validity concerns when interpreting and applying the findings to clinical practice and policymaking.

For Paper IV the qualitative methodology employed was structured, transparent, and internationally recognized. In contrast to other reviews in the field, the systematic review exclusively incorporates studies featuring a control group of patients. While this selective approach may have reduced the number of studies included in the synthesis, it substantially bolsters the evaluation of PNA utilization, adopting a scientific approach with reduced risk of systematic bias. Another notable strength of Paper IV lies in the impartial stance of the expert group. This stands in stark contrast to many published studies, which often receive sponsorship from companies providing the products under evaluation, thus ensuring a neutral evaluation process.

In Papers V and VI, rigorous methodologies were employed to extract and analyze proteins from fresh frozen human peripheral nerves. This involved careful sample preparation, selection of appropriate extraction techniques, accurate quantification methods, and utilization of advanced analytical instruments, like mass spectrometry. Quality control measures ensured reliability, while standardization efforts aimed at reproducibility. Nevertheless, one of the primary challenges in proteomic studies persists in grappling with the intricate biological structures and physiological mechanisms involved. The large amount of data generated by this technology poses significant hurdles in terms of data processing, analysis, and result interpretation. Addressing these challenges is essential for gaining meaningful insights into the complex mechanisms governing peripheral nerve injury and repair.

Future perspectives

In the years ahead, our comprehension of peripheral nerve injuries should broaden beyond the injury itself to encompass the unique characteristics of the individual affected. It is imperative to pinpoint those at risk of poorer outcomes, enabling targeted resource allocation and customized interventions. Expanding our national registers to encompass additional facets of peripheral nerve injury promises valuable insights into their epidemiology and long-term ramifications.

Furthermore, subjecting new methodologies to rigorous evaluation via robust randomized controlled trials (RCTs) during their infancy stages would facilitate precise comparisons and well-informed clinical decisions.

Incorporating proteomics and genomics into our research efforts is crucial for unravelling the complex mechanisms underlying peripheral nerve injuries. Collaborative endeavors across borders are essential to leverage diverse datasets and facilitate advancements in this field. For instance, initiatives, like the UK Biobank (https://www.ukbiobank.ac.uk), spearheaded by researchers, such as Dr. Akira Wiberg and Professor Dominic Furniss, offer invaluable resources for investigating conditions, like carpal tunnel syndrome (CTS), and hold the potential for studying nerve injury and genetics in the future. Utilizing data from biobanks and biopsy samples in conjunction with surgical procedures can provide invaluable insights into the temporal dynamics of nerve injuries and the impact of surgical interventions in humans. This approach may shed light on why outcomes differ between nerve types, such as the ulnar and median nerves, and help elucidate the underlying factors contributing to variation in outcomes observed in animal models.

In summary, advancing our understanding of peripheral nerve injuries requires a multifaceted approach that considers both individual characteristics and biological mechanisms. By harnessing the power of large-scale registers, conducting rigorous clinical trials, and embracing interdisciplinary collaboration, we can pave the way for improved diagnostics, treatments, and outcomes in individuals with peripheral nerve injuries.

Conclusion

In conclusion, this thesis has extensively investigated surgically treated peripheral nerve injuries in the upper limb, aiming to understand various injury types, analyze patient outcomes relative to socioeconomic status, predict functional recovery, evaluate processed nerve allografts, and explore proteomic patterns early post-injury. The research contributes insights to enhance diagnostic and surgical practices, improve patient outcomes, and deepen our understanding of these injuries. Through a multifaceted approach, spanning from clinical insights to molecular mechanisms, this thesis strives to advance the management of peripheral nerve injuries, ultimately aiming to improve the lives of affected individuals.

The specific conclusions for the papers included in the thesis were as follows:

Paper I Improved attention to the effects of non-biological factors, including immigration, history of previous sick leave, and education level, on outcome after nerve surgery is needed to improve prognosis in socioeconomically deprived individuals.

Paper II Cold sensitivity is common after a digital nerve repair and impacts self-reported disability. A concomitant injury, particularly multiple injuries, predicts postoperative cold sensitivity.

Paper III Cold sensitivity after surgery for a major nerve trunk injury in the upper extremity can be substantial with impaired ability to perform daily activities, whereas an ulnar nerve injury may have a worse outcome.

Paper IV Properly conducted randomized controlled trial studies on the use of PNA in the reconstruction of peripheral nerve injuries are needed to establish recommendations in clinical practice.

Paper V The use of Ripa buffer is recommended, in combination with 8 M Urea and Bullet Blender, for extracting proteins from fresh-frozen human nerves weighing ≥ 1.2 mg.

Paper VI Investigation of proteins, with functional annotations analysis, in proximal and the distal ends of human injured digital nerves, revealed dynamic cellular responses aimed at promoting tissue degeneration and restoration while suppressing non-essential processes.

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Appendix 1

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

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

HAKIR
Hand Surgery Quality Record

Filled in by staff
☐ **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

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Injury, repair, and reconstruction of peripheral nerves in the upper limb

The thesis delves into the multifaceted landscape of peripheral nerve injuries, exploring the intricate interplay between different surgical interventions, the patient reported outcomes, the often-overlooked, influence of socioeconomic factors and cold sensitivity but also the complicated proteomic perspective of these injuries. From the common digital nerve injury to the more complex injuries of a major nerve trunk in the forearm, the spectrum of impairments encompasses mild discomfort to severe, lifelong challenges. Through a diverse approach, spanning from clinical insights to molecular mechanisms, this thesis strives to advance the management of peripheral nerve injuries, ultimately aiming to improve the lives of affected individuals.

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