Carpal Tunnel Syndrome: Incidence, Occupational Risk, Treatment and Outcome Meassures

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Incidence, Occupational Risk, Treatment and Outcome Measures

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KAMELIA MÖLLESTAM is a specialist in orthopedic surgery at Hässleholm-Kristianstad Hospitals in southern Sweden. Her thesis explores Carpal Tunnel Syndrome, one of the most common conditions affecting the hand.

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DOCTORAL DISSERTATION

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Carpal Tunnel Syndrome: Incidence, Occupational Risk, Treatment and Outcome Measures

Abstract

Purpose: To 1) investigate the change in incidence of referred carpal tunnel syndrome (CTS) and carpal tunnel release (CTR) surgery over time and asses possible regional variations; 2) investigate the association of clinically relevant CTS with work and education; 3) assess score agreement between the Atroshi-Lyrén (A-L) 6-item CTS symptoms scale and the Boston 11-item symptom severity scale in patients with CTS before and after CTR surgery; 4) evaluate the placebo-controlled treatment efficacy and effect durability of wrist splinting in patients with primary idiopathic CTS.

Patients and methods:

Paper I: Nationwide register-based epidemiological study of patients with CTS diagnosis and CTR surgery between 2001 and 2009, investigating change in incidence over time and regional variations.

Paper II: Population-based case-control study on type of work and education level among persons in Skåne (aged 17-57 years) with CTS, during 2004–2008, compared with population controls without CTS.

Paper III: Prospective cohort study comparing the A-L and Boston scales using classical and item response theory (IRT) based analyses.

Paper IV: Study protocol of a randomized controlled trial (RCT) designed to assess the efficacy of a conventional (rigid) wrist splint compared with soft wrist bandage (placebo) in the treatment of CTS. Primary outcomes are the change in scores in the A-L scale from baseline to 12 weeks and the rate of CTR surgery at 52 weeks.

Results:

Paper I: Diagnosis and surgery for CTS in Sweden increased over time. Proportion of CTS-diagnosed individuals treated with surgery varied across counties from 53% to 81% in women and from 51% to 77% in men.

Paper II: Compared with white-collar workers, the odds ratio (OR) for CTS among blue-collar workers was 1.67 (95% CI 1.54-1.81) and compared with light work, OR in light-moderate work was 1.37 (1.26-1.50), moderate work 1.70 (1.51-1.91), and heavy manual labor 1.96 (1.75-2.20). Compared with low-level education, OR for CTS in intermediate-level was 0.82 (0.76-0.89) and high-level 0.48 (0.44-0.53).

Paper III: With IRT-based scoring, the A-L scale had significantly higher responsiveness than the Boston scale, both overall (Cohen's d 2.02 vs. 1.59), in women (2.22 vs. 1.77) and in men (1.74 vs. 1.36).

Conclusions:

The incidence of CTS and of CTR surgery increased over time in both sexes, with large regional variations found in the incidence rates and in the proportion of individuals treated with surgery.There is significant association with a dose–response pattern between clinically relevant CTS and increasing manual work load and lower education level. When using IRT-based scoring, the A-L scale demonstrated significantly higher responsiveness than the Boston scale. An ongoing RCT will assess the effectiveness of wrist splinting in patients with CTS.

Key words

Carpal tunnel syndrome, epidemiology, incidence, occupation, item response theory, patient-reported outcome measures, non-surgical treatment, splinting

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To my children – Kyler and Kiara,
my wish for you is that life
becomes all that you want it to.

Table of Contents

List of Publications

This dissertation is based on the following papers, referred to in the text by their Roman numerals. The original articles have been reprinted with the permission of the publishers.

The author of this dissertation formerly went by the surname Tadjerbashi; but, as of the year 2020, the author goes by the name Möllestam.

Paper I **Tadjerbashi K**, Åkesson A, Atroshi I. Incidence of referred carpal tunnel syndrome and carpal tunnel release surgery in the general population: Increase over time and regional variations. *J Orthop Surg (Hong Kong)*. 2019; 27(1): 2309499019825572.

Paper II **Möllestam K**, Englund M, Atroshi I. Association of clinically relevant carpal tunnel syndrome with type of work and level of education: a general-population study. *Sci Rep*. 2021; 11(1): 19850.

Paper III **Möllestam K**, Rosales RS, Lyrén PE, Atroshi I. Measuring symptoms severity in carpal tunnel syndrome: score agreement and responsiveness of the Atroshi-Lyrén 6-item symptoms scale and the Boston symptom severity scale. *Qual Life Res*. 2022; 31(5): 1553-1560.

Paper IV Atroshi I, **Tadjerbashi K**, McCabe SJ, Ranstam J. Treatment of carpal tunnel syndrome with wrist splinting: study protocol for a randomized placebo-controlled trial. *Trials*. 2019; 20(1): 531.

Abbreviations

2-PD	Two-Point Discrimination
A-L	Atroshi-Lyrén
BMI	Body Mass Index
CCC	Concordance Correlation Coefficient
CI	Confidence Interval
CTR	Carpal Tunnel Release
CTS	Carpal Tunnel Syndrome
CTS-6	6-item CTS symptoms scale (also known as Atroshi-Lyrén scale)
DASH	Disabilities of the Arm, Shoulder and Hand
EMG	Electromyography
EQ-5D	EuroQol 5-Dimensions
GPCM	Generalized Partial Credit Model
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
IQR	Interquartile Range
IRR	Incidence Rate Ratio
IRT	Item Response Theory
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market Studies
OR	Odds Ratio
PCM	Partial Credit Model
PROM	Patient-Reported Outcome Measure
QuickDASH	11-item Disabilities of the Arm, Shoulder and Hand
RCT	Randomized Controlled Trial
SD	Standard Deviation
SHR	Skåne Healthcare Register
SSYK	Swedish Standard Classification of Occupations

Populärvetenskaplig Sammanfattning

Karpaltunnelsyndrom är en vanlig åkomma som orsakas av inklämning av medianusnerven i handledsnivå. Patienterna får domningar, stickningar och värk i handen samt svaghet i tummen och funktionsnedsättning. Förekomsten av karpaltunnelsyndrom i den vuxna befolkningen är cirka 5 % bland kvinnor och 2 % bland män. Vanliga riskfaktorer är övervikt, hög ålder, graviditet och vissa sjukdomar, såsom diabetes, ledgångsreumatism och underfunktion i sköldkörteln.

Några få tidigare studier från Nordamerika och Europa har visat betydande variationer i frekvensen av karpaltunneloperation mellan regioner inom samma land; det finns emellertid inga liknande uppgifter för Sverige.

Sambandet mellan typ av arbete och förekomsten av karpaltunnelsyndrom diskuteras fortfarande flitigt men få stora befolkningsstudier finns. Väldigt lite är känt om det möjliga sambandet mellan karpaltunnelsyndrom och utbildningsnivå.

Hos patienter med karpaltunnelsyndrom är förändring i symtomens svårighetsgrad vanligtvis det viktigaste behandlingsresultatet och används ofta som huvudutfallsmått i kliniska prövningar av behandlingsnyttan. Symtom mäts med patient-besvarade enkäter. Boston 11-punktsskalan är en enkät som har varit det vanligaste måttet på symtomens svårighetsgrad vid karpaltunnelsyndrom och har blivit översatt till flera språk. Atroshi-Lyrén 6-punktsskalan har utvecklats från Boston-skalan med hjälp av modern mätmetodik, som används för att utveckla bland annat frågeformulär, enkäter och skattningsskalor. Sedan Atroshi-Lyrén-skalan utvecklades har den översatts till olika språk och använts i kliniska studier. Det är inte känt om poängen på Boston- och Atroshi-Lyrén-skalorna är likvärdiga för att möjliggöra direkta poängjämförelser mellan studier som har använt endera skalan och vilken skala som har större känslighet att kunna mäta förbättringsgraden efter behandling.

Målet med behandling av karpaltunnelsyndrom är att lindra symtomen och förbättra handfunktionen. Kirurgisk behandling har i många studier visat sig vara mycket effektiv för att lindra symtom samt förbättra handfunktion och livskvalitet. Även om kirurgi är en effektiv behandling och rapporteras ha de bästa långsiktiga resultaten, finns flera nackdelar, såsom kirurgirelaterad smärta och handsvaghet. Dessutom är kirurgi förknippat med högre kostnader inklusive sjukskrivning efter operation. För närvarande är den vanligaste icke-kirurgiska behandlingen över hela världen stel handledsskena, även om det vetenskapliga stödet för denna behandling

i allmänhet är svagt, och den långsiktiga effekten har inte fastställts. I de studier som är gjorda är följsamhet (verklig användning av skenan) sällan utvärderad på ett säkert sätt.

Syftet med denna avhandling har varit att öka kunskapen om karpaltunnelsyndrom med fokus på förekomst i befolkningen, arbetsrelaterade riskfaktorer, behandling och utfallsmått.

I *studie 1* har rikstäckande registerdata använts för att ta reda på hur många patienter som fått diagnosen karpaltunnelsyndrom och genomgått karpaltunneloperation mellan åren 2001 och 2009. Resultaten visade att diagnos och operation för karpaltunnelsyndrom i Sverige har ökat över tid. Andelen individer som behandlades med kirurgi varierade mellan Sveriges regioner från 53 % till 81 % hos kvinnor och från 51 % till 77 % hos män.

I *studie 2* har regionala registerdata använts för att ta fram uppgifter om typ av arbete och utbildningsnivå bland personer (17-57 år) i Skåne med karpaltunnelsyndrom mellan åren 2004 och 2008, och jämföra dessa med personer utan karpaltunnelsyndrom. Bland arbetare var det högre andel som hade karpaltunnelsyndrom jämfört med tjänstemän. Ju högre manuell belastning i arbetet desto högre andel individer med karpaltunnelsyndrom. Bland individer med låg utbildningsnivå var det högre andel som hade karpaltunnelsyndrom jämfört med de som hade utbildning på medelnivå och hög nivå.

I *studie 3* har Atroshi-Lyrén-skalan och Boston skalan jämförts med syftet att bedöma poängöverensstämmelsen mellan skalorna hos patienter med karpaltunnelsyndrom före och efter operation för karpaltunnelsyndrom, och jämföra skalornas känslighet för förändring i symtom. Atroshi-Lyrén-skalan hade högre känslighet för förändring i patienternas symtom än Boston-skalan, både bland kvinnor och män.

Studie 4 är en pågående klinisk prövning som bedömer nyttan av en stel handledsskena jämfört med mjukt handledsbandage vid behandling av karpaltunnelsyndrom. Huvudutfallsmått är förändringen i Atroshi-Lyrén-skalan 12 veckor efter behandlingsstart samt frekvensen av operation efter 1 år. Studien kommer troligen att vara den första som använder en elektronisk övervakningsanordning för att mäta den verkliga användningen av bandagen.

Sammanfattningsvis har avhandlingen påvisat att diagnosen karpaltunnelsyndrom och kirurgisk behandling har ökat över tid hos både kvinnor och män, med stora regionala variationer i andelen individer som behandlades med operation. Medvetenhet om dessa regionala variationer i både diagnos och operation skulle kunna leda till att läkare överväger hur de hanterar patienter med karpaltunnelsyndrom och kan minska ojämlik sjukvård för detta tillstånd. Det finns ett tydligt samband mellan karpaltunnelsyndrom och ökande manuell arbetsbelastning samt lägre utbildningsnivå. Dessa fynd kan vara viktiga vid

utformning och implementering av förebyggande åtgärder. Atroshi-Lyrén-skalan hade högre känslighet för att mäta förbättring i symtom efter operation än Boston-skalan. Därmed skulle Atroshi-Lyrén-skalan kunna vara måttet att föredra när man ska utvärdera symtomens svårighetsgrad vid karpaltunnelsyndrom. Slutligen kan resultaten som genereras från den pågående behandlingsstudien förväntas ha stor betydelse för framtida patienter och samhället. Om studien skulle visa att effekten av handledsskena är marginell kan nyttan med nuvarande rutinbehandling vara osäker, vilket kommer påverka framtida behandlingar som erbjuds patienter med karpaltunnelsyndrom.

Background

Carpal tunnel syndrome (CTS) refers to compression of the median nerve at the wrist and is the most frequently diagnosed nerve compression worldwide.[1,2] Patients report symptoms of paresthesia and/or numbness in the median nerve distribution (thumb, index finger, middle finger, and radial side of the ring finger).[3] Nighttime paresthesia in the three radial digits of the hand are essentially diagnostic of CTS. Especially the early stage of CTS is defined by intermittent symptoms that are only present at night.[4] Paresthesia is also common in fixed wrist activities, such as reading a book or newspaper, cycling and driving. Patients may have pain in the hand and wrist and, with progressive nerve compression, weakness and atrophy of the thenar muscles.[2] Although CTS is mainly a clinical diagnosis based on symptoms and physical findings, electrodiagnostic studies are useful to confirm the clinical diagnosis of CTS and to establish the diagnosis in less typical cases.

Anatomy

The flexor retinaculum, which runs from the hamate and triquetrum on the ulnar side to the scaphoid and trapezium on the radial side, forms the roof of the carpal tunnel. This tunnel contains the median nerve as well as the flexor tendons (flexor pollicis longus tendon, four flexor digitorum superficialis tendons, and four flexor digitorum profundus tendons).[2,4] The median nerve is located just under the flexor retinaculum. At the distal end of the flexor retinaculum, the median nerve gives off the recurrent motor branch to innervate the abductor pollicis brevis muscle, superficial head of the flexor pollicis brevis muscle, and opponens pollicis muscles and then separates into the digital nerves that provide sensation to the thumb and index finger, middle finger, and radial half of the ring finger.[1,4]

Pathophysiology

A number of studies propose that neural ischemia contributes to compression neuropathies.[5,6] According to this theory, chronic nerve compression begins with breakdown of the blood-nerve barrier, followed by endoneurial edema and, subsequently, perineurial thickening (Figure 1). Increased endoneurial pressure

leads to alterations in the microneural circulation,[4] rendering the nerve prone to dynamic ischemia. As compression increases, there will be localized demyelination, followed by more diffuse demyelination and then axonal degeneration.[1] Within the nerve, superficial fascicles will be affected sooner, which may result in varying patient symptoms.[7] Therefore, in the early stages of CTS, the superficial fascicles to the long finger and ring finger are often impaired before those to the thumb and index finger. In general, a patient's sensory complaints will follow histopathologic alterations and will proceed from intermittent paresthesia to constant numbness (Figure 1). Depending on the degree of nerve compression, the effect on sensory tests will also differ. Initially, threshold measurements will be altered, and if nerve compression progresses, two-point discrimination (2-PD) deficiencies will develop.

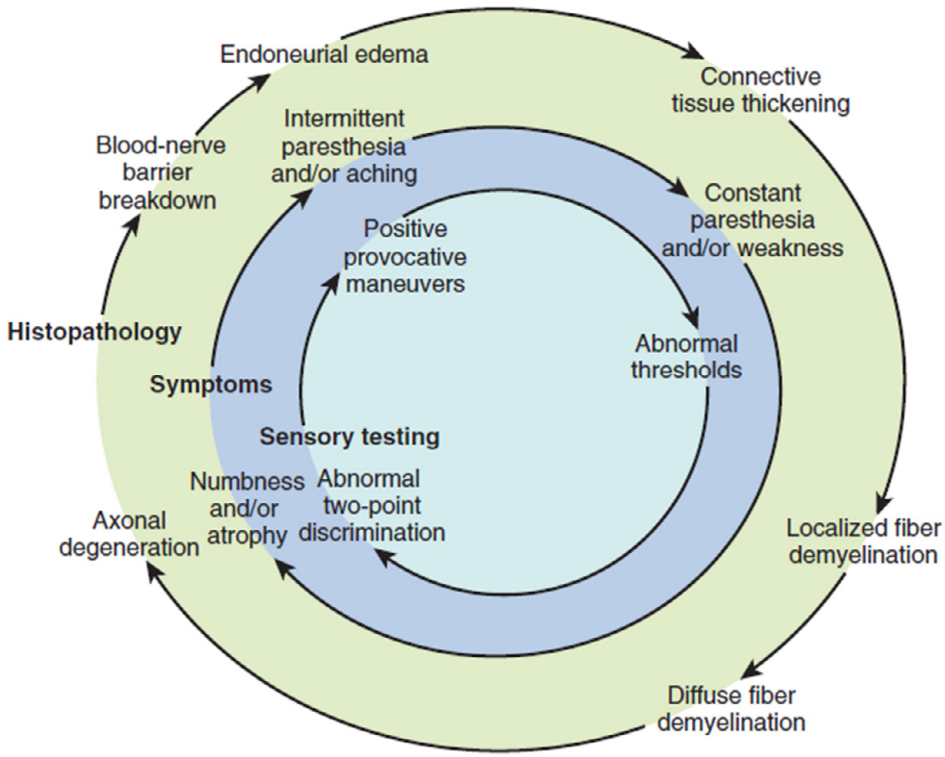

Figure 1. The pathophysiology of compression neuropathies.

Chronic nerve compression begins with the collapse of the blood-nerve barrier and progresses to axonal degeneration with continuous compression. The patient's symptoms and clinical tests will mirror the nerve's histopathologic alterations. Image from Mackinnon et al., Compression Neuropathies in *Green's Operative Hand Surgery*, with permission from Elsevier.[1]

Epidemiology

It has been estimated that there is a 10% lifetime risk of developing CTS.[2,8] In a Swedish general population study conducted 1997, the prevalence of CTS in adults was approximately 5% in women and 2% in men.[9] No newer general population prevalence studies have been published. According to studies that have estimated the incidence of CTS in general populations, there appears to be large differences between countries.[10-14] However, there are only little data available on geographical differences in the incidence of CTS within a country. A few studies from North America and Europe have demonstrated large within-country regional variations in the incidence of carpal tunnel release (CTR) surgery.[15-18]

Risk factors for development of CTS

Genetics

Genetic predisposition has been suggested to explain some clinical presentations of CTS. For example, a positive family history has been reported in 17-39% of patients with CTS.[19,20] Furthermore, a large twin study in the UK showed that close to 50% of women's susceptibility to CTS is genetically determined (heritability estimate of 0.46), suggesting that genetics is the single strongest risk factor for CTS.[21] A large UK genome-wide association study identified 16 genome-wide significant susceptibility loci for CTS and suggested that variants in genes involved in skeletal growth and extracellular matrix architecture contribute to the genetic predisposition to CTS by affecting the environment through which the median nerve passes.[22] A recent expansion of this study found 50 genetic loci associated with CTS, demonstrating a genetic correlation between CTS and height, body mass index (BMI), early hormone replacement therapy, osteoarthritis and restlessness, and also showing a higher genetic component in patients with bilateral, recurrent or persistent CTS.[23]

Personal factors and medical conditions

Previous studies that investigated the etiology of CTS have concluded that CTS is mainly associated with individual risk factors, including female sex and higher age.[24] Other systemic conditions and lifestyle variables, such as rheumatoid arthritis, diabetes mellitus, hypothyroidism, pregnancy, excessive alcohol consumption, obesity, tobacco use and hand/wrist trauma, have also been linked to CTS.[25-31] However, some of these studies also identified several occupational activities that may lead to an increased risk of CTS.[28,29]

Occupation

In the 1990s, the causal association between nerve compression syndromes and occupation was extremely controversial.[32,33] Work-related aspects of these conditions are still the subject of debate.[34-36] Historically, it has generally been believed that CTS is a multifactorial disease and that occupation is only one of several variables that contribute to and exacerbate compression neuropathy.[34,37] Nonetheless, more recent studies have reported a significant association between occupation and CTS.[36,38] Occupational activities such as vigorous manual labor, forceful gripping, extremely repetitive wrist flexion and extension, extreme wrist postures, and the use of vibratory equipment may increase the risk of CTS.[28,29,38-52] Extensive research has been conducted on the association between CTS and work-related activities, which has led to the publication of numerous systematic reviews (Table 1). Furthermore, certain occupational groups, such as those dealing with assembly, food processing, and packaging, especially in cold environments and industrial settings, have been reported to have a high prevalence of CTS.[28,49,53,54]

Table 1. Example of review articles (including systematic reviews and meta-analyses) that examine the association between CTS and occupational activities.

Authors	Study type	Study period	Studies included, n	Occupational factors associated with CTS
Palmer et al. 2007[28]	SR	1981-2004	38	Repetition (especially with forceful grip) Vibration
van Rijn et al. 2009[55]	SR	1966-2007	44	Hand force Repetition Vibration Wrist postures
Barcenilla et al. 2012[29]	MA	1980-2009	37	Hand force Repetition Vibration
You et al. 2014[40]	MA	1980-2012	9	Wrist postures
Kozak et al. 2015[38]	SR + MA	1998-2014	17	Hand force (dose-response relationship) Repetition (dose-response relationship) Vibration Wrist postures
Newington et al. 2015[42]	NR	1992-2014	9	Repetition Vibration (especially with a forceful grip)

MA = meta-analysis, NR = narrative review, SR = systematic review

In a large population-based study in Southern Sweden, the prevalence of CTS among active blue-collar workers was significantly higher than that among white-collar employees even after adjusting for sex, age, and BMI.[9] Another study from Italy showed that surgically treated CTS was three to seven times more common (depending on age/sex) in blue-collar than in white-collar workers.[41] The reason for the higher prevalence of CTS among blue-collar workers is believed to be that certain occupational risk factors are more common among blue-collar workers, such

as forceful manual work, extreme wrist postures and use of vibratory tools. Previous studies have mainly focused on specific occupational cohorts and applied a variety of case definitions for CTS, not always based on a physician's diagnosis. Other studies have only included surgical cohorts, therefore the conclusions about correlations would only apply to CTS patients who have undergone surgical treatment.[56] No previous studies that investigated the association between CTS and work have included the whole general population of individuals who have sought medical care for hand problems that were diagnosed by a physician as CTS.

Education

In contrast to the widespread interest in the relationship between CTS and work, little is known regarding the possible association between CTS and education level. Although a prior population-based study indicated a probable relationship between education level and having had surgery for CTS,[57] no studies have examined the association for all clinically relevant CTS.

Diagnosis

Clinical diagnosis

Patient history

A thorough clinical history is long-recognized as the gold standard for diagnosis, together with the exclusion of other potential causes.[2] Usually, at onset of symptoms, CTS is characterized by intermittent, nocturnal paresthesia that with disease progress occurs more frequently, even during waking hours. In the later stages of the disease, axonal degeneration leads to a loss of sensation, as well as weakness and atrophy of the thenar muscles.[58] This pattern of symptoms is relatively typical, appearing seldom in conditions other than CTS.

Theoretically, symptoms should be limited to the median nerve distribution of the hand;[3] nevertheless, in clinical practice, symptoms are not restricted to the first three digits but might include all fingers and the entire palmar surface.[2] In a previous study of 255 hands, symptoms from the 5th digit was reported in 40%.[59] The distribution of symptoms in the median nerve innervated area alone might be suggestive of more severe nerve conduction velocity abnormalities.[60]

Provocative tests

The *Tinel* sign is a nerve percussion test conducted by repeated digital percussion to the suspected entrapment location (in this case over the carpal tunnel). If there is a tingling sensation in the sensory neural distribution of the median nerve, the test

is considered positive. The sensitivity of the Tinel test ranges from 38% to 100%, and the specificity ranges from 55% to 100%,[61] with an estimated average of 50% sensitivity and 77% specificity.[62]

The *Phalen* test is another typical provocative test used to diagnose CTS. It involves flexing the wrist (should be maintained for one minute) to create pressure on the median nerve.[63,64] The test is considered positive if symptoms are reproduced in the appropriate neural distribution. The sensitivity of the Phalen test ranges from 42% to 85%, and the specificity ranges from 54% to 98%,[61] with an estimated average of 68% sensitivity and 73% specificity.[62]

Sensory tests

Numerous instruments and assessment devices for evaluating sensibility have been described, but no single test has been acknowledged as the gold standard. This is due in part to the differing capacity of the sensory tests to assess various nerve function characteristics.

Semmes-Weinstein monofilaments are nylon monofilaments that differ in diameter, and consequently, in application force and pressure thresholds. Each subsequent nylon strand is subjected to pressure until it barely begins to bend. The pressure threshold is defined as the smallest monofilament that a patient can perceive. Each monofilament diameter corresponds to a degree of sensory impairment (e.g., normal, diminished light touch, diminished protective sensation). The diameter of monofilaments and the testing technique must be consistent in order to ensure reliability.[65,66] Cutaneous pressure thresholds will allow for the assessment of early changes associated with chronic nerve compression, and pressure thresholds have been demonstrated to be sensitive in testing for CTS.[1,4]

Two-point discrimination is used to evaluate tactile discrimination, which represents the number of innervated sensory receptors. Changes in sensory receptor innervation density will occur in the later stages of chronic nerve compression, and as a result, 2-PD measurements will only become abnormal in the more severe stages of nerve compression. Consequently, this test is not sensitive for individuals with mild or moderate chronic nerve compression.[1]

Electrodiagnostic studies

Electrodiagnostic studies consist of nerve conduction studies and electromyography (EMG). Electrodiagnostic studies have demonstrated a high sensitivity and specificity of 78-92% and 80-91%, respectively, for CTS,[67-69] but also a false-negative rate of 10-25%.[70,71] Therefore, the tests cannot replace a thorough clinical evaluation performed by an experienced physician, and for the majority of patients with typical CTS, negative findings on electrodiagnostic tests will not impact the decision regarding treatment.[72] However, electrodiagnostic studies can complement

the clinical examination by helping to identify the level and severity of nerve compression in patients with CTS,[1,73] which could have implications for prognosis.[2] Electrodiagnostic studies are also helpful for evaluating differential diagnoses, such as cervical disk disease and polyneuropathies.[1,2,4]

One limitation of the nerve conduction part of the electrodiagnostic study is that only large myelinated fibers are evaluated.[74] In chronic nerve compression, the earliest abnormalities are changes in unmyelinated nerve fibers, which means that early CTS cannot be properly evaluated using electrodiagnostic studies.[75] Furthermore, early nerve compression is characterized by dynamic ischemic episodes affecting the nerve, and electrodiagnostic studies may not be able to detect these variations in blood flow that cause intermittent abnormalities in peripheral nerve function, resulting in normal test results at this stage of the disease. As nerve compression progresses, demyelination and a slowing of conduction velocity will occur at the site of nerve compression, resulting in abnormal latencies on nerve conduction studies. Typically, axonal degeneration does not develop until the later stages of neuropathy. In addition, EMG is often normal until the advanced stages of the disease,[1] and it might not be particularly useful in most patients with CTS, as it doesn't substantially improve the diagnostic sensitivity.[73]

Treatment of CTS

Splinting

A rigid wrist splint is frequently recommended as a nonsurgical treatment option for CTS,[76] and it is currently the most common non-surgical treatment worldwide.[77] The rationale behind wrist splinting is that it limits wrist flexion, which is known to increase carpal tunnel pressure.[78] Wrist splints are most effective in relieving symptoms of CTS when placed in a neutral position[79] as this will reduce carpal tunnel pressure. However, the functional position of the wrist is 30 degrees of extension. Due to the restriction of wrist movement in a nonfunctional position, wrist splinting is usually recommended at night and not during normal daily activities.[1]

Some data suggest that wrist splinting may be effective in the short term,[80-82] but the evidence is typically weak, the appropriate treatment duration is unknown, and the long-term efficacy has not been proven.[83,84] In studies that compared wrist splinting with surgery,[81,85] the advantage of splinting was frequently enhanced by a high cross-over to surgery, despite the fact that the treatment effect of wrist splinting was frequently small and of short duration.[86] Furthermore, the duration of splinting (4 to 6 weeks) commonly applied in clinical practice is not supported by factual evidence.[83] This brief duration of wrist immobilization may not have a significant impact on the pathophysiological processes involved in the development of CTS. It

is unknown why the benefit of wrist splinting in idiopathic CTS continues after splinting has been discontinued.

Although splinting is a simple and safe procedure, it does have disadvantages. Patients may feel that wearing a splint is inconvenient and restricts their ability to do certain tasks or everyday activities. Also, the costs related to the splint and treatment appointments might be high.[87]

Injections

Injection of corticosteroids have been used to treat CTS with varying results.[76,88,89] Evidence from placebo-controlled studies supports the short-term effectiveness of local steroid injection.[90] In a randomized, placebo-controlled trial assessing the effectiveness of steroid injection, Atroshi et al. found temporary alleviation in symptoms, with a significant change in the probability of surgery within one year. However, even with prior steroid injection, three out of four patients had surgery within one year.[88] Green observed that temporary improvement following steroid injection in the carpal tunnel was a good predictor of successful carpal tunnel surgery.[91] However, it is still an invasive procedure that is not routinely accessible in primary care, and referral to specialists may be necessary. Injection of steroids have been linked to complications, including median nerve injury. This, together with only brief symptom relief, makes it not routinely indicated.[1]

Therapy

Nerve gliding exercises have been utilized to improve nerve compression symptoms. A Cochrane review from 2012 concluded that there is a broad collection of exercise and mobilization therapies for CTS but the evidence of their benefits is limited and of an overall very low quality.[92] Therefore, more research is needed to evaluate the efficacy of manual therapy in patients with CTS, particularly with regard to the treatment's durability and effects over the long term. More recently, a systematic review found that manual therapy, based on soft tissue and neurodynamic mobilization, is effective in reducing pain intensity and improving function (as measured by the Boston Carpal Tunnel Syndrome Questionnaire) and nerve conduction studies in patients with CTS.[93] However, the results should be regarded with caution due to factors such as the lack of randomized controlled trials (RCTs) and that the included studies showed methodological heterogeneity.

Surgery

When conservative treatment options fail to improve the patient's symptoms, surgical median nerve decompression is usually advised. Herbert Galloway

allegedly conducted the first CTR in 1924.[1] There have been several descriptions of techniques for CTR, ranging from an open procedure to a minimal incision to endoscopic release. The debate concerning open versus endoscopic CTR continues, with the decision primarily relying on the surgeon's and patient's preferences, since studies have not shown any significant difference in long-term functional outcome.[94-96] A meta-analysis in 2004, evaluating the effects of endoscopic and open CTR, concluded that data regarding symptom relief and return to work are inconclusive and that endoscopic release increases the risk of nerve injury.[97] An RCT by Atroshi et al. concluded that endoscopic surgery was associated with less postoperative pain than open surgery, but the differences were generally small, and there were no differences in any other outcomes, such as work absence after surgery.[98] An extended follow-up of that randomized trial showed no significant long-term differences in symptoms and function.[96,99] An RCT comparing one incision to two incisions (open technique) found no long-term differences between the two surgical approaches.[100]

After CTR surgery, a bulky dressing is used. The patient is instructed in finger, wrist, and arm range-of-motion exercises. The dressing and sutures are removed two weeks postoperatively. At one month following surgery, patients are allowed to use their hand in all activities without restrictions. Depending on occupation, patients might need up to 6-8 weeks before they can return to full work.

There is substantial evidence that CTR surgery is very efficient in reducing symptoms, improving hand function, and enhancing quality of life,[9] and that the effect is long-lasting.[96] The long-term effectiveness of other treatment methods has not been clearly proven.[83,84] Surgery has shown higher long-term effectiveness than non-surgical treatment,[101] and surgery has also been superior to non-surgical treatment in terms of improving electrophysiological measurements.[102]

Aims

The general aim of this thesis is to improve knowledge on CTS regarding epidemiology, occupational risk factors, treatment and patient-reported outcome measures (PROMs).

Paper I

To investigate the change in the nationwide sex- and age-specific incidence of referred CTS and CTR surgery over time and assess possible regional variations.

Paper II

To investigate the association between clinically relevant CTS and type of work and level of education in a general population.

Paper III

To assess the score agreement between the Atroshi-Lyrén (A-L) 6-item CTS symptoms scale and the Boston 11-item symptom severity scale in patients with CTS before and after surgical treatment and compare their responsiveness.

Paper IV

To evaluate the placebo-controlled treatment efficacy and effect durability of wrist splinting in patients with primary idiopathic CTS up to 12 months after treatment start.

Patients and Methods

A graphic presentation of the study designs, study populations and time frame of the papers included in the thesis is shown below (Figure 2).

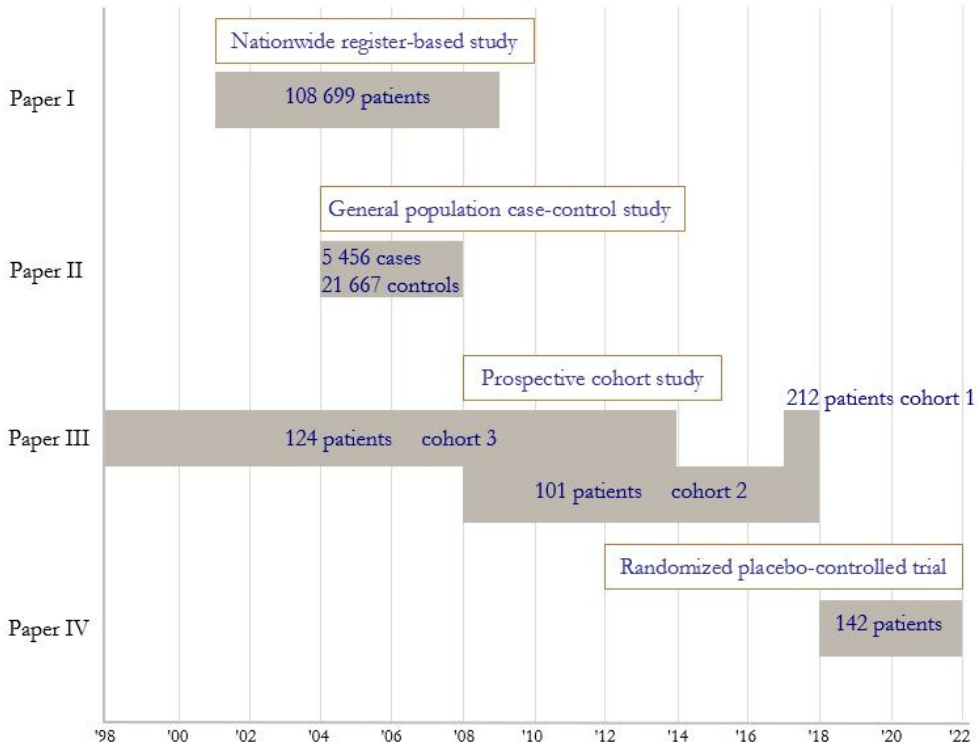

Figure 2. Timeline of study populations included in the thesis.

Paper I

Study population

This was a population-based retrospective study. Data were acquired from the Swedish National Board of Health and Welfare's Center for Epidemiology's patient registry. All individuals aged ≥18 years who visited a physician between January 2001 and December 2009 and were diagnosed with CTS – code G560 according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) system – were identified. In connection with the CTS diagnosis, all patients who had CTR surgery (ACC51 according to the Swedish Classification of Healthcare Interventions[103]) were also identified. Data collected included sex, age at time of diagnosis or surgery, consultation dates, surgery dates, health care facility, region of residence, type of visit (outpatient or inpatient), primary diagnosis and any additional associated diagnoses (up to eight diagnoses were permitted), and surgical procedures and other interventions performed. Each individual was only included once in the analyses (first-time diagnosis and first-time surgery). Annual data on population statistics were retrieved from Statistics Sweden.[104] For each study year, the population statistics from December 31 of the preceding year were utilized.

Registers and databases

The Center for Epidemiology at the Swedish National Board for Health and Welfare's patient registry

This nationwide register includes all patient visits (outpatient and inpatient care) to a physician at secondary and tertiary-level health care institutions (i.e. hospital or equivalent specialized health care facility) as well as all medical procedures done at these facilities. The registry does not describe how the physician made the diagnosis of CTS (on clinical grounds only or in combination with nerve conduction tests). Since 2001, the patient register includes data from both public and private health care providers. The coverage rate of the register is assumed to be high, as anyone conducting specialized health care activities is required by law to report to the patient register. However, the National Board of Health and Welfare lacks the authority to impose on institutions to report to the register.[105]

Statistical analysis

Using Poisson regression models, the sex and age-specific incidence rates of CTS and CTR surgery (overall rates and for the 21 regions) and 95% confidence intervals (CIs) were calculated. Analyses of incidence patterns over time were made. The population at risk was standardized using the 2013 European standard population

weights. In order to get an adequate sample size for each age group the region with the largest population was selected as a reference. The age-adjusted incidence rate ratios (IRR) and 95% CIs were estimated using incidence rates from the study's last three years (2007–2009) for regional comparisons. Statistical significance was defined as a p-value <0.05. STATA (STATA SE 14.2, StataCorporation, College Station, TX, United States) was used to conduct all analyses.

Paper II

Study population

This was a case–control study based on a general population. Using the Skåne Healthcare Register (SHR), new cases of physician-diagnosed primary CTS in the population of Skåne region in southern Sweden (1.2 million inhabitants, one-eighth of Sweden's population) throughout a 5-year period (from January 1, 2004 through December 31, 2008) were identified. The inclusion criteria were as follows: (1) age 17-57 years at diagnosis; (2) primary diagnosis of CTS by a physician; and (3) residency in the region for at least three calendar years prior to the date of diagnosis. Individuals who had obtained a CTS diagnosis within three years prior to the first CTS diagnosis registered during the study period were excluded.

For each CTS case 4 matched referent individuals were randomly sampled from the general population. The matching variables were gender, birth year, and residential district. The referents had to be residents in the region and not have been diagnosed with CTS. No further exclusion criteria were used. Therefore, all individuals (cases and randomly selected referents) were included, regardless of their employment status.

Information regarding occupation and education level was retrieved from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA).[106]

Registers and databases

Skåne Healthcare Register

All inpatient and outpatient care, both public and private, including primary care, provided in the Skåne region, by all medical professionals (physicians, nurses, physiotherapists etc.) is documented in the SHR since 1998. This documentation serves as the basis for the health care provider's economic reimbursement. Consequently, it is anticipated that the SHR includes the great majority of all health care provided. The majority of consultations documented in the SHR have a diagnosis. Diagnoses are classified in accordance with the ICD-10 system. In 2004,

the proportion of physician visits that had an assigned diagnosis was highest for inpatient care (close to 100%) and lowest for primary care (around 80%). However, this proportion has increased significantly over time, and in 2017, nearly 100% of all physician visits were accompanied by a diagnosis.[107]

Longitudinal Integrated Database for Health Insurance and Labor Market Studies

LISA is a national database, a part of Statistics Sweden, that integrates existing data from the labor market, educational sector and social sector, and is updated with annual registers.[106] All residents, aged 16 years or older, in Sweden are covered, and data is available from 1990 and onward. The coverage rate of the register has increased significantly over time. As of 2019, data on occupation have a completeness of 95% and education data are available in >98% of all individuals.[108]

Definitions

Type of work

Two separate classifications of occupation were used. Based on the Swedish Standard Classification of Occupations (SSYK),[109] type of work was categorized as blue-collar or white-collar.[110]

The SSYK is based on the International Standard Classification of Occupation.[109] There are two versions of the SSYK, SSYK 96 and the updated SSYK 2012; the former version was used in this study. The SSYK has a hierarchical structure with several subgroups in each category, but the 10 main groups are as follows (Table 2):

Table 2. Occupational groups according to SSYK 96.

Group number	Occupational group
1	Managers
2	Occupations requiring advanced level of higher education
3	Occupations requiring higher education qualifications or equivalent
4	Administration and customer service clerks
5	Service, care and shop sales workers
6	Agricultural, horticultural, forestry and fishery workers
7	Building and manufacturing workers
8	Mechanical manufacturing and transport workers, etc.
9	Elementary occupations
0	Armed forces occupations

Groups 0-4 are classified as white-collar workers, except occupations 4131 (warehouse manager), 4132 (vehicle manager, traffic manager, transport manager etc.), 4150 (postman, postal manager etc.) and 4213 (casino staff, croupier, dealer), which are classified as blue-collar.

Groups 5-9 are classified as blue-collar workers, except occupations 5111 (flight attendants), 5113 (guides and tour guides) and 5227 (telemarketer), which are classified as white-collar.

Based on a recent study by Wolf et al.,[111] occupations were additionally classified as light, light-moderate, moderate, or heavy manual work.

Level of education

Level of education was classified according to the Swedish Education Classification: levels 1 and 2 (primary and lower secondary education up to 9 years) as “low”, levels 3 and 4 (upper secondary education 2 or 3 years) as “intermediate”, and levels 5 to 7 (post-secondary education and postgraduate education) as “high”.[112]

Statistical analysis

The Chi-square test was used to compare the CTS cohort with the referent cohort, in terms of occupation and degree of education, stratified by sex. Using three conditional logistic regression models, the odds ratios (OR) and 95% CIs for CTS were estimated. The objective of the first model was to assess the entire effect of education, therefore education, but not occupation, was included (because occupation is an intermediate in the relationship between education and CTS). Age and sex did not differ between matched sets; therefore they were controlled for through design and conditional regression. In two additional models, the overall effect of occupation after adjusting for education was estimated (as education is a possible confounding variable in the connection between work and CTS). A separate model was employed for each categorization of occupations, one for "blue collar/white collar" job classification and one for "light/light-moderate/moderate/heavy" occupational categories. The "blue/white collar" model did not contain "occupational group", and vice versa. A p-value <0.05 was used to determine statistical significance. The analyses were conducted using STATA version 16.0. (Stata Corporation, College Station, TX, United States).

Paper III

Study population

This was a prospective cohort study at the Department of Orthopedics, Hässleholm-Kristianstad, in southern Sweden. The department is the only institution in a 300,000-person region that performs CTR surgery. The study includes data from three cohorts of patients who completed the Boston 11-item symptom severity scale, the A-L 6-item CTS symptoms scale and the QuickDASH on the same occasion. All patients were diagnosed with CTS by orthopedic or hand surgeons based on history and physical examination, with or without nerve conduction studies. The inclusion criteria were a diagnosis of CTS and subsequent surgery consisting solely of unilateral CTR (i.e., no concomitant procedures).

Cohort 1 (preoperative/short-term postoperative cohort) consisted of 317 patients (329 hands) who completed the scales at the hospital either immediately before surgery or within 8 weeks before surgery, and 239 patients (284 hands) who completed the scales between 3 weeks and 17 months after surgery (between May 2017 and October 2018). Of these, 212 patients (235 hands) completed the scales both before and after surgery. The scales were mailed to the patients postoperatively. Patients who had surgery on both hands throughout the study period typically underwent the second procedure after at least a 3-month interval.

Cohort 2 (mid-term postoperative cohort) consisted of 101 patients (101 hands) who participated in a randomized placebo-controlled trial of steroid injection and then underwent surgery.[88] Five years following randomization, the patients completed the scales as part of a follow-up done on all study participants.[113] Patients were sent the questionnaires by mail. All study participants provided follow-up data.

Cohort 3 (long-term postoperative cohort) consisted of 124 patients who participated in an RCT comparing open versus endoscopic CTR.[98] Twelve to 14 years following surgery, patients completed both scales (questionnaires were mailed to patients).[96] Three of the initial 128 patients were deceased, and one declined to answer the follow-up questionnaire.

In all three cohorts, the questionnaires contained the Boston 11-item symptom severity scale, the A-L scale, and the QuickDASH.

The flowchart below illustrates the number of hands analyzed in the three cohorts (Figure 3).

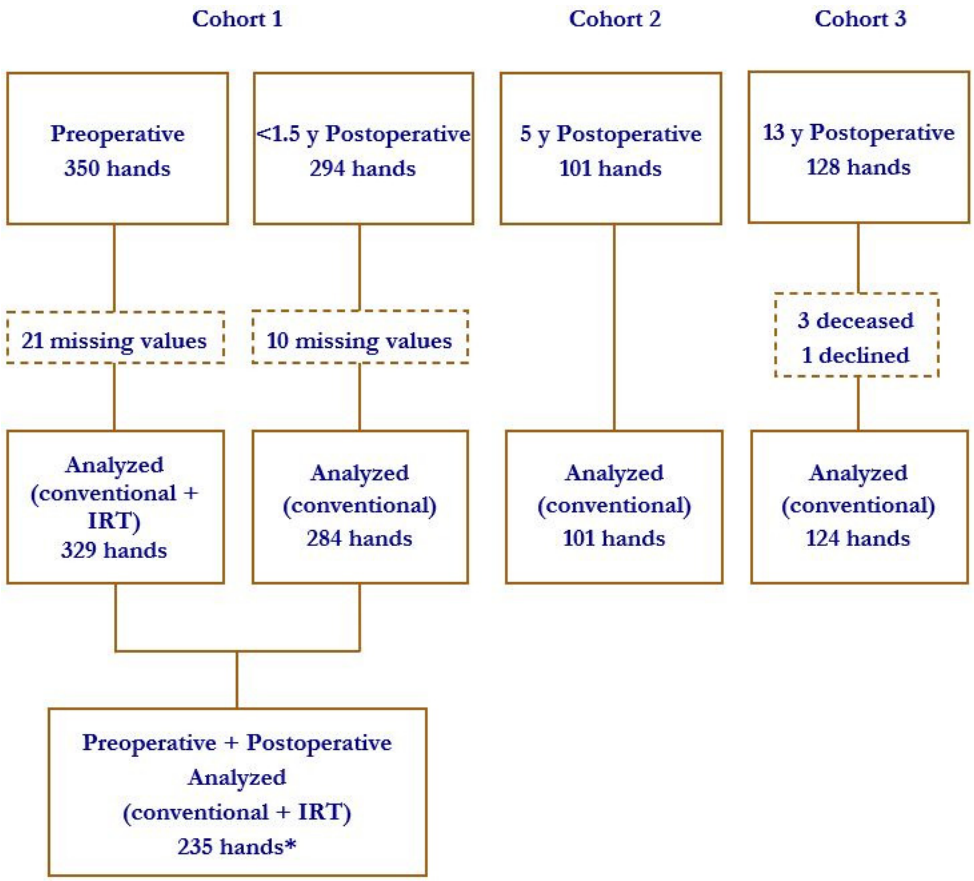

Figure 3. Flowchart of number of hands analyzed in the 3 cohorts.

* In the analyses of the Boston and A-L scales (for the QuickDASH scale 231 hands were included).

Patient-reported outcome measures

Change in symptom severity is often the most important treatment outcome for patients with CTS and is frequently used as the primary endpoint in randomized clinical studies assessing therapy efficacy.[81,85,88,98] Generally, symptom severity is assessed using PROMs.

Boston Carpal Tunnel Questionnaire

The Boston carpal tunnel questionnaire, developed almost thirty years ago, is a disease-specific measure that allows particular items relevant to CTS to be evaluated from the patient's perspective and has been demonstrated to be reliable, valid, and responsive to change.[114-120] The questionnaire consists of two parts, assessing symptom severity (11 items) and functional status (8 items). Each question is scored

on a Likert scale ranging from 1 to 5, with higher values indicating a worsening in status. The final score is the mean value of all item scores. The 11-item symptom severity scale of the Boston questionnaire has been the most extensively used measure of symptom severity in CTS and has been translated into several languages.[118,120-123]

Atroshi-Lyrén 6-item CTS symptoms scale

In a prior study, the Boston scale was examined using modern measurement methodology based on item response theory (IRT) in a stepwise process that resulted in the elimination of four items that did not fit well in the scale and the merger of two other items.[124] A 6-item symptoms scale was developed that demonstrated strong internal consistency, test–retest reliability, and validity when compared to the Boston scale, and it exhibited no gender-specific differential item functioning.[124] In addition, the responsiveness of the 6-item scale has been established.[125] Since its development, the A-L 6-item CTS symptoms scale has been translated into several languages and used in clinical studies.[126-130] The scale can be scored based on IRT scoring, but it may also be scored conventionally on a scale ranging from 1 (no symptoms) to 5 (most severe symptoms), similar to the Boston scale. With conventional scoring, the final mean A-L symptom score can range from 1.0 (best) to 5.0 (worst).

When the A-L scale was initially developed, it was referred to as the CTS-6.[124,125] However, this was confused with a CTS checklist developed by Graham et al. that uses the same abbreviation.[72,131] The CTS-6 evaluation tool developed by Graham et al. is a clinical aid assessing the likelihood of CTS, whereas the 6-item CTS symptoms scale is a PROM of symptom severity. To avoid confusion, the 6-item CTS symptoms scale is now referred to as the A-L scale.

Disabilities of the Arm, Shoulder and Hand questionnaire

The Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire is the most commonly used measure of activity limitations and symptoms related to upper-extremity conditions. It consists of 30 items and enables comparison of the impact of different upper-extremity conditions.[132] Symptom severity and functional status are scored from 1 to 5, with higher scores implying greater disability levels.

QuickDASH

The QuickDASH is a short version of the DASH, measuring upper extremity-related disability.[133,134] The QuickDASH is region-specific, with the majority of questions addressing activity limitation. The final score can range from 0 (no disability) to 100 (most severe disability).

Statistical analysis

Separate analyses were conducted for each of the three cohorts (cohorts were not combined).

Conventional scoring

The mean score and standard deviation (SD) for each scale in each cohort was calculated. The unadjusted difference between the Boston and A-L scale scores was calculated. In the preoperative/short-term postoperative cohort, a multivariate multiple linear regression analysis was conducted to investigate whether age, sex, and time after surgery are confounders in the difference of the change (preoperative to postoperative) scores between the Boston and A-L scales. The scores were compared based on the sequence in which the scales appeared in the questionnaire, without any significant differences; consequently, this variable was not further explored.

Score agreement

Lin's concordance correlation coefficient (CCC)[135] was used to evaluate absolute agreement in conventional scores between the Boston and A-L scales. The Passing and Bablok regression analysis[136,137] was performed to assess the difference in systematic error of measurement between the two scales.

IRT analyses

The IRT analyses were conducted exclusively on responses from the preoperative/short-term postoperative cohort. In the analyses of the Boston and A-L scales data from all hands with preoperative responses (n = 329) were included, as well as data from the hands that had both preoperative and short-term postoperative responses (n = 235). In the analyses of the QuickDASH scores all hands with responses to at least 6 of the 11 items were included (n = 231).

The partial credit model (PCM) was used as the item response model in the development of the A-L scale.[124] Nevertheless, based on the results of the previous research, it was predicted that the PCM would have a relatively poor fit with the Boston scale items. Consequently, given the goal of this study, a more generic model, the generalized partial credit model (GPCM) was chosen.[138]

The software ConQuest (version 4.0) was used for parameter estimation.[139] For parameter estimates in the GPCM weighted likelihood estimation (WLE) was used.[140] Parameter estimation was performed in two steps. First, item parameters were estimated from the whole preoperative data set in order to maximize the quantity of data used in the estimation of item parameters. In the second step, these pre-estimated item parameters were used to estimate the severity of preoperative and postoperative symptoms in hands with both preoperative and postoperative responses. Following these steps would ensure that the item parameters are as robust

as possible and that the preoperative and postoperative estimations of symptom severity are on the same scale.

Using infit and outfit statistics, item fit was determined. The expected value for both infit and outfit is 1, and according to Wilson[141], the acceptable range for fit values is between 0.75 and 1.33.

Reliability

The Cronbach alpha coefficient was calculated to analyze reliability.

Responsiveness

The overall and sex-specific effect size for each scale in patients who had both preoperative and postoperative scores was calculated. As a measure of effect size, Cohen's d with 95% CI was used (mean difference between preoperative and postoperative scores divided by the pooled SD). Using STATA version 16.0 (Stata Corporation, College Station, TX, United States), this was determined for both the conventional and IRT-based scores. The z-test was then used to compare d for the Boston and A-L scales.

Explanation of statistical models

IRT models

IRT models are statistical models of the relationship between an individual's score on the latent trait being assessed and the likelihood of selecting each response on each item measuring that trait. With the use of IRT models, you can not only enhance scoring accuracy[142] but also reduce test administration time by using only the discriminative items and thereby shortening outcome questionnaires.[143] These features may explain why IRT models have gained in popularity in health outcomes and clinical research in recent years.[142]

The PCM and GPCM are widely utilized item response models for ordered polytomous data (items with several answer alternatives expressing, for example, varying levels of symptom severity). They both model the likelihood of selecting the higher of two adjacent answer alternatives given the latent trait (symptom severity in this study). Both models have a set of threshold parameters describing the item location (or difficulty), i.e., the likelihood of reporting a problem on the item. In addition, the GPCM has a discrimination parameter that may be viewed as an item weight. A larger discrimination parameter for a particular item indicates a stronger association between the latent trait and the expected score on that item (i.e., an item with a large discrimination parameter is more effective at distinguishing between low and high levels of symptom severity). This is in contrast to the PCM, where the discrimination parameter is fixed at 1 for all items.

Infit and outfit statistics

Infit and outfit are both Chi-square-like statistics (squared standardized residuals), indicating how accurately or predictably data fit the model. However, infit is based on information weighted residuals whereas outfit is not. This suggests that, according to the model, infit is sensitive to unexpected responses near the person's location on the scale (symptom severity in our study), whereas outfit is more sensitive to unexpected responses further away from the person's location (i.e. outlier responses). Therefore, infit values are of higher concern, as outfit values can be significantly influenced by a small number of outliers.

Paper IV

Study population

This is a study protocol for a prospective randomized parallel-group superiority clinical trial. The trial has been undertaken at the Department of Orthopedics, Hässleholm-Kristianstad, in collaboration with a number of primary care institutions in the region of Northeastern Skåne in southern Sweden (population of 300,000). The department is the primary referral facility in the region for patients with CTS. The trial followed the guidelines proposed in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.

Patients with symptoms indicative of CTS who consulted a primary care physician or an occupational therapist at primary health care centers were screened. Patients judged to be potentially eligible were referred to the orthopedic department and scheduled for evaluation by two surgeons (a senior hand surgeon and an orthopedic specialist) within one to two weeks after referral. Both surgeons were present when a complete patient history was obtained, but only the orthopedic specialist performed the subsequent physical examination. Patients who fulfilled the eligibility criteria (Table 3) and who provided written informed consent were then enrolled in the study. After enrollment, participants underwent baseline evaluation. Nerve conduction testing was done as soon as feasible, but no later than two weeks after enrollment. Only one hand was included in the trial (where bilateral symptoms were present, the hand with the higher A-L score was included). Each participant was only permitted enrollment once.

Table 3. Patient eligibility criteria.

Inclusion criteria
Primary, idiopathic CTS
Age 25–65 years, either sex
Symptoms of classic or probable CTS according to the criteria in the Katz hand diagram[144]
Two surgeons (specialists in orthopedic or hand surgery) independently diagnose the patient's CTS
Symptom duration of at least 1 month
Exclusion criteria
CTS classified as severe (thenar muscle atrophy or 2-PD exceeding 8mm in at least one finger)
Treatment of the study hand with a wrist splint in the past 12 months
Previous steroid injection for CTS in the study hand
Inflammatory joint disease
Vibration-induced neuropathy
Polyneuropathy
Current pregnancy
Trauma to the study hand in the past 12 months
Previous CTS surgery in the study hand
Inability to complete questionnaires because of language difficulties or cognitive disorder
Severe medical illness
Known abuse of drugs or alcohol or both

Randomization

Patients were randomly allocated according to a computer-generated randomization list (1:1 ratio).[145] The randomization was stratified by patient sex and conducted in random blocks of varying sizes (4, 6, and 8). An administrative assistant not involved in the trial created sequentially numbered, opaque, sealed envelopes holding the group allocation. Immediately after the baseline evaluation by the orthopedic surgeon was concluded, the patient was received by the hand therapist, who opened the envelope with the lowest number and supplied the patient with either a wrist splint with a metal bar or a soft bandage according to treatment allocation.

Blinding of patients, and the hand therapist providing the wrist splint/soft bandage, to type of treatment was not possible. However, all other involved medical personnel and assessors were blinded to the treatment allocation.

Interventions

Group A: Splint with metal bar

The patients were provided with a conventional splint (model Base, Catell AB, Hägersten, Sweden) with the wrist in neutral position to be worn at night and, if feasible, throughout the day. If the patient reported significant improvement after six weeks, no additional treatment was offered. If the patient reported minimal or no improvement, the same splint was used for a further four weeks. If the patient

reported minimal or no improvement after 10 weeks of splinting, surgery was offered. Surgery was not conducted until twelve weeks had passed since the commencement of therapy.

Group B: Soft bandage

The patients were provided with a neoprene wrist bandage to be worn at night and, if feasible, throughout the day. If the patient reported significant improvement after six weeks, no additional treatment was offered. If the patient reported minimal or no improvement surgery was offered. Surgery was not conducted until twelve weeks had passed since the commencement of therapy.

Outcome measures

At baseline, 6, 12, 24, and 52 weeks following therapy initiation, patients completed a questionnaire containing disease-specific and generic PROMs. At 52 weeks, patients underwent a physical examination and a nerve conduction test. If the date of subsequent surgery would occur more than two weeks before or more than two weeks after the scheduled follow-up dates, participants undergoing surgery were requested to complete the questionnaire prior to surgery. The questionnaires and case report forms (CRFs) are stored in the department's databases accessed only by the trial researchers.

Patient-reported outcome measures

The questionnaires contained the A-L 6-item CTS symptoms scale and the QuickDASH, both previously described (see page 38). The questionnaires also contained the EuroQol 5-dimensions (EQ-5D), which is a frequently applied measure of overall health and quality of life.[146] The questionnaires further included the palmar pain scale, which is a 2-item scale that measures severity of pain in the proximal palm and related activity impairments; a higher score (0 to100) implies more pain and activity limitations.[147] Finally, on a visual analog scale (VAS) ranging from 0 to 100, patients were asked to assess their satisfaction with their hand status in terms of symptoms and ability to use it for everyday tasks (a higher score implies a greater level of satisfaction).

Physical examination

The physical examination included measurement of 2-PD (on the radial and ulnar sides of each digit) using the Dellon-McKinnon Disk-Criminator, and measurements of grip and pinch strength using the Jamar dynamometer and pinch gauge, respectively.

Nerve conduction tests

The nerve conduction tests were performed by a qualified research nurse and analyzed by a neurophysiologist. The measurements included median nerve distal motor latency and wrist-digit distal sensory latency in the index finger (median nerve), ring finger (median and ulnar nerves), and small finger (ulnar nerve). In line with conventional neurophysiological criteria,[148,149] the results were categorized as normal, mild, moderate, or severe median neuropathy.

Measurement of actual splint and bandage use

Both the rigid splint and the soft bandage were equipped with a temperature-monitoring device that measures temperature differences depending on whether it is in touch with the skin. The Thermochron® iButton® gadget (Maxim Integrated, San Jose, CA, USA) is a small disk that records the temperature at predetermined intervals and saves the data in a memory. This type of temperature sensor is routinely used to monitor the cold chain in the food industry, as well as for pharmaceutical and medical items; a comparable device has previously been used in clinical research.[150,151] The recording intervals in this trial were set at 40 minutes.

Surgery

The patients were allowed to decide whether to undergo surgery based on the severity of symptoms and activity limitations, in consultation with an orthopedic surgeon who was not engaged in the trial and was blinded to the patient's group assignment. All surgeries were conducted by orthopedic or hand surgery specialists who were not engaged in the trial.

Assessments of efficacy

The primary and secondary endpoints of this study are shown below (Table 4).

Table 4. Trial endpoints.

Primary endpoints
Change in the A-L 6-item CTS symptoms scale score from baseline to 12 weeks
Rate of surgery at 52 weeks
Secondary endpoints
Change in the A-L 6-item CTS symptoms scale score from baseline to 6 weeks and 52 weeks
Change in QuickDASH score from baseline to 12 weeks and 52 weeks
Change in patient satisfaction score at 12 weeks and 52 weeks
Change in EQ-5D index from baseline to 12 weeks and 52 weeks
Cost-effectiveness at 52 weeks
Palmar pain score at 52 weeks
Time to surgery within 52 weeks
Duration of sick leave during 52 weeks
Change in grip strength from baseline to 52 weeks
Adverse events at 52 weeks

Sample size

In a previous study, patients with idiopathic CTS improved by an average of 1.6 points on the A-L scale 12 weeks following surgery.[147] There is no previous data regarding change in A-L score after the use of wrist splint or soft bandage. A score improvement of 0.7 corresponds to improvement by one severity level in four of the six items (i.e., from very severe to severe, severe to moderate, moderate to mild, or mild to no symptoms, in more than half of the items). If the soft bandage is assumed to have no effect, it would be equivalent to "no treatment". A previous study showed that the mean change in A-L score for a group of patients who completed the A-L scale on two occasions separated by 1–3 weeks without treatment was 0.03 (95% CI 0.07-0.12).[124] With 90% power, 5% significance level, two-tailed tests, and mean changes (baseline to 12 weeks) in the A-L score of 0.7 in the splint group (SD 0.9) and 0.1 in the soft-bandage group, 48 patients are required per group. In order to account for potential dropouts, the intention was to recruit 112 patients.

However, it was decided to continue patient recruitment for an additional nine months after patient number 112 had been included. Patient 113 and onwards were followed-up for 12 weeks (according to the trial's first primary outcome measure), but they were not asked to attend physical examination at 52 weeks. The purpose of this additional recruitment was to compensate for the possible impact of the pandemic on treatment adherence and surgery, as well as to enhance the precision of the trial's primary outcomes. Compliance influences the first primary outcome measure of the study (change in the A-L score from baseline to 12 weeks). In addition, the pandemic has likely affected the study's second primary outcome measure (rate of surgery at 52 weeks), as access to elective surgery has been severely limited.

Statistical analysis

Primary analyses

The change in A-L score from baseline to 12 weeks will be compared between the two groups using a mixed model analysis of repeated measurements with baseline score adjustment.

The rate of surgery at 52 weeks will be compared using Cox regression with fixed follow-up time and the Huber–White estimator[152,153] while adjusting for age, study hand dominance, and baseline A-L score; relative risks with 95% CIs will be estimated. The Chi-square test will also be conducted as a supporting analysis.

Secondary analyses

The mean changes in the QuickDASH score, EQ-5D index, and grip strength will be compared over time (from baseline to 52 weeks) using a mixed model analysis

of repeated measurements while controlling for baseline values for each variable. The *t* test will be used to compare the mean treatment satisfaction and palmar pain scores at 12 and 52 weeks between the groups. Using Satterthwaite's *t* test, the mean total duration of sick absence from the start of therapy to 52 weeks will be analyzed. Time to surgery will be evaluated using Kaplan–Meier curves and the log-rank test to compare the groups. The incremental cost-effectiveness ratio will be used to assess cost-effectiveness. Three subgroup analyses will be conducted: baseline A-L score (≥3.0 vs. <3.0), baseline nerve conduction findings (severe/moderate vs. mild/normal), and duration of symptoms (≥6 vs. <6 months). All adverse events recorded during the trial will be compared in the two groups. In all statistical tests a p-value <0.05 will be used as significance level.

Ethics

All studies were conducted in accordance with the Declaration of Helsinki.

Paper I

The study was approved by the Regional Ethical Review Board of Lund University, Sweden (Dnr 2010/139 and 2011/96).

Paper II

The study received approval from the Regional Ethical Review Board of Lund University, Sweden (Dnr 2011/432). The Ethical Review Board waived the need for informed consent. As advised by the Ethical Review Board, the population in the Skåne region was notified of the study by newspaper advertisements and given the choice to "opt-out". This is a common procedure for population-based studies employing register data.

Paper III

The studies that generated the data were approved by the Regional Ethical Review Board of Lund University, Sweden (Dnr 2008/119, 2013/307 and 2015/906).

Paper IV

The trial was approved by the Regional Ethical Review Board of Lund University, Sweden (Dnr 2018/16 and 2021-00656). All participants provided written informed consent.

Results

The following is a summary of the findings of each paper, for more in-depth look at the results, see each individual publication.

Paper I

Incidence of referred CTS

During 2001 to 2009, the mean incidence (95% CI) of first-time CTS was 232 (230–233) per 100,000 person-years in women and 104 (103–105) in men. The incidence of first-time CTS diagnoses increased with time; the mean increase (95% CI) per year was 1.8% (1.5–2.1, p<0.01) in women and 3.9% (3.5–4.4, p<0.01) in men (Figure 4). Compared to the referent age-group (≥85 years), the IRR for first-time CTS in women varied from 0.05 to 1.74 and in men from 0.04 to 1.97 (Appendix 1A).

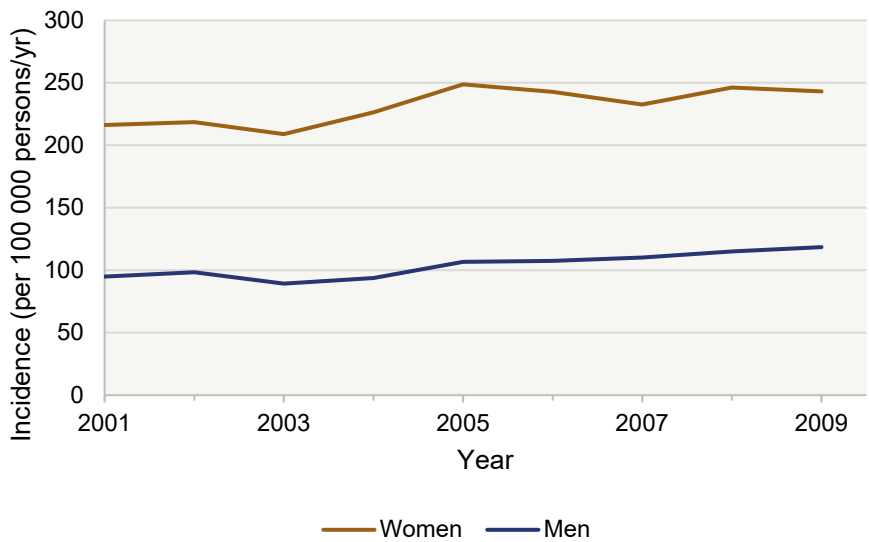

Figure 4. Incidence of CTS per 100 000 persons per year from 2001–2009.

During the three-year period from 2007 to 2009, the crude regional incidence of CTS diagnosis varied from 199 to 324 per 100,000 person-years in women and from 85 to 187 per 100,000 person-years in men, with significant regional variations in the age-standardized incidence (Figure 5). In comparison to the referent county (Stockholm), the age-standardized incidence rates of CTS diagnosis in the other counties were higher by 7-63% (mean 37%) in women and 18-126% (mean 59%) in men (Appendix 1B).

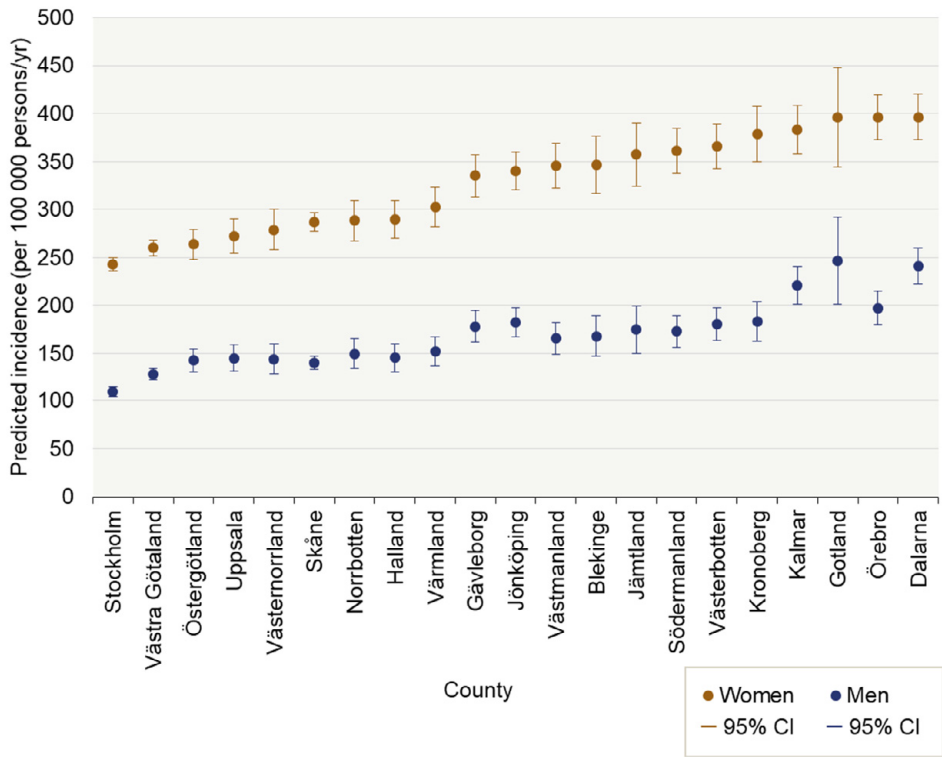

Figure 5. Regional variation in the age-standardized incidence of first-time CTS diagnosed at secondary or tertiary level 2007–2009.

Incidence of first-time CTR surgery

Of the 108,699 patients diagnosed with CTS, 70,120 (65%) had CTR surgery, with 49,440 (65%) being women and 20,680 (63%) men. The incidence (95% CI) of first-time CTR surgery was 151 (150–152) per 100,000 person-years in women and 65 (64–66) in men. The incidence of CTR surgery increased with time in both women and men, with a mean increase of 5.1% (4.7–5.4, $p<0.01$) per year for women and 6.2% (5.6–6.7, $p<0.01$) per year for men (Figure 6). Compared to the referent age-group (≥85 years), the IRR for CTR surgery was between 0.03 and 1.74 for women and between 0.02 and 2.02 for men (Appendix 1A).

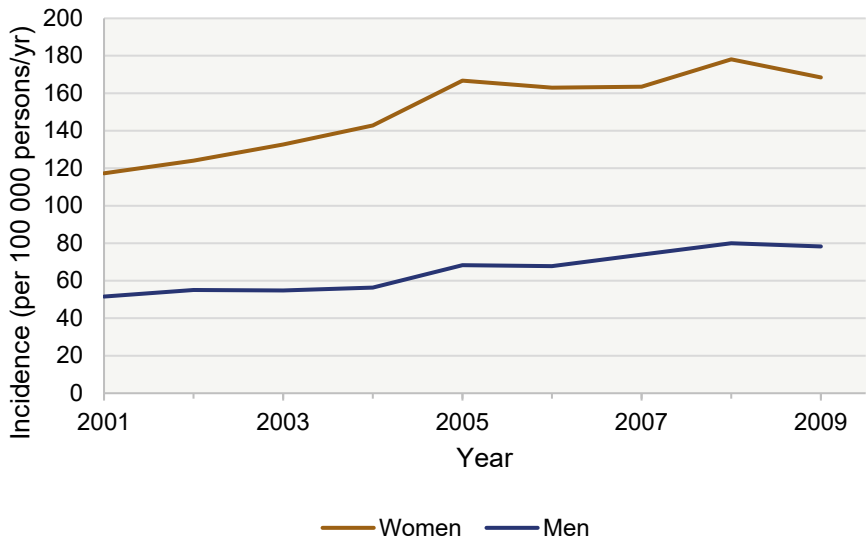

Figure 6. Incidence of CTR surgery per 100 000 persons per year from 2001–2009.

During the three-year period from 2007 to 2009, the crude regional incidence of first-time CTR surgery varied from 126 to 316 per 100,000 person-years in women and from 52 to 142 per 100,000 person-years in men, with significant regional variations in the age-standardized incidence (Figure 7). In comparison to the referent county (Stockholm), the age-standardized incidence rates of first-time CTR surgery in the other counties were 6–152% (mean 60%) and 20– 182% (mean 85%) higher in women and men, respectively (Appendix 1B).

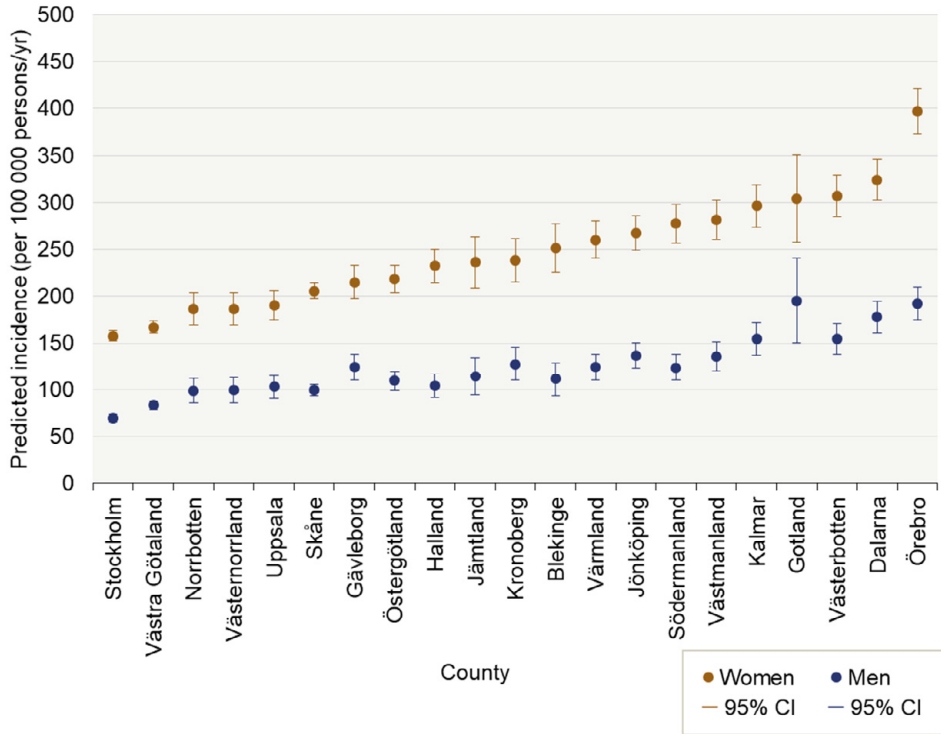

Figure 7. Regional variation in the age-standardized incidence of first-time CTR surgery 2007–2009.

Proportion treated with surgery

The proportion of individuals with CTS who had CTR surgery varied across counties from 53% to 81% in women (<60% in 3 counties, 60–70% in 11 counties, and >70% in 7 counties) and from 51% to 77% in men (<60% in 5 counties, 60–70% in 15 counties, and >70% in 1 county) (Figure 8).

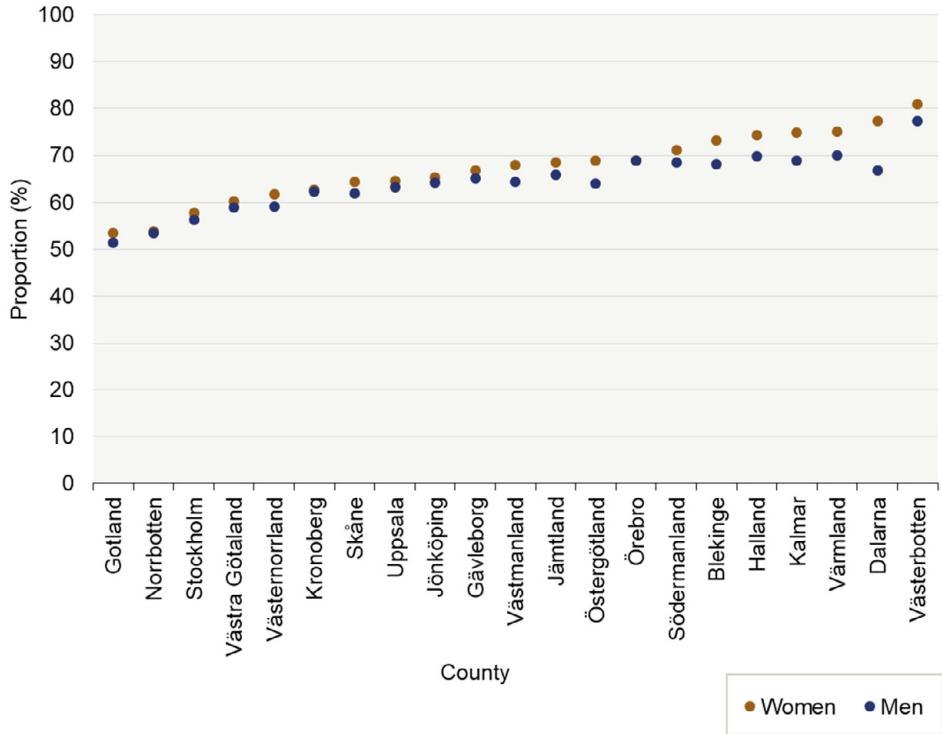

Figure 8. Regional variation in the proportion of CTR surgery per CTS diagnoses 2001-2009.

Paper II

Study cohorts

The study population has been previously described.[154] During the five calendar years (2004–2008), 7108 subjects, aged 17 to 57 years and residents of the Skåne region for three years preceding the diagnosis, received a primary physician-made diagnosis of CTS. Of these, 1641 persons were excluded because they had received a CTS diagnosis in the three years prior to the date of their initial diagnosis in the study period, and 11 individuals were excluded because no matched referents could be identified. The final cohorts consisted of 5456 individuals with CTS and 21,667 referents without a CTS diagnosis from the general population. The mean age of the CTS and general population cohorts was 43 years, and 73% were women (Table 5). CTS was most common among those aged 45 to 57 (47% of women and 50% of men).

Table 5. Characteristics in the CTS cohort and the matched reference cohort without CTS.

	Women		Men	
	CTS (n = 3966) n (%)	Referents (n = 15,756) n (%)	CTS (n = 1490) n (%)	Referents (n = 5911) n (%)
Age group				
17–34	857 (21.6)	3381 (21.5)	308 (20.7)	1215 (20.6)
35–44	1250 (31.5)	4978 (31.6)	436 (29.2)	1728 (29.2)
45–57	1859 (46.9)	7397 (46.9)	746 (50.1)	2968 (50.2)
Type of work				
Blue-collar	2045 (51.6)	6351 (40.3)	968 (65.0)	2729 (46.2)
White-collar	1336 (33.7)	7006 (44.5)	317 (21.3)	2192 (37.1)
Unknown*	585 (14.8)	2399 (15.2)	205 (13.8)	990 (16.7)
Occupational group				
Light manual work	1399 (35.3)	7024 (44.6)	297 (19.9)	2005 (33.9)
Light-moderate manual work	1277 (32.2)	4378 (27.8)	115 (7.7)	581 (9.8)
Moderate manual work	482 (12.2)	1290 (8.2)	163 (10.9)	514 (8.7)
Heavy manual work	223 (5.6)	665 (4.2)	710 (47.7)	1821 (30.8)
Unknown*	585 (14.8)	2399 (15.2)	205 (13.8)	990 (16.7)
Level of education				
Low	754 (19.0)	2329 (14.8)	406 (27.2)	1169 (19.8)
Intermediate	2193 (55.3)	7767 (49.3)	856 (57.4)	3092 (52.3)
High	988 (24.9)	5542 (34.5)	216 (14.5)	1568 (26.5)
Unknown	31 (0.8)	218 (1.4)	12 (0.8)	82 (1.4)

*Includes true missing as well as unemployed, students, disability pensions, early retirements, entrepreneurs and project employments.

CTS and type of work

Among the women with CTS 52% were blue-collar workers and 34% were white-collar workers, compared to 40% and 44% in the general population ($p<0.001$). Among men with CTS, 65% were blue-collar workers and 21% were white-collar workers, compared to 46% and 37%, respectively, in the general population ($p<0.001$).

Among the women with CTS 35% had light manual work, 32% had light-moderate manual work, 12% had moderate manual work and 6% had heavy manual work, compared to 45%, 28%, 8% and 4% respectively, in the general population ($p<0.001$). Among the men with CTS 20% had light work, 8% had light-moderate work, 11% had moderate work and 48% had heavy manual work, compared to 34%, 10%, 9% and 31% respectively, in the general population ($p<0.001$).

Compared to white-collar workers, blue-collar workers had an OR for CTS of 1.67 (95% CI 1.54–1.81) Compared to light work, the OR for CTS was 1.37 (95% CI 1.26–1.50) for light-moderate work, 1.70 (95% CI 1.51–1.91) for moderate work, and 1.96 (95% CI 1.75–2.20) for heavy manual work (Table 6).

Table 6. Association between level of education and type of work and CTS.

Model	Odds ratio (95% CI)*
Level of education**	
Low	Referent
Intermediate	0.82 (0.76–0.89)
High	0.48 (0.44–0.53)
Type of work***	
White-collar	Referent
Blue-collar	1.67 (1.54–1.81)
Occupational group****	
Light manual work	Referent
Light-moderate manual work	1.37 (1.26–1.50)
Moderate manual work	1.70 (1.51–1.91)
Heavy manual work	1.96 (1.75–2.20)

* ORs with 95% CIs from conditional logistic regression models; age and sex did not vary within matched sets and thus adjusted for by design and use of conditional regression.
** Estimating the effect of education (model does not include type of work or occupational group).
*** Estimating the effect of type of work (white-collar/blue-collar) adjusted for education (model does not include occupational group variable).
**** Estimating the effect of occupational group (light/light-moderate/moderate/heavy) adjusted for education (model does not include type of work variable).

CTS and level of education

Among the women with CTS 19% had a low level of education, 55% had an intermediate level, and 25% had a high level of education, compared to 15%, 49%, and 35%, respectively, in the general population ($p<0.001$). Among men with CTS 27% had a low level of education, 57% had an intermediate level, and 15% had a high level of education, compared to 20%, 52%, and 27%, respectively, in the general population ($p<0.001$).

Compared to persons with low-level education, the OR for CTS was 0.82 (95% CI 0.76–0.89) among those with intermediate-level education and 0.48 (95% CI 0.44–0.53) among those with high-level education (Table 6).

Paper III

Conventional scoring

In all of the three cohorts, the average A-L score was somewhat (0.1 to 0.2 score units) lower than the average Boston score (Table 7). The percentage mean difference (with Boston as the reference) was -9.8% at the short-term, -5.1% at the mid-term and -6.1% at the long-term follow-up. The multivariate multiple linear regression analysis of change scores among patients with both preoperative and short-term postoperative scores found that age, sex, and time since surgery were not

confounding variables in the difference of the change (preoperative to postoperative) scores between the Boston and A-L scales.

Table 7. Scale scores (conventional scoring).

Scale	Preoperative mean (SD)	Short-term post-operative mean (SD)	Mid-term post-operative mean (SD)	Long-term post-operative mean (SD)
Boston	3.12 (0.76)	1.69 (0.75)	1.56 (0.66)	1.41 (0.65)
A-L	3.06 (0.84)	1.51 (0.72)	1.47 (0.66)	1.30 (0.55)
Score difference	−0.06 (0.40)	−0.19 (0.36)	−0.09 (0.28)	−0.11 (0.23)

Boston and A-L scale scores range from 1 (no symptoms) to 5 (most severe symptoms).

Score agreement

Lin's CCCs were high, ranging from 0.81 to 0.91. In all cohorts, the Passing-Bablok regression analysis showed a statistically significant constant and proportional disagreement, except for Cohort 1's preoperative-to-postoperative change, where it showed constant agreement but proportional disagreement.

IRT

All infit and outfit values for average item locations in the Boston and A-L scales were within the 0.75–1.33 range, suggesting acceptable fit. All QuickDASH items demonstrated acceptable fit, with values between 0.98 and 1.05. Using IRT-based scoring, the mean Boston score was −0.12 (SD 1.02) preoperatively and −1.68 (SD 0.94) postoperatively, whereas the mean A-L score was −0.03 (SD 1.02) preoperatively and −2.33 (SD 1.24) postoperatively.

Reliability

The Cronbach alpha estimates were high for all scales. The preoperative and postoperative alpha were 0.88 and 0.93 for the Boston scale, 0.89 and 0.91 for the A-L scale, and 0.91 and 0.94 for the QuickDASH.

Responsiveness

With both conventional and IRT-based scoring, Cohen's d was high for all scales (>1.3 for CTS scales and >0.9 for QuickDASH) (Table 8). With both conventional and IRT-based scoring, the A-L scale had larger overall and sex-specific d values than the Boston scale; the A-L scale's larger IRT-based d values were statistically significant ($p<0.001$).

Table 8. Overall and sex-specific responsiveness of the scales.

Scale	Conventional scoring			IRT scoring		
	Preoperative mean (SD)	Postoperative mean (SD)	d (95% CI)	Preoperative mean (SD)	Postoperative mean (SD)	d (95% CI)
All hands (n = 235)						
Boston	3.03 (0.72)	1.68 (0.73)	1.86 (1.64–2.08)	−0.12 (1.02)	−1.68 (0.94)	1.59 (1.38–1.80)
A-L	2.98 (0.82)	1.47 (0.68)	2.00 (1.77–2.21)	−0.03 (1.02)	−2.33 (1.24)	2.02 (1.79–2.24)**
QuickDASH*	44 (22)	18 (19)	1.25 (1.04–1.45)	−0.15 (1.24)	−1.82 (1.55)	1.19 (1.00–1.39)
Women (n = 141)						
Boston	3.05 (0.71)	1.59 (0.65)	2.14 (1.84–2.43)	−0.10 (1.01)	−1.76 (0.86)	1.77 (1.49–2.04)
A-L	3.01 (0.81)	1.40 (0.62)	2.22 (1.93–2.52)	−0.01 (1.03)	−2.46 (1.17)	2.22 (1.92–2.52)**
QuickDASH*	47 (22)	17 (19)	1.47 (1.19–1.74)	0.05 (1.21)	−1.78 (1.49)	1.35 (1.09–1.61)
Men (n = 94)						
Boston	3.0 (0.74)	1.82 (0.81)	1.52 (1.20–1.85)	−0.15 (1.04)	−1.55 (1.03)	1.36 (1.04–1.67)
A-L	2.94 (0.84)	1.58 (0.76)	1.70 (1.37–2.04)	−0.06 (1.01)	−2.12 (1.33)	1.74 (1.41–2.08)**
QuickDASH*	39 (21)	19 (20)	0.95 (0.65–1.26)	−0.44 (1.24)	−1.89 (1.64)	0.99 (0.69–1.30)

Boston and A-L scale scores range from 1 (no symptoms) to 5 (most severe) and the QuickDASH from 0 (no disability) to 100 (most severe).
Cohen's d values shown as absolute values.
* No conventional QuickDASH scores because of ≥2 missing items in 11 women hands (5 preoperative and 6 postoperative) and 3 men hands (2 preoperative and 1 postoperative); 4 hands (3 women and 1 man) with ≥5 missing QuickDASH items were not included in the IRT analyses.
** p<0.001 (A-L vs. Boston).

Paper IV

Baseline characteristics

Patient recruitment started June 4th, 2018 and ended December 21st, 2021. Data collection will be concluded by the end of 2022. A total of 142 patients (90 women (63%) and 52 men (37%)) were enrolled (Figure 9). The average age of women was 46 years (SD 11), while the average age of men was 45 years (SD 11). The average BMI was 27.8 (SD 5.5) for women and 31.3 (SD 5.1) for men. The median duration of symptoms at time of enrollment was 1 year [Interquartile Range (IQR) 0.5-5.0] for women and 1.5 years [IQR 0.4-3.9] for men. In 70% of women and 63% of men, the study hand was their dominant hand. Moreover, 69% of women and 67% of men had bilateral symptoms of CTS. Baseline characteristics of the trial participants are further described in Table 9.

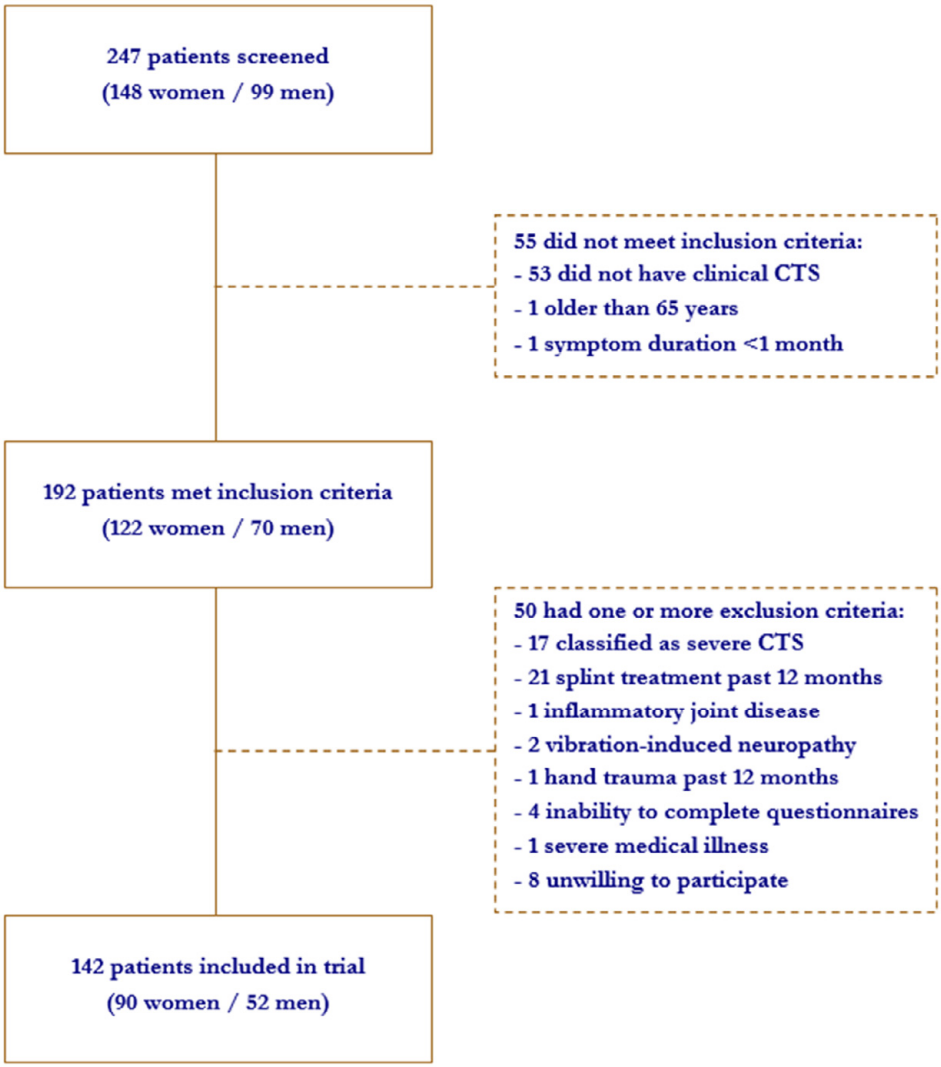

Figure 9. Flowchart showing the patient enrollment process in the RCT.

Table 9. Baseline characteristics of trial participants in the RCT.

Characteristic, *n* (%)	Women n = 90	Men n = 52
Age group		
25-34	19 (21.1)	11 (21.2)
35-44	16 (17.8)	12 (23.1)
45-54	30 (33.3)	19 (36.5)
55-65	25 (27.8)	10 (19.2)
BMI		
< 25	29 (32.2)	6 (11.5)
≥ 25 and < 30	36 (40.0)	14 (26.9)
≥ 30 and < 40	23 (25.6)	30 (57.7)
≥ 40	2 (2.2)	2 (3.9)
Comorbidities		
Diabetes	6 (6.7)	4 (7.7)
Thyroid disease	7 (7.8)	1 (1.9)
Neck-shoulder problems	24 (26.7)	12 (23.1)
Duration of symptoms		
< 6 months	20 (22.2)	14 (26.9)
≥ 6 months and < 2 years	37 (41.1)	15 (28.8)
≥ 2 years	33 (36.7)	23 (44.2)
Presence of typical CTS symptoms		
Tingling	79 (87.8)	49 (94.2)
Numbness	90 (100)	51 (98.1)
Nighttime symptoms	76 (84.4)	37 (71.2)
Combination of all 3 above listed symptoms	67 (74.4)	34 (65.4)
Involved digits		
Symptoms in all 3 radial digits only	21 (23.3)	12 (23.1)
Symptoms involving 5th digit	46 (51.1)	22 (42.3)
Other symptom pattern*	23 (25.6)	18 (34.6)
Provocative tests		
Positive Tinel's sign	45 (50.0)	25 (48.1)
Positive Phalen's test	78 (86.7)	38 (73.1)
Missing	1 (1.1)	0 (0.0)
Combination of both positive Tinel and Phalen	45 (50.0)	22 (42.3)
Nerve conduction tests**		
Normal	11 (12.2)	1 (1.9)
Mild CTS	22 (24.4)	12 (23.1)
Moderate CTS	52 (57.8)	30 (57.7)
Severe CTS	4 (4.4)	6 (11.5)
Missing***	1 (1.1)	3 (5.8)

* But still classic or probable CTS according to Katz hand diagram.
** 1 patient (woman) had test results decribed as "mild-moderate CTS", while 2 patients (1 woman and 1 man) had test results decribed as "moderate-severe CTS". These patients were categorized in the more severe group (moderate and severe CTS respectively).
*** 3 patients (1 woman and 2 men) were offered several appointments for nerve conduction testing but did not attend, and 1 patient (man) had test results described as ”unreliable”.

Discussion

Epidemiology of CTS and CTR surgery

Paper I demonstrates that CTS diagnosis and CTR surgery are common in the general population, more prevalent in women than in men, and increasing with age. Although it is generally recognized that CTS affects women more than men, the higher rate of diagnosis may also be influenced by whether more women than men seek health care. In contradiction to this speculation however, compared to CTR, the incidence of ulnar nerve decompression for cubital tunnel syndrome in Sweden between 2005 and 2019 was similar for men and women (Figure 10).[155]

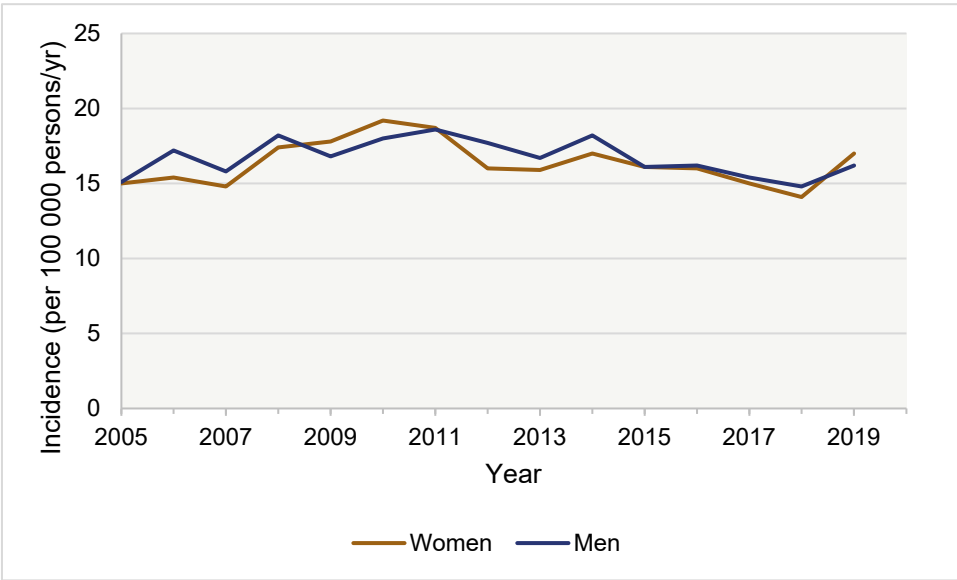

Figure 10. Incidence of cubital tunnel release surgery per 100 000 persons per year in the adult population (≥20 years) in Sweden 2005–2019.

Similar to the findings in *paper I*, previous research has generally demonstrated an upward trend in CTS incidence over time.[10,11,156] Possible explanations include the

increasing prevalence of risk factors, such as obesity and diabetes, in the general population of Sweden over time,[157,158] the general increase in average lifespan, improved public health resulting in better recognition of CTS by health care providers and patients, and increased use of nerve conduction tests resulting in an increase in CTS diagnoses.

Also similar to the findings in *paper I*, several studies have demonstrated an upward trend in the incidence of CTR surgery over time.[156,159] It seems logical that if the rate of CTS diagnosis grows, so too will the incidence of surgery. However, the percentage of CTS patients who had surgery has also increased over time. This trend may be due to the increasing evidence confirming the efficacy of CTR[9] and the durability of the benefit,[96] as well as greater access to surgery. *Paper I* shows that, on average, surgery has increased by 5–6% every year. Awareness of this increasing trend should have importance for clinical practice and for providers and planners of health care.

Paper I reveals large geographical disparities in the proportion of CTS patients treated surgically. The data imply that the diagnosis and management of CTS varies across regions in Sweden. In other countries, regional variations have also been observed. In 1993, a study from the United States revealed that the incidence of CTR surgery varied significantly by area, ranging from 82 to 287 per 100,000 persons.[18] An Italian study from 1997 to 2002, found CTR surgery rates ranging from 50 to 132 per 100,000 persons per year.[16] In Spain, one study from Catalonia reported CTR rates ranging from 76 to 172 between 1995 and 2000, whereas a study from Valencia reported rates ranging from 11 to 128 per 100,000 persons in 2006.[17] In a more recent nationwide study comprising 72,599 patients at 130 veteran health care facilities in the United States, the proportion of CTS patients who underwent CTR surgery ranged from 0% to 24%.[160] There was also wide facility-level variation in the usage of diagnostic and non-surgical treatment services for CTS, such as electrodiagnostic studies, steroid injection, splint treatment and physical/occupational therapy. Although these findings are in line with *paper I*, the methodology in *paper I* is unique in that it is based on data from a whole country over a three-year period (2007–2009). Occupation-related characteristics may influence regional variations in diagnosis and treatment. Nevertheless, based on the population characteristics of the counties, the observed substantial variations cannot be solely attributed to demographic or occupational variables. Access to specialist care and the competence to diagnose and treat may be important elements.

A prior population-based study from Skåne county in southern Sweden, shows an incidence of doctor-diagnosed CTS (including in primary care) per 100,000 person-years of 428 (95% CI 416–440) for women and 182 (95% CI 174–190) for men between 2006 and 2008.[161] In *paper I*, the incidence of referred CTS for Skåne county was 250 (95% CI 245–255) in women and 113 (95% CI 110–117) in men, which is lower since it excludes patients managed only in primary care. This indicates that around 60% of individuals diagnosed with CTS in primary care are referred for assessment by a specialist.

Occupation and risk of CTS

In both men and women, the findings in *paper II* suggest a significant association between physician-diagnosed CTS and occupation (greater risk in blue-collar versus white-collar work). These findings are consistent with existing research. In a regional Italian study, both female and male blue-collar workers had greater age-specific rates of surgically treated CTS than white-collar workers at all ages.[41] Blue-collar work is a risk factor for surgically-treated CTS in both women and men, according to a second Italian study.[56] Similarly, a recent study from the United States showed that the labor industry has a stronger association with work-related CTS than the clerical industry.[162]

Even after controlling for sex, age, and BMI, the prevalence of CTS among active blue-collar workers was significantly greater than that of white-collar workers in a large population-based study conducted in southern Sweden.[163] It is thought that the higher prevalence of CTS among blue-collar workers is due to the presence of specific occupational risk factors, such as forceful manual labor, extreme wrist postures, and the use of vibratory tools.[41] These hypotheses are consistent with the findings in *paper II* that a significant association exists between heavy manual labor and CTS in both women and men. The results in *paper II* suggest a dose–response relationship between increased manual load and CTS, with the heavy occupation group having nearly double the odds of CTS compared to the reference group.

The findings in *paper II* complement those of earlier research concerning the relationship between occupational load and CTS. A Finnish study showed that hand grip with high forces was associated with an increased prevalence of CTS (OR 1.7, 95% CI 1.2–2.5).[46] Although this was a population-based study, subjects were recruited via interviews (conducted by nurses) and clinical health assessments, whereas the study sample in *paper II* comprises of individuals who sought medical care for hand problems and were diagnosed with CTS by their treating physician. Two Danish population-based studies found that rapid wrist motions, defined as wrist angular velocity, and repetitive movements, measured as mean power frequency, were associated with an elevated risk of CTS (IRR 2.31 [95% CI 2.09–2.56] and 1.83 [1.68–1.98], respectively), and there was a positive correlation between hand load and incidence rates of CTS.[44,48] These studies only covered CTS cases diagnosed in hospitals, excluding any patients treated solely in primary care (and possibly in private practice by specialists). *Paper II* revealed similar results to these population-based studies that employed more accurate exposure measurements, with the added benefit that it included all clinically significant cases of CTS.

Education and risk of CTS

The findings in *paper II* also demonstrate a significant relationship between CTS and education level, where the risk of CTS decreases as education level increases, with the highest education level having less than half the odds of having CTS compared to the reference group. The relationship between CTS and education level has been the subject of very few prior studies. A Finnish study analyzed data from 6256 individuals aged ≥30 years who had undergone surgery for CTS and found that individuals with low education were more likely to undergo surgery for CTS than those with high education.[57] In a Brazilian study examining the characteristics of a retrospective hospital cohort of 150 patients with CTS, more than half had less than a high school education.[164]

Individuals with higher degree of education usually have professions that are less likely to require physically demanding manual labor, whereas those with lower levels of education are more likely to have manual labor.[165] The relationship between low socioeconomic status and poor health has been well-established.[166,167] In addition to the importance of education in defining career prospects (lower education is more common in professions with greater physical exposure), its link with CTS may also be mediated by other mechanisms, such as a higher BMI, a well-known and significant risk factor for CTS.[36,38,39,168,169]

Atroshi-Lyrén and Boston scale comparison

In patients with CTS in *paper III*, before and after surgery, the mean conventional scores on the A-L scale were consistently 0.1 to 0.2 score units lower than the Boston scale. However, this small difference is not deemed clinically significant. Consequently, in pre-post intervention study designs, it is anticipated that the mean change scores for both measures would be close to comparable.

The A-L scale has previously shown strong construct validity and reliability for evaluating symptom severity in CTS, both after surgery[124,128] and after steroid injection.[126] This also held true for the analysis in *paper III* (Cronbach alpha estimates 0.89–0.91). In a recent sample of patients referred for diagnostic workup for CTS with nerve conduction studies, the Norwegian version of the A-L scale demonstrated good measurement properties, as assessed by internal consistency, test–retest reliability and construct validity.[129] Similar results were confirmed for the Polish version of the A-L scale.[130] Another study, comparing the A-L and Boston scales using IRT (Rasch model) in patients with surgically treated CTS, indicated that the A-L scale had superior psychometric properties based on analysis of item thresholds and differential item functioning.[128]

Which of the two scales should be used to measure the severity of CTS-related symptoms if the scales are not equivalent? A scale may have good reliability and validity, but a poor responsiveness.[137] Hence, it would be preferable to utilize the scale that has shown greater responsiveness. *Paper III* demonstrates that the A-L scale was more responsive than the Boston scale; particularly when IRT-based scoring was used there was statistically significant difference in both overall and sex-specific responsiveness. Furthermore, it has been suggested that since the A-L scale is shorter, it is more practical for physicians to use than any other CTS-related questionnaire.[130] It has also been argued that, in a research setting, a short scale increases the chances of patient acceptance for inclusion, and improves patient response rates at follow-up.[170]

In *paper III*, the QuickDASH responded similarly to both conventional and IRT scoring, however showing lower responsiveness than both the A-L and Boston scales. Even while the QuickDASH demonstrated satisfactory item fit and reliability, i.e., the scale met some of the requirements for measuring an intended construct, it was not developed specifically to measure the severity of CTS symptoms. Previous research has also demonstrated that the A-L scale is more responsive than the QuickDASH, perhaps because the former is a disease-specific symptom measurement.[125]

A benefit of IRT-based scoring is that it can utilize data from patients with more missing responses than conventional scoring permits. Although, to calculate IRT-based scores, one must have access to a software application. Given the high responsiveness of the A-L with both scoring techniques, conventional scoring would be more applicable in clinical settings.

Treatment of CTS with wrist splinting

CTS is a widespread condition that affects millions of individuals worldwide.[161] Despite limited evidence, wrist splinting is currently the most frequent non-surgical therapy in the world, either alone or in combination with other therapies. Moreover, limited evidence exists regarding the required duration of treatment.

Based on the results in *paper III*, that the A-L scale is a more efficient measure than the Boston scale for assessing the severity of CTS symptoms, the A-L scale was selected in the RCT (*paper IV*) as the disease-specific PROM and one of the primary outcomes to evaluate the efficacy of wrist splinting. The A-L scale is also being utilized more frequently in other RCTs. For instance, an ongoing Dutch RCT comparing corticosteroid injection to surgery in patients with CTS uses the A-L scale to evaluate recovery at 18 months as a primary outcome measure.[170]

Using the Boston 11-item symptom severity scale, which is similar to the A-L 6-item CTS symptoms scale for measuring symptoms,[124] a few prior studies have assessed

wrist splinting in the treatment of CTS. A previous study that most closely resembled a placebo-controlled design compared two types of splints: a traditional rigid wrist splint (n = 46) and a soft splint (n = 45) that limits movement of the metacarpophalangeal joints but does not immobilize the wrist (however it is unclear whether full flexion was possible).[171] At baseline, the mean symptom severity score was 2.9 in both groups, and despite a slight to moderate improvement at 3 months, the results after 9 months indicated only a minor mean score change (0.4 and 0.3, respectively), a difference of questionable clinical significance. In a trial comparing steroid injection to nighttime wrist splinting for one month, the baseline mean symptom severity score of 2.0 in the splint group (n = 25) decreased by 0.38 after 8 months.[172] In a different trial comparing platelet-rich plasma injection to 6-month nighttime wrist splinting, the mean symptom severity scores in the splint group (n = 60) were 1.7 at baseline and 1.5 after 6 months.[173] In a randomized trial comparing electroacupuncture to 4-month nighttime wrist splinting, the mean symptom severity score in the splint group (n = 91) was 2.4 at baseline and had improved only by 0.09 after 4 months.[174] In another trial comparing ultrasound-guided pulsed radiofrequency to nighttime wrist splinting for 12 weeks, the mean symptom severity score in the splint group (n = 18) decreased from 3.0 at baseline to 2.0 after 12 weeks.[175] Consequently, although the studies evaluating wrist splinting alone have had contradictory outcomes, the majority have demonstrated minimal improvements in the symptom severity score, even with splinting for longer than what is often applied in clinical practice.

In a previous primary care multicenter study comparing wrist splinting with local steroid injection in CTS, the mean Boston symptom severity score of the wrist splint group improved by 0.48 at 6 weeks and 0.73 at 6 months compared to baseline.[176] The latter value (at 6 months) is comparable to the value regarded a clinically significant A-L score change in the sample size calculation in *paper IV*. In a 24-month follow-up of this study there was continued symptomatic improvement, and surgery rate was only 16% for patients in the wrist splint group,[177] which is substantially lower than those reported in studies based in secondary care.[178] However, the response rate was only 71% and in the presence of missing data it was assumed surgery did not occur, rendering the conclusions of the study questionable. Furthermore, the low proportion of patients undergoing surgery following initial conservative treatment is anticipated to vary between those treated in primary and secondary care for a number of reasons, including the fact that in primary care, patients are believed to present at an earlier stage of the disease.

A prior Dutch study concluded that surgery was more cost-effective than wrist splinting for the treatment of CTS.[87] Although it is well-established that CTR is an effective treatment for CTS with favorable long-term outcomes,[96] it does come with disadvantages, including surgery-related pain and hand weakness that can persist for many months.[98] Moreover, surgery is linked with both direct and indirect costs due to work absence following surgery.[154]

Strengths and Limitations

Paper I

One limitation is that, because the patient registry does not include primary care, the CTS incidence rates in the study apply only to referred cases diagnosed at the secondary and tertiary levels and does not include patients who are managed exclusively at primary care. However, the estimated incidence of CTR surgery in the study is representative of the incidence of the procedure in the general population, as the majority of all health care facilities that perform CTR surgery (both public hospitals and private practices) report to the registry. Another possible limitation is that the completeness and accuracy of reporting diagnosis and intervention codes may have influenced the regional variation observed in the study. With this consideration in mind, for the regional variation analysis, data from the final 3 years of the 9-year study period were used. Also, as CTR is a very common surgical procedure, it is expected to be properly registered.

Paper II

One limitation is that individuals with CTS were identified based on their health care attendance. It is possible that blue-collar workers with manually demanding professions are more likely to seek medical care for hand symptoms that impede their ability to work. Secondly, the period of employment was not reported, hence the duration of occupational exposure is uncertain. Nevertheless, past research indicates that even brief exposure times might be sufficient to cause work-related CTS.[38] Thirdly, the study did not employ direct measurements to estimate the degree of exposure for each type of job since it would have been challenging to do so in a study of the general population. The findings, however, are consistent with those of earlier research conducted on employees in specialized sectors and population-based studies that utilized direct exposure assessments. Lastly, the data did not allow for correction for any confounding factors.

The strengths of the study include a genuinely population-based design (all incident cases and randomly selected matched referents from an entire general population) and CTS of clinically significant severity (individuals who sought health care but not limited to surgically treated patients). In addition, the patients were diagnosed

with CTS by a medical doctor as part of standard health care at all levels of care, including primary care, where a considerable number of those seeking medical care for CTS are managed.

Paper III

The study is limited in that it only included patients whose symptoms necessitated surgical treatment. Consequently, the findings are applicable primarily to surgically treated patients. Furthermore, although standardized item questionnaires enable comparison of scores and responses between patients and conditions, these generalized questionnaires may not reflect individual changes in each patient, or necessarily what is the most essential items for each patient. However, in research, it is still necessary to be able to generalize findings on a group level, and with the conclusions that PROMs generate, the treating physician can still provide guidance regarding the expected outcomes of various treatments, thereby assisting the individual patient in making an informed decision regarding their treatment plan.

Paper IV

One possible limitation of this study could be the length of follow-up for the primary outcome, i.e. the rate of surgery at 52 weeks. Many patients may endure their symptoms for several years before opting to undergo surgery. Therefore, there is a possibility that these patients have not yet decided on surgery within the first year. Future evaluation of the wrist splint's long-term efficacy may require an even longer follow-up period. Additionally, the study is conducted in Sweden, thus the secondary outcome of cost-effectiveness might not be applicable to other countries.

The main strength of this study is its randomized placebo-controlled design. Another strength is that this study had stricter eligibility requirements than many prior clinical studies; for instance, two surgeons were involved in the screening process; if either surgeon determines that the patient's medical history does not clearly imply a CTS diagnosis, the patient will be excluded. This is essential since an inaccurate diagnosis affects the evaluation of the intervention's effectiveness. Further adding to the diagnostic accuracy in this study is that nerve conduction tests are performed on all patients enrolled in the trial. The baseline nerve conduction tests are a study strength and are crucial when reporting the outcomes of the trial since they indicate the disease severity features of the trial participants.

Conclusions

Paper I

The incidence of CTS diagnosis and CTR surgery in the general population of Sweden has increased over time among both women and men, with a yearly increase of 2-4% in diagnosis and 5-6% in surgery. Women are about twice as likely as men to present, however their rate of surgery is comparable, at roughly two-thirds. There are large regional variations in the incidence of CTS and CTR, as well as the proportion of CTS patients who undergo surgery.

Paper II

There is evidence of a dose-response relationship between both type of work and education level and the risk of CTS, with the risk increasing with higher occupational load and lower level of education.

Paper III

The A-L 6-item CTS symptoms scale and the Boston 11-item symptom severity scale show good agreement in measuring the severity of CTS-related symptoms. The A-L scale displayed greater responsiveness than the Boston scale when employing IRT-based scoring. As the more efficient measure, the A-L scale would be the preferred scale to use for assessing the severity of CTS symptoms.

Paper IV

This could be the first randomized, placebo-controlled trial to investigate the effectiveness of wrist splinting in patients with CTS and the first to employ an electronic monitoring device to record active splint usage time as a measure of compliance.

Future Perspectives

Awareness of the geographical differences in both diagnosis and surgery may prompt doctors to reevaluate how they manage patients with CTS and might eliminate or at least minimize unexplained variations in health care for this disorder and decrease waste in the health care system. Numerous expert groups in Sweden are currently developing national care programs for management of common diagnoses in the musculoskeletal system as well as in other medical fields.[179] Given that CTS is one of the most common diagnoses at orthopedic clinics, it would be ideal if this thesis could support the development of a national care program for CTS. The importance for clinicians to comprehend the extent of treatment variability for CTS, as well as the need to develop strategies to optimize health care for CTS patients, has also been recognized in other countries.[160]

Awareness of the association between type of work and level of education with increased risk of CTS may be useful for designing and implementing preventive measures at the workplace. Although CTS is a multifactorial disease and many previous studies have concluded that it is mainly associated with individual risk factors, extensive research conducted throughout the years has established a correlation between CTS and certain work tasks and occupations. Due to this expanding scientific evidence, insurance companies may soon need to be weighing in on the question of whether or not CTS should be considered a work injury.

Since the A-L scale has been demonstrated to be more efficient than the Boston scale, it would be intriguing to see whether this will lead to a wider predominance of the A-L scale in future research. In the RCT (*paper IV*), the A-L scale was chosen as the CTS-specific PROM.

The results of the RCT are anticipated to have significant implications for patients and society. If splint usage does not provide benefit in the long term and only delays the time until surgery, current treatment guidelines for CTS might need to be revised.

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Appendix

Appendix 1A. Comparison of incidence of first-time CTS and CTR surgery 2001-2009 among age groups.

	CTS				CTR			
Age group*	Women		Men		Women		Men	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
80-84	1.53	1.45 - 1.62	1.96	1.79 - 2.13	1.63	1.53 - 1.74	2.03	1.83 - 2.24
75-79	1.06	1.00 - 1.11	1.55	1.42 - 1.68	1.11	1.04 - 1.18	1.70	1.54 - 1.87
70-74	0.83	0.79 - 0.88	1.32	1.21 - 1.43	0.83	0.78 - 0.89	1.36	1.23 - 1.49
65-69	0.83	0.79 - 0.87	1.40	1.29 - 1.52	0.81	0.76 - 0.86	1.30	1.18 - 1.43
60-64	1.34	1.28 - 1.40	1.97	1.82 - 2.12	1.37	1.29 - 1.45	1.73	1.58 - 1.90
55-59	1.74	1.66 - 1.82	1.86	1.72 - 2.00	1.74	1.64 - 1.84	1.69	1.54 - 1.85
50-54	1.65	1.58 - 1.73	1.68	1.55 - 1.81	1.65	1.56 - 1.75	1.46	1.34 - 1.61
45-49	1.28	1.22 - 1.34	1.59	1.47 - 1.72	1.29	1.22 - 1.36	1.37	1.25 - 1.50
40-44	1.24	1.18 - 1.30	1.52	1.41 - 1.64	1.22	1.15 - 1.29	1.29	1.18 - 1.42
35-39	1.14	1.09 - 1.20	1.15	1.06 - 1.24	1.08	1.02 - 1.15	0.97	0.88 - 1.07
30-34	0.95	0.90 - 0.10	0.84	0.77 - 0.91	0.80	0.75 - 0.85	0.67	0.60 - 0.74
25-29	0.54	0.51 - 0.57	0.46	0.42 - 0.51	0.43	0.40 - 0.46	0.35	0.31 - 0.40
20-24	0.22	0.21 - 0.24	0.22	0.19 - 0.24	0.17	0.16 - 0.19	0.15	0.13 - 0.18
18-19	0.05	0.04 - 0.06	0.04	0.03 - 0.05	0.03	0.02 - 0.04	0.02	0.01 - 0.03

* 85+ was used as referent group.
For CTS $p<0.01$ for all comparisons, except for women in age group 30-34 and 75-79 ($p<0.05$); for CTR $p<0.01$ for all comparisons, except for women in age group 35-39 ($p<0.05$) and men in age group 35-39 (non-significant).

Appendix 1B. Comparison of incidence of first-time CTS and CTR surgery 2007-2009 among counties.

Region*	CTS				CTR			
	Women		Men		Women		Men	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Uppsala	1.12	1.04 - 1.20	1.33	1.20 - 1.47	1.21	1.11 - 1.32	1.48	1.30 - 1.69
Södermanland	1.49	1.39 - 1.59	1.59	1.43 - 1.76	1.76	1.62 - 1.91	1.79	1.57 - 2.04
Östergötland	1.09	1.02 - 1.16	1.31	1.19 - 1.44	1.39	1.29 - 1.49	1.58	1.41 - 1.76
Jönköping	1.40	1.31 - 1.49	1.67	1.52 - 1.83	1.70	1.57 - 1.83	1.98	1.76 - 2.21
Kronoberg	1.56	1.44 - 1.69	1.68	1.49 - 1.90	1.51	1.36 - 1.68	1.84	1.59 - 2.14
Kalmar	1.58	1.47 - 1.69	2.02	1.83 - 2.24	1.88	1.73 - 2.04	2.23	1.97 - 2.52
Gotland	1.63	1.42 - 1.86	2.26	1.87 - 2.73	1.93	1.65 - 2.25	2.82	2.22 - 3.57
Blekinge	1.43	1.30 - 1.56	1.54	1.35 - 1.76	1.60	1.43 - 1.78	1.61	1.35 - 1.90
Skåne	1.18	1.13 - 1.23	1.29	1.20 - 1.38	1.31	1.24 - 1.38	1.43	1.31 - 1.55
Halland	1.19	1.11 - 1.28	1.33	1.19 - 1.49	1.47	1.35 - 1.60	1.50	1.31 - 1.72
Västra Götaland	1.07	1.03 - 1.12	1.18	1.10 - 1.25	1.06	1.01 - 1.12	1.20	1.10 - 1.30
Värmland	1.25	1.16 - 1.34	1.40	1.25 - 1.56	1.65	1.52 - 1.79	1.79	1.58 - 2.03
Örebro	1.63	1.53 - 1.74	1.81	1.64 - 2.00	2.52	2.35 - 2.70	2.77	2.49 - 3.09
Västmanland	1.42	1.32 - 1.53	1.52	1.36 - 1.69	1.79	1.64 - 1.94	1.96	1.72 - 2.23
Dalarna	1.63	1.53 - 1.74	2.21	2.02 - 2.42	2.06	1.91 - 2.22	2.56	2.30 - 2.86
Gävleborg	1.38	1.29 - 1.48	1.63	1.47 - 1.81	1.36	1.25 - 1.49	1.79	1.58 - 2.04
Västernorrland	1.15	1.06 - 1.25	1.32	1.17 - 1.49	1.18	1.07 - 1.31	1.43	1.24 - 1.66
Jämtland	1.47	1.33 - 1.62	1.60	1.38 - 1.85	1.50	1.33 - 1.69	1.65	1.37 - 1.99
Västerbotten	1.50	1.40 - 1.61	1.65	1.49 - 1.83	1.95	1.80 - 2.11	2.23	1.98 - 2.52
Norrbotten	1.19	1.10 - 1.29	1.37	1.23 - 1.54	1.18	1.07 - 1.31	1.42	1.23 - 1.64

* Stockholm (county with lowest incidence) was used as referent group.
For CTS $p<0.01$ for all comparisons, except for women in Östergötland county ($p<0.05$); for CTR $p<0.01$ for all comparisons, except for women in Västra Götaland county ($p<0.05$).

Paper I

Article

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Incidence of referred carpal tunnel syndrome and carpal tunnel release surgery in the general population: Increase over time and regional variations

Kamelia Tadjerbashi[1,2], Anna Åkesson[3] and Isam Atroshi[1,2]

Abstract

Purpose: To investigate the change in incidence of referred carpal tunnel syndrome (CTS) and carpal tunnel release (CTR) surgery over time and regional variations. **Methods:** From the nationwide patient registry, we identified all adult individuals who had received first-time CTS diagnosis (International Classification of Diseases, 10th Revision code G560) at secondary or tertiary level and first-time CTR surgery during the period of 9 years. **Results:** From 2001 through 2009, the incidence (per 100,000 person-years) of CTS diagnosed at secondary or tertiary level increased from 216 to 243 in women and from 95 to 119 in men and of CTR from 117 to 168 in women and from 52 to 78 in men. The mean annual increase in first-time CTR (95% confidence interval) was 5.1% (4.7–5.4) in women and 6.2% (5.6–6.7) in men. The age-standardized 3-year (2007–2009) incidence varied significantly across Sweden's 21 counties; compared to the county with the lowest incidence of CTR, the incidence rates in the other counties were higher by 6–152% (mean 60%) in women and by 20–182% (mean 85%) in men. The proportion of CTS-diagnosed individuals treated with surgery varied across counties from 53% to 81% in women and from 51% to 77% in men. **Conclusion:** The incidence of referred CTS and of CTR surgery increased over time in both sexes, with large regional variations found in the incidence rates and in the proportion of individuals treated with surgery.

Keywords

carpal tunnel syndrome, epidemiology, incidence, regional variations

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Introduction

Carpal tunnel syndrome (CTS) is a common cause for patients to seek health care.[1] Reported risk factors for CTS are obesity, higher age, pregnancy, work activities demanding frequent use of force and of hand-held vibratory tools, and medical conditions, such as diabetes, rheumatoid disease, and thyroid disorders.[2] Although nonoperative treatments may be effective, many patients still need carpal tunnel release (CTR) surgery. There is strong evidence supporting that CTR is highly effective in relieving symptoms and improving function and quality of life[3] and that the benefit is durable.[4] Long-term efficacy of other

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treatments has not been established.[5,6] Despite the continuing research about various treatment methods in CTS, little is known about whether treatment trends have changed over time. For a common condition such as CTS, knowledge about whether and to what extent use of surgical treatment increases would be important for clinical practice and for health-care planners and providers.

Based on studies that have estimated incidence of CTS, there appears to be large differences between countries.[7–11] However, little data exist on regional variations in the incidence of CTS within counties. A few studies from North America and Europe have shown substantial within-country regional variations in the incidence of CTR.[12–15] However, these studies were limited to specific regions within a country rather than to a whole general population. Variations in the incidence of CTS and CTR between countries and between different regions could reflect true differences in incidence but may also reflect differences in the way doctors diagnose and treat patients with CTS. The aim of our study was to investigate the change in the nationwide sex- and age-specific incidence of referred CTS and of CTR surgery over time and regional variations.

Materials and methods

This is a retrospective population-based study. Data were retrieved from the patient registry managed by the Center for Epidemiology at the Swedish National Board for Health and Welfare. This nationwide registry covers all patient visits (outpatient and inpatient care) to a medical doctor at secondary- and tertiary-level health-care facilities (i.e. hospital or similar specialist health-care facility) and all medical interventions performed at these facilities. We identified all individuals aged ≥18 years who had consulted a medical doctor during a 9-year period (January 2001 through December 2009) and received the diagnosis CTS (International Classification of Diseases, 10th Revision (ICD-10) code G560). The registry does not specify how the diagnosis of CTS has been made by the physician (on clinical grounds only or in combination with nerve conduction tests). We also identified all individuals who had CTR surgery (received the code ACC51 according to the Swedish Classification of Healthcare Interventions) in conjunction with CTS diagnosis. Data collected included sex, age at the time of diagnosis or surgery, consultation dates, surgery dates, health-care facility, county of residence, type of visit (outpatient or inpatient), primary diagnosis and any other associated diagnoses (up to eight diagnoses were allowed), and surgical procedures and other interventions performed. Each individual was included in the analyses only once (first-time diagnosis and first-time surgery). The study was approved by the Regional Ethical Review Board.

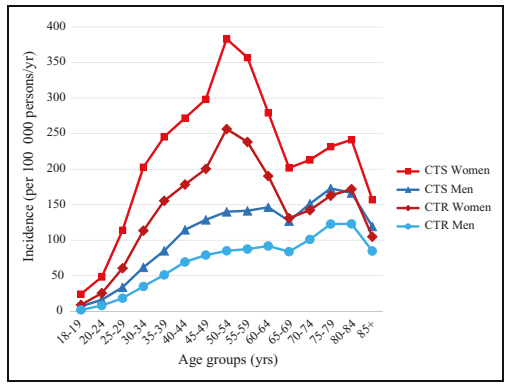

Figure 1. Sex-specific incidence of first-time carpal tunnel syndrome diagnosed at secondary or tertiary level and of first-time carpal tunnel release surgery 2001–2009.

Statistical analysis

We retrieved annual data on population statistics from Statistics Sweden.[16] For each study year, we used the population data on December 31 in the preceding year. We calculated the sex- and age-specific incidence rates of CTS and CTR surgery (overall rates and for the 21 counties) and 95% confidence intervals (CIs) using Poisson regression models. Analyses of incidence trends over time were performed. The at-risk population was standardized with weights from the 2013 European standard population. We used the county with the highest population as referent to obtain adequate number of individuals in all age-groups. For county comparisons, we used the incidence rates during the study's last 3 years (2007–2009) to reflect the most recent data and calculated age-adjusted incidence rate ratios (IRR) and 95% CIs. Statistical significance was defined as a p-value of <0.05. All analyses were performed with STATA (STATA SE 14.2, StataCorp, College Station, Texas, USA).

Results

Incidence of referred CTS

During the 9-year study period, 75,799 women and 32,900 men were diagnosed with CTS at a secondary- or tertiary-level health-care facility. The incidence (95% CI) of first-time CTS per 100,000 person-year was 232 (230–233) in women and 104 (103–105) in men. The incidence of first-time CTS diagnosis increased over time; the mean increase (95% CI) per year in women was 1.8% (1.5–2.1, $p < 0.01$) and in men was 3.9% (3.5–4.4, $p < 0.01$). The incidence peaked in ages 50–54 years in women and 75–79 years in men (Figure 1); this was consistent across the country. Compared to the referent age-group (≥85 years), the IRR

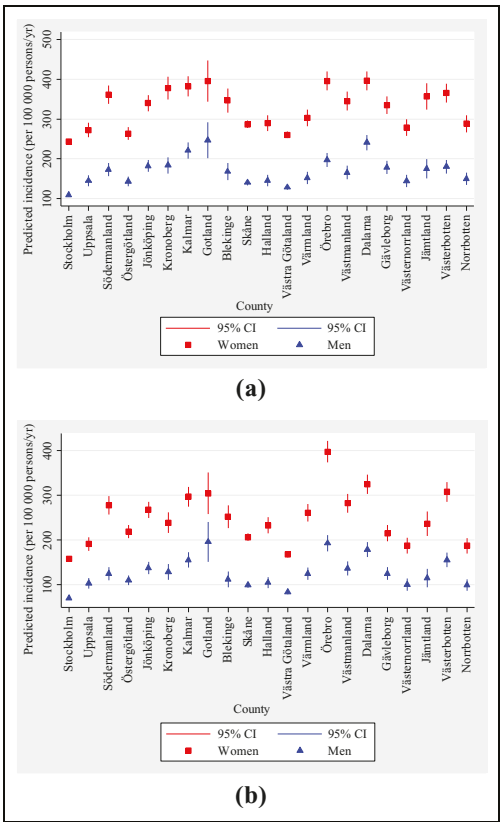

Figure 2. Regional variation in the age-standardized incidence of (a) first-time carpal tunnel syndrome diagnosed at secondary or tertiary level and (b) first-time carpal tunnel release surgery 2007–2009.

for first-time CTS ranged from 0.05 to 1.74 in women and from 0.04 to 1.97 in men (Supplementary Table S1).

The crude regional incidence of CTS diagnosis during the 3-year period 2007–2009 ranged from 199 to 324 per 100,000 person-year in women and from 85 to 187 per 100,000 person-year in men, with significant regional variations shown in the age-standardized incidence (Figure 2(a)). Compared to the referent county, the age-standardized incidence rates of CTS diagnosis in the other counties were higher by 7–63% (mean 37%) in women and by 18–126% (mean 59%) in men (Supplementary Table S2).

Incidence of first-time CTR surgery

Of the 108,699 individuals with CTS diagnosis, 70,120 (65%) had CTR surgery, of them 49,440 (65%) were women and 20,680 (63%) were men. The incidence (95% CI) of first-time CTR surgery per 100,000 person-year was 151 (150–152) in women and 65 (64–66) in men. The incidence of CTR surgery increased over time both in women and in men; the mean increase (95% CI) per year was 5.1% (4.7–5.4, $p < 0.01$) in women and 6.2% (5.6–6.7, $p < 0.01$) in men. The incidence of CTR surgery peaked in ages 50–54 years in women and 75–84 years in men (Figure 1); this was consistent across the country. Compared to the referent age-group (≥85 years), the IRR for CTR surgery ranged from 0.03 to 1.74 in women and from 0.02 to 2.03 in men (Supplementary Table S1).

The crude regional incidence of first-time CTR surgery during the 3-year period 2007–2009 ranged from 126 to 316 per 100,000 person-year in women and from 52 to 142 per 100,000 person-year in men, with significant regional variations shown in the age-standardized incidence (Figure 2(b)). Compared to the referent county (county with the lowest incidence), the age-standardized incidence rates of first-time CTR in the other counties were higher by 6–152% (mean 60%) in women and by 20– 182% (mean 85%) in men (Supplementary Table S2).

Proportion treated with surgery

The proportion of individuals with CTS who had CTR surgery was the lowest in the ages 18–29 years (women 52%, men 52%) and highest in the age ≥80 years (women 69%, men 73%). The proportion across counties ranged from 53% to 81% in women (<60% in 3 counties, 60–70% in 11 counties, and >70% in 7 counties) and from 51% to 77% in men (<60% in 5 counties, 60–70% in 15 counties, and >70% in 1 county).

Discussion

Our study shows that CTS diagnosis and CTR surgery are common in the general population, more common in women than in men, and increase with age. The incidence rates of CTS and of CTR surgery peak at ages 50–59 years in women, but in men they continue to increase with age, up to 85 years. However, the proportion of CTS-diagnosed persons treated surgically is similar in women and men in all age-groups. An interesting feature was the bimodal incidence of presentation and surgery present in both women and men with peaks at around 50–60 years and 75–84 years and a dip at 65–69 years (Figure 1). Although it is well established that CTS affects women more than it affects men the higher incidence of diagnosis may also be influenced by whether more women than men seek health care. However, data regarding ulnar nerve decompression for cubital tunnel syndrome in Sweden during 2005–2016 show that, unlike CTR, the incidence in men and women was similar (ranging from 15 to 18 per 100,000 adults per year).[17]

Similar to our results, other studies have generally shown a trend for increasing incidence of CTS over

time.[7,8,18] Possible explanations are higher prevalence of risk factors, such as obesity and diabetes, in the general population of Sweden over time,[19,20] general increase in the life span, improved public health leading to better recognition of CTS by medical professionals and patients, and increased use of nerve conduction tests leading to increased CTS diagnoses.

Also similar to our results, other studies have shown a trend for increasing incidence of CTR surgery over time.[18,21] In our study, the incidence of CTR surgery per 100,000 person-year was 151 in women and 65 in men. In a previous study that compared the incidence in Sweden and the United States during 1999–2008,[1] the annual incidence of CTR surgery per 100,000 persons (standardized to US population) in women was 166 in Sweden and 171 in the United States, and in men was 58 and 96, respectively. As the incidence of CTS diagnosis increases, it is also reasonable that the incidence of surgery increases. However, the proportion of individuals with CTS who had surgery has also increased over time. Reasons for this increase could be the increasing evidence supporting the effectiveness of CTR[3] and durability of the benefit[4] as well as possibly improved access to day surgery. Our study shows that surgery has on average increased by 5–6% annually. This should have implications for clinical practice and for health-care providers and planners.

Our study shows substantial regional variations in the proportion of persons diagnosed with CTS (at specialist health-care facilities) who are treated with surgery. The findings suggest differences in CTS diagnosis and treatment across different regions in Sweden. Regional variations have also been shown in other countries. A previous study from the United States has shown large regional variation in the incidence of surgery for CTS, ranging from 82 to 287 per 100,000 persons in 1993.[12] A study from Italy reported rates from 50 to 132 per 100,000 person-year from 1997 to 2002.[14] A study from Catalonia, Spain, reported CTR rates ranging from 76 to 172 between 1995 and 2000, while another study from Valencia reported rates from 11 to 128 per 100,000 persons in 2006.[15] To the best of our knowledge, our study is the first to be based on data from an entire country over a time period of 3 years (2007–2009). Regional variations in diagnosis and treatment may be influenced by occupational factors. However, based on the population characteristics in the counties, the large variations shown cannot be explained only by demographic or occupational factors. Access to specialist care and the ability to diagnose and treat may be important factors.

The CTS incidence rates in our study apply to referred CTS diagnosed at secondary and tertiary levels because the patient registry does not cover primary care. Little has been known previously about the incidence of CTS diagnosed beyond primary care (i.e. patients who had not responded to treatment or the diagnosis was uncertain at primary care and therefore referred to specialist care). In a previous population-based study in Skåne county in southern Sweden, the incidence (2006–2008) of doctor-diagnosed CTS (including in primary care) per 100,000 person-year was 428 (95% CI: 416–440) in women and 182 (95% CI: 174–190) in men.[1] Our results for Skåne county showed the incidence of referred CTS was 250 (95% CI: 245–255) in women and 113 (95% CI: 110–117) in men, which is lower because it did not include patients exclusively managed at primary care. This suggests that about 60% of patients who are diagnosed with CTS in primary care are referred for specialist evaluation.

The incidence of CTR surgery estimated in our study represents the incidence of the procedure in the general population because almost all health-care facilities where CTR surgery is performed report to the registry. It is possible that some procedures performed in small individual private practices may not have been registered, but the majority of surgical procedures in Sweden are performed in public hospitals. Also, a large proportion of surgeries performed in private practice are done in health-care facilities that report to the registry. A possible limitation of our study is that the regional variation could be influenced by the completeness and accuracy of reporting diagnosis and intervention codes. However, for analysis of regional variations, we used data from the last 3 years of the 9-year study and CTR, being a common surgical procedure, is expected to be well registered. The patient registry contains only the diagnosis of CTS with no details on how it was established. The diagnosis could have been made on clinical grounds only or also confirmed with nerve conduction tests, but for a nationwide registry-based study, it is not possible to access patients' individual medical records for further information.

Conclusion

Our study shows that during the years 2001–2009, the incidence of CTS diagnosis and of CTR surgery in the general population of Sweden increased over time among both women and men; the mean annual increase in CTS diagnosis was 2–4% and of surgery was 5–6%. Women are approximately twice as likely as men to present, but the rate of surgery is similar in women and men, at approximately two-thirds. It also shows substantial regional variations in the incidence of CTS and of CTR as well as in the proportion of CTS-diagnosed persons who receive surgical treatment. Awareness of these regional variations in both diagnosis and surgery would stimulate clinicians to consider how they manage patients with CTS and may reduce unexplained variation in health care for this condition.

Author contributions

Isam Atroshi contributed to conception and design of the study; Kamelia Tadjerbashi and Isam Atroshi contributed to data acquisition; Kamelia Tadjerbashi, Anna Åkesson and Isam Atroshi performed data analysis and data interpretation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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Paper II

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Association of clinically relevant carpal tunnel syndrome with type of work and level of education: a general-population study

Kamelia Möllestam[1,2]✉, Martin Englund[1] & Isam Atroshi[1,2]

Carpal tunnel syndrome (CTS) is a common cause of work disability. The association with occupational load and education level has not been established in general-population studies. The purpose of this study was to investigate the association of clinically relevant CTS with work and education. From the Healthcare Register of Skane region (population 1.2 million) in southern Sweden we identified all individuals, aged 17–57 years, with first-time physician-made CTS diagnosis during 2004–2008. For each case we randomly sampled 4 referents, without a CTS diagnosis, from the general population matched by sex, age, and residence. We retrieved data about work and education from the national database. The study comprised 5456 individuals (73% women) with CTS and 21,667 referents. We found a significant association between physician-diagnosed CTS and type of work and level of education in both women and men. Compared with white-collar workers, the odds ratio (OR) for CTS among blue-collar workers was 1.67 (95% CI 1.54–1.81) and compared with light work, OR in light-moderate work was 1.37 (1.26–1.50), moderate work 1.70 (1.51–1.91), and heavy manual labor 1.96 (1.75–2.20). Compared with low-level education, OR for CTS in intermediate level was 0.82 (0.76–0.89) and high-level 0.48 (0.44–0.53). In women and men there is significant association with a dose–response pattern between clinically relevant CTS and increasing manual work load and lower education level. These findings could be important in design and implementation of preventive measures.

Carpal tunnel syndrome (CTS) is a frequent cause of hand symptoms and activity limitations, most commonly affecting people of working age[1,2]. The potential association between the occurrence of CTS and work-related factors has been extensively debated. Most previous studies that investigated the etiology of CTS have concluded that CTS is mainly associated with individual risk factors, such as higher age, female sex, obesity, rheumatoid arthritis, diabetes mellitus, hypothyroidism, acromegaly, pregnancy and trauma[3,4]. However, several studies have suggested an important relationship between work and CTS[5]. Occupational activities, such as forceful manual work, highly repetitive flexion and extension of the wrist, extreme wrist postures, and use of vibratory tools, may lead to an increased risk of CTS[3–12]. High prevalence has been shown in certain occupational groups, for example those working with assembly, food processing, packaging, particularly in industries and cold conditions[3,13,14]. Previous research has mostly involved specific occupational cohorts and used various case definitions for CTS, not always based on diagnosis made by physicians. Other studies have included only surgical cohorts and thus the findings regarding associations would only apply to surgically treated CTS. To our knowledge, no previous studies assessing the association between CTS and work have involved all individuals in a general population who have sought health care for hand problems that were diagnosed by a physician as CTS[15,16]. As opposed to the large interest in the relationship with work, little is known about the possible association between CTS and level of education. Although one previous population-based study found a possible association between level of education and having undergone surgery for CTS, no studies have addressed the association with all clinically relevant CTS[17].

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Methods

The aim of this case–control study based on a general population was to investigate the association between clinically relevant CTS and type of work and level of education.

Data collection. Using the Skane Healthcare Register (SHR), we identified new cases with physician-diagnosed CTS in the population of Skane region in southern Sweden (1.2 million inhabitants, one-eighth of the population of Sweden). All inpatient and outpatient healthcare provided in the region, including primary care, is registered in the SHR. Diagnoses are chosen and registered by the doctors according to the International Classification of Diseases and Related Health Problems 10 (ICD-10) system. From the SHR, we retrieved data on all subjects who were given a physician-made primary diagnosis of CTS during a 5-year period (from January 1, 2004 through December 31, 2008). The inclusion criteria were; (1) age at diagnosis within range of 17 years to 57 years, (2) primary diagnosis of CTS made by a medical doctor, and (3) resident in the region during 3 calendar years prior to the date of diagnosis. We excluded subjects who had received a diagnosis of CTS during 3 years before the date of first CTS diagnosis registered in the study period.

For each CTS case we randomly sampled 4 matched referent individuals from the general population. The matching variables were sex, year of birth, and district of residence. The referent individuals had to be residents in the region and had no CTS diagnosis. No other exclusion criteria were used. Therefore, all individuals (the cases and the randomly selected referents) irrespective of their work status were included.

We retrieved data regarding type of work and level of education from a national database, the Longitudinal integrated database for health insurance and labor market studies (LISA). The LISA database is part of Statistics Sweden, and integrates existing data from the labor market, educational sector and social sector, which is updated with annual registers[18].

Definitions. We first classified type of work as blue-collar or white-collar based on the Swedish Standard Classification of Occupations (SSYK 96) (Appendix)[19, 20]. We also used a second classification of occupations, based on a previous study by Wolf et al., in which occupations were categorized as light, light-moderate, moderate or heavy manual work[21]. We classified the level of education according to the Swedish Education Classification (SUN): levels 1 and 2 (primary and lower secondary education up to 9 years) are classified as "low", levels 3 and 4 (upper secondary education 2 or 3 years) as "intermediate", and levels 5 to 7 (post-secondary education and postgraduate education) as "high"[22]. All definitions were made before data analysis.

Statistical analysis. We used the Chi-square test to compare the CTS cohort with the referent cohort regarding type of work and level of education, stratified according to sex. We estimated the odds ratios (OR) with 95% confidence intervals (CI) of CTS using three conditional logistic regression models. The first model was to estimate the total effect of education, and thus education but not occupation was included (because occupation is an intermediate in the association between education and CTS). Age and sex did not vary within matched sets and were thus adjusted for by design and use of conditional regression. In two additional models, we estimated the total effect of occupation adjusted for education (because education is a potential confounder of the association between occupation and CTS). A separate model for each of the classifications of occupations was used, one for type of work "blue/white collar" and one for occupational groups "light/light-moderate/moderate/heavy". These two models included only one occupational variable (ie, the model analyzing "blue/white collar" did not include "occupational group", and vice versa). A p-value below 0.05 was used for statistical significance. The analyses were performed with STATA v 16.0 (Stata Corporation, College Station, TX).

Ethical approval. The study was conducted according to the Declaration of Helsinki and was approved by the Ethical Review Board of Lund University (Dnr 2011/432). Need for informed consent was waived by the Ethical Review Board of Lund University. The population in the Skane region was informed of the study via an advertisement in newspapers and were offered the option to "opt-out", which is a standard process for population-based studies using register data as recommended by the Ethical Review Board.

Results

Study cohorts. The study population has been described previously[23]. During the 5 calendar years (2004–2008), a primary physician-made diagnosis of CTS was received by 7108 subjects, aged 17 to 57 years, who were residents of Skane region 3 years prior to the diagnosis. We excluded 1641 individuals because they had received a CTS diagnosis also during the 3 years preceding the date of first diagnosis in the study period and another 11 because no eligible matched referents could be found. The final cohorts comprised 5456 individuals with CTS and 21,667 matched reference individuals from the general population without CTS diagnosis. The mean age for the CTS and general population cohorts was 43 years and 73% were women (Table 1). The diagnosis of CTS was most common in the age group 45–57 years (47% in women and 50% of men).

Work. Of the women with CTS 52% were blue-collar workers and 34% white-collar workers compared to 40% and 44%, respectively, of the general population referents ($p < 0.001$) (Table 1). Among the men with CTS 65% were blue-collar workers and 21% white-collar workers compared to 46% and 37%, respectively, of the general population referents ($p < 0.001$).

Among the women with CTS 35% had light manual work, 32% had light-moderate manual work, 12% had moderate manual work and 6% had heavy manual labor, compared to 45%, 28%, 8% and 4% respectively, of the general population referents ($p < 0.001$). Among the men with CTS 20% hade light work, 8% had light-moderate

	Women		Men	
	CTS	Referents	CTS	Referents
	n = 3966	n = 15,756	n = 1490	n = 5911
	n (%)	n (%)	n (%)	n (%)
Age group				
17–34	857 (21.6)	3381 (21.5)	308 (20,7)	1215 (20.6)
35–44	1250 (31.5)	4978 (31.6)	436 (29.2)	1728 (29.2)
45–57	1859 (46.9)	7397 (46.9)	746 (50.1)	2968 (50.2)
Type of work				
Blue-collar	2045 (51.6)	6351 (40.3)	968 (65.0)	2729 (46.2)
White-collar	1336 (33.7)	7006 (44.5)	317 (21.3)	2192 (37.1)
Unknown[a]	585 (14.8)	2399 (15.2)	205 (13.8)	990 (16.7)
Occupational group				
Light manual work	1399 (35.3)	7024 (44.6)	297 (19.9)	2005 (33.9)
Light-moderate	1277 (32.2)	4378 (27.8)	115 (7.7)	581 (9.8)
Moderate	482 (12.2)	1290 (8.2)	163 (10.9)	514 (8.7)
Heavy	223 (5.6)	665 (4.2)	710 (47.7)	1821 (30.8)
Unknown[a]	585 (14.8)	2399 (15.2)	205 (13.8)	990 (16.7)
Level of education				
Low	754 (19.0)	2329 (14.8)	406 (27.2)	1169 (19.8)
Intermediate	2193 (55.3)	7767 (49.3)	856 (57.4)	3092 (52.3)
High	988 (24.9)	5542 (34.5)	216 (14.5)	1568 (26.5)
Unknown	31 (0.8)	218 (1.4)	12 (0.8)	82 (1.4)

Table 1. Characteristics in the carpal tunnel syndrome (CTS) cohort and the matched reference cohort without CTS. [a]Includes true missing as well as unemployed, students, disability pension, early retirements, entrepreneurs and project employments.

work, 11% had moderate work and 48% had heavy manual labor, compared to 34%, 10%, 9% and 31% respectively, of the general population referents ($p < 0.001$).

Education. Among women with CTS level of education was classified as low in 19%, intermediate in 55%, and high in 25%, compared to 15%, 49% and 35%, respectively, among the population referents ($p < 0.001$) (Table 1). Among men level of education was classified as low in 27%, intermediate in 57%, and high in 15%, compared to 20%, 52% and 27% respectively, among the population referents ($p < 0.001$).

Association with CTS. Compared with white-collar workers the OR for CTS among blue-collar workers was 1.67 (95% CI 1.54–1.81) (Table 2). Compared with light work, the OR for CTS was 1.37 (95% CI 1.26–1.50) for light-moderate work, 1.70 (95% CI 1.51–1.91) for moderate work, and 1.96 (95% CI 1.75–2.20) for heavy manual labor. Compared with persons with low-level education, the OR for CTS among those with intermediate-level education was 0.82 (95% CI 0.76–0.89) and among those with high-level education was 0.48 (95% CI 0.44–0.53).

Discussion

Our results show significant relationship between physician-diagnosed CTS and type of work (higher risk in blue-collar vs white-collar) in both women and men. These results are in line with previous studies. In a study from a region in Italy, both female and male blue-collar workers had higher age-specific rates of surgically-treated CTS than white-collar workers at all ages[8]. Another study from Italy showed that blue-collar work is a risk factor for surgically-treated CTS in both women and men[16]. However, the study, besides involving only patients with surgically-treated CTS, was not truly population-based but rather based on random sampling of 20 cases and 40 controls from discharge records of local hospitals.

In a large population-based study in Southern Sweden, the prevalence of CTS among active blue-collar workers was significantly higher than that among white-collar employees even after adjusting for sex, age, and body mass index[1]. The reason for the higher prevalence of CTS among blue-collar workers is believed to be that certain occupational risk factors are more common among blue-collar workers, such as forceful manual work, extreme wrist postures and use of vibratory tools[8]. These theories are in agreement with our results where there is a significant association between heavy manual work and CTS in both women and men. Our findings suggest a dose–response relationship between increasing manual load and CTS, with the heavy occupation group almost at twice the odds of having CTS compared with the referent group.

Our results support those of previous studies regarding the association between occupational load and CTS. A study from Finland investigated the relationship between exposures to different physical load factors and CTS in 6254 individuals aged 30 years or older, and found that hand grip with high forces was related to an

Model	Odds ratio (95% CI)[a]
Level of education[b]	
Low	Referent
Intermediate	0.82 (0.76–0.89)
High	0.48 (0.44–0.53)
Type of work[c]	
White-collar	Referent
Blue-collar	1.67 (1.54–1.81)
Occupational group[d]	
Light manual work	Referent
Light-moderate	1.37 (1.26–1.50)
Moderate	1.70 (1.51–1.91)
Heavy	1.96 (1.75–2.20)

Table 2. Association between level of education and type of work and carpal tunnel syndrome. [a]Odds ratios with 95% confidence intervals from conditional logistic regression models; age and sex did not vary within matched sets and thus adjusted for by design and use of conditional regression. [b]Estimating the effect of education (model does not include type of work or occupational group). [c]Estimating the effect of type of work (white-collar/blue-collar) adjusted for education (model does not include occupational group variable). [d]Estimating the effect of occupational group (light/light-moderate/moderate/heavy) adjusted for education (model does not include type of work variable).

increased prevalence of CTS (OR 1.7, 95% CI 1.2–2.5)[15]. Although this study was population-based, subjects were recruited through interviews (performed by nurses) and clinical health examinations, whereas our study population consists of individuals who had sought healthcare for hand problems and were diagnosed with CTS by the treating physician. Two population-based studies from Denmark investigated the association between occupational load and CTS using direct exposure measures and found that rapid wrist movements, measured as wrist angular velocity, and repetitive movements, measured as mean power frequency, were associated with increased risk of CTS (incidence rate ratio 2.31 [95% CI 2.09–2.56] and 1.83 [1.68–1.98], respectively), and that there was a positive association between hand load and incidence rates of CTS[11,24]. These studies included only hospital-diagnosed CTS and thus all cases treated exclusively in primary care (and possibly in private practice by specialists) were not included. Our study has shown similar findings to these population-based studies that used more precise exposure measures, but with the additional advantage that it included all cases of clinically relevant CTS.

Several previous studies concerning the relationship between work and CTS have been conducted on various industrial cohorts. A 3-year follow-up study of 1107 newly-hired workers in the United States found that forceful gripping (OR 2.59, 95% CI 1.12–5.99) and lifting > 1 kg (OR 3.27, 95% CI 1.27–8.44) were significantly associated with incident CTS[2]. In Italy, a 10-year longitudinal study on a group of industrial and service workers, that classified exposure with respect to action limit and threshold limit values (as proposed by the American Conference of Governmental Industrial Hygienists) found increased incidence of CTS among workers exposed between the action limit and threshold limit values (hazard ratio 2.18, 95% CI 1.86–2.56) and for workers exposed above the threshold limit value (hazard ratio 2.07, 95% CI 1.52–2.81)[12].

Our results also show significant association between CTS and level of education, with higher risk of physician-diagnosed CTS among individuals with low level of education. Our logistic regression model indicates that the risk of CTS decreases with increasing education level, with the highest education level at less than half the odds of having CTS compared with the referent group. The association between CTS and level of education has been investigated in very few previous studies. A study from Finland, analyzed data from 6256 individuals aged ≥ 30 years who had undergone surgery for CTS, with regard to level of education, BMI, smoking, leisure time physical activity, workplace physical exposures, and medical conditions (diabetes, RA, hypothyroidism and osteoarthritis) and found that individuals with low education were more likely than those with high education to undergo surgery for CTS[17]. A Brazilian study about the characteristics of a retrospective hospital cohort of 150 patients diagnosed with CTS found that more than half had a lower education level than high school[25].

Individuals with the highest levels of education more often have occupations that less likely involve highly demanding manual work tasks, whereas individuals with lower education are probably more likely to have heavy manual work[26]. Moreover, level of education (and income) usually defines socioeconomic status. The association between low socioeconomic status and inferior health is well established[27,28]. In addition to the role of education in determining job opportunities (lower education more likely in higher physical exposure jobs), its association with CTS may also be through other mechanisms such as increasing BMI, which is an important risk factor in CTS.

Our study has limitations. First, we identified the individuals with CTS through their health care attendance and it is possible that blue-collar workers with manually high demanding jobs are more likely to seek health care for hand symptoms that cause work limitations. Second, duration of employment was not specified, so the occupational exposure time is unknown. However, previous studies have indicated that even short periods of exposure can be sufficient for developing occupational CTS[5]. We did not use direct measures to determine the

level of exposure for each type of work, as it would be difficult to accomplish in a general population study. Our findings however support both those of previous studies performed on workers in specific industries as well as those of previous population-based studies that used direct exposure measures. Furthermore, the data did not permit adjustment for possible confounding factors. For example, obesity is considered an important confounder in some studies[5]. The strengths of our study include the truly population-based design (all incident cases and randomly chosen matched referents from a whole a general population) and CTS of clinically important severity (individuals sought healthcare) but not restricted to surgically treated. Further, the cases were diagnosed with CTS by a medical doctor within usual healthcare at all levels of healthcare including primary care where a substantial proportion of individuals seeking healthcare for CTS are managed.

Conclusion

Using a large population-based data set we found evidence of a dose–response relationship between both level of education and type of work with the risk of clinically relevant CTS, with increased risk the higher the occupational load and the lower the level of education. These findings could be important in design and implementation of preventive measures.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to that individual patient privacy could be compromised, but are available from the corresponding author on reasonable request.

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The final manuscript has been read and approved by all authors, and each individual named as an author meets the Uniform Requirements for Manuscripts Submitted to Biomedical Journals criteria for authorship.

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Competing interests
The authors declare no competing interests.

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Paper III

Quality of Life Research
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Measuring symptoms severity in carpal tunnel syndrome: score agreement and responsiveness of the Atroshi-Lyrén 6-item symptoms scale and the Boston symptom severity scale

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Abstract

Purpose To assess score agreement between the Atroshi-Lyrén 6-item symptoms scale and the Boston 11-item symptom severity scale and compare their responsiveness in patients with carpal tunnel syndrome before and after carpal tunnel release surgery.

Methods This prospective cohort study included 3 cohorts that completed the A-L and Boston scales (conventional score 1–5) on the same occasion: a preoperative and short-term postoperative cohort (212 patients), a mid-term postoperative cohort (101 patients), and a long-term postoperative cohort (124 patients). Agreement was assessed with Lin's concordance correlation coefficient and Passing-Bablok regression analysis. Analyses using item response theory were conducted on responses from the preoperative/short-term postoperative cohort including testing of item infit/outfit. Reliability was assessed with Cronbach alpha. Overall and sex-specific effect sizes were calculated using Cohen's d.

Results Lin's CCCs were high (0.81–0.91). Passing-Bablok analysis showed constant and proportional differences in all cohorts except preoperative to short-term postoperative change. Both scales showed high reliability (alpha, 0.88–0.93). The IRT-based analyses showed infit/outfit values within the desired range. With IRT-based scoring, the A-L scale had significantly higher responsiveness than the Boston scale, overall (d, 2.02 vs 1.59), in women (d, 2.22 vs 1.77) and in men (d, 1.74 vs 1.36).

Conclusion The Atroshi-Lyrén 6-item symptoms scale and the Boston 11-item symptom severity scale show good agreement but are not equivalent in measuring CTS-related symptoms severity. When using IRT-based scoring, the Atroshi-Lyrén scale demonstrated significantly higher responsiveness.

Keywords Carpal tunnel syndrome · Carpal tunnel release surgery · Item response theory · Patient-reported outcome measures · Symptom severity scale

Introduction

In patients with carpal tunnel syndrome (CTS), change in symptom severity is usually the most important treatment outcome and often used as primary endpoint in randomized clinical trials of treatment effectiveness [1–4]. Symptom severity is usually measured with patient-reported outcome measures. The Boston 11-item symptom severity scale, developed almost three decades ago, has been the most commonly used measure of symptom severity in CTS and has been translated to several languages [5–9]. In our previous research we investigated the Boston scale using modern measurement methodology based on item response theory (IRT) in a stepwise process that resulted in removal of 4 items that did not fit well in the scale and merging of 2

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other items in that scale [10]. We developed a 6-item symptoms scale that demonstrated good internal consistency, test–retest reliability and validity in a comparison with the Boston scale and it did not exhibit differential item functioning with regard to gender [10]. The responsiveness of the 6-item scale has also been established [11]. Since its introduction, the Atroshi-Lyrén (A-L) 6-item CTS symptoms scale has been translated to various languages and used in clinical studies [12–14]. It is not known whether the scores of the Boston and the A-L scales are equivalent to enable direct score comparisons across studies that have used either scale. In addition, the two scales have not been compared with regard to responsiveness, which is probably the most clinically relevant psychometric property. When choosing a condition-specific patient-reported outcome measure for use in clinical research or practice it would be important to consider the responsiveness as well as efficiency of the measure. The purpose of this study was to assess the score agreement between the A-L 6-item CTS symptoms scale and the Boston 11-item symptom severity scale in patients with CTS before and after carpal tunnel release (CTR) surgery and compare their responsiveness. Since the A-L scale was developed using IRT, we hypothesized that the A-L scale would demonstrate higher responsiveness than the Boston scale.

Materials and methods

We conducted a prospective cohort study at one orthopedic department in Southern Sweden. The department is the only facility in which carpal tunnel release surgery is performed in a region with 300,000 inhabitants. The study included data from 3 cohorts of patients who completed both scales on the same occasion. All patients were diagnosed with CTS by orthopedic or hand surgery specialists based on history and physical examination with or without nerve conduction tests. The inclusion criteria were a diagnosis of CTS and subsequent surgery with unilateral carpal tunnel release as the only procedure (ie, no concomitant procedures). All surgeries were done under local anesthesia and tourniquet. Postoperatively, a soft dressing was applied until suture removal at 12–14 days and patients received instructions about range of motion exercises and use of the hand as tolerated; hand therapy was not routinely prescribed.

Study cohorts

Cohort 1 (preoperative/short-term postoperative cohort) comprised 317 patients (329 hands) who completed the scales at the hospital either immediately before surgery or within 8 weeks before surgery, and 239 patients (284 hands) who completed the scales at 3 weeks to 17 months after surgery, from May 2017 through October 2018) (Fig. 1). Of these, 212 patients (235 hands) completed the scales both before and after surgery (Table 1). Postoperatively the scales were sent to the patients by mail. In patients who had surgery on both hands during the study period, the second surgery was usually performed after a minimum interval of 3 months.

Cohort 2 (mid-term postoperative cohort) comprised 101 patients (101 hands) who participated in a randomized placebo-controlled trial of steroid injection and subsequently had surgery [1]. The patients completed the scales as part of a follow-up conducted on all trial participants at 5 years after randomization [15]. The questionnaires were mailed to the patients. All trial participants provided follow-up data.

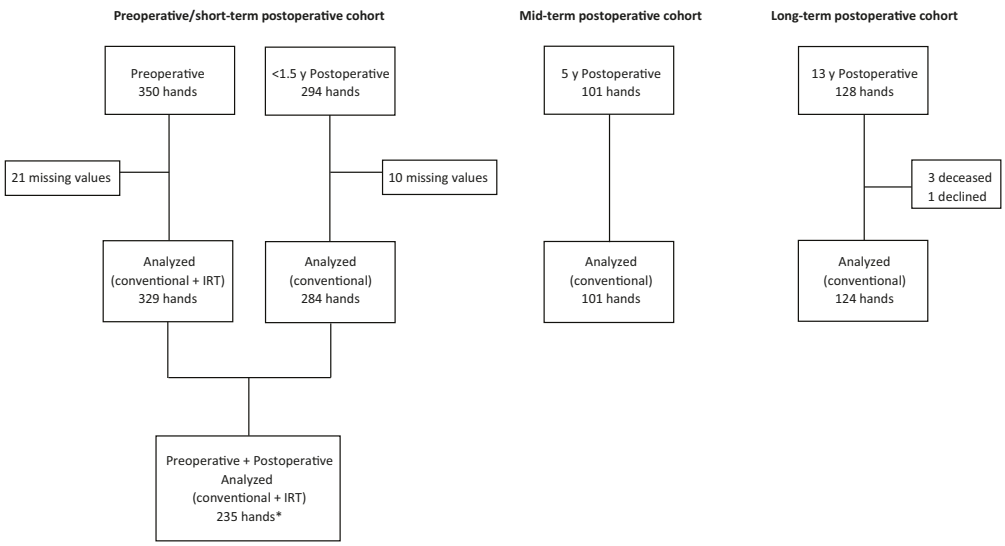
Cohort 3 (long-term postoperative cohort) comprised 124 patients who participated in a randomized controlled trial of open versus endoscopic CTR [16]. The patients completed both scales (questionnaires mailed to the patients) 12 to 14 years after surgery. Of the initial 128 participants 3 had died and 1 declined to answer the follow-up questionnaire.

In all 3 cohorts the questionnaires included the Boston scale, the A-L scale, and the 11-item disabilities of the arm, shoulder and hand (QuickDASH) scale. In the preoperative/short-term postoperative cohort, the Boston items in the preoperative questionnaire were placed first followed by the QuickDASH items and then the A-L items. In the postoperative questionnaire this order was used in 140 hands, but the two scales were placed in reverse order (separated by the QuickDASH) in 144 hands; this was randomly done according to surgery date. For the mid-term and long-term postoperative cohorts, the Boston items were placed before the A-L items separated by the QuickDASH.

Scales

The Boston scale consists of 11 items that, referring to a specific side (right or left hand), inquire about the severity and frequency of pain, numbness and tingling as well as about other issues such as weakness and ability to hold small objects. Each item has 5 response choices score from 1 (no symptom) to 5 (most severe). The mean scale score is the mean value of all item scores. In conventional scoring a missing item response is usually replaced by the score mean for the other items. Although no rules exist about how many missing values are allowed for a conventional score to be computed, we allowed a maximum of 2 missing responses in this study. The final mean Boston symptom severity score may be any value between 1.0 (best) to 5.0 (worst).

The A-L scale consists of 6 items that inquire about severity and frequency of night and daytime numbness and



* In the analyses of the Boston and A-L scales (for the QuickDASH scale 231 hands were included).

Fig. 1 Flow chart of number of hands analyzed in the 3 cohorts

Table 1 Characteristics of the patients in the 3 cohorts of patients with carpal tunnel syndrome treated with carpal tunnel release

Characteristic	Preoperative[a]	Short-term postoperative[b]	Mid-term postoperative	Long-term postoperative
Number of hands (patients)	329 (317)	284 (239)	101 (101)	124 (124)
Female sex, *n* (%)	202 (61)	174 (61)	76 (75)	93 (75)
Age at surgery, mean (SD) y	56 (15)	59 (15)	53 (11.5)	45 (8.6)
Dominant hand operated, *n* (%)	No data	No data	81 (80)	99 (80)
Right hand operated, *n* (%)	187 (57)	162 (57)	79 (78)	105 (85)
Time from surgery, mo				
Mean (SD)	NA	9.6 (4.4)	68 (8)	153 (15)
Median (range)	NA	7.4 (0.6–17)	69 (46–84)	149 (136–188)

[a]Scales completed immediately before surgery in 201 hands and within 8 weeks before surgery in 128 hands

[b]For 235 hands (212 patients) the scales were completed both preoperatively and postoperatively

NA Not applicable

tingling and pain (also referring to a specific side). Although the scale has been scored with IRT-based scoring it can also be scored conventionally on a scale from 1 (no symptoms) to 5 (most severe symptoms), with only 1 missing item response allowed with conventional scoring. Similarly, with conventional scoring the final mean A-L symptoms score may be any value between 1.0 (best) to 5.0 (worst).

The QuickDASH is an 11-item measure of upper extremity-related disability [17, 18]. The QuickDASH is not disease-specific but region-specific, and most items inquire about activity limitation. The QuickDASH score may range from 0 (no disability) to 100 (most severe disability), with only 1 missing item response allowed in conventional scoring.

Missing data

The preoperative/short-term postoperative cohort initially comprised 350 hands preoperatively and 294 hands postoperatively, of which 21 and 10 respectively had missing values precluding calculation of a conventional score for one or both CTS scales and these were therefore excluded. No missing values occurred in the mid-term and long-term postoperative cohorts. Hands for which conventional CTS scores could be calculated but had 2 or more missing item responses on the QuickDASH were not excluded.

Statistical analyses

The data from each of the 3 cohorts were analyzed separately (cohorts were not combined).

Conventional scoring: In each cohort we calculated the mean score and SD for all scales. We calculated the unadjusted difference between the Boston and A-L scale scores. In the preoperative/short-term postoperative cohort we also conducted a multivariate multiple linear regression analysis to determine whether age, sex, and time from surgery could be confounders in the difference of the change (preoperative to postoperative) scores between the Boston and A-L scales. We compared the scores according to the order in which the scales were placed in the questionnaire but found no differences and therefore we did not consider this factor further.

Score agreement: Absolute agreement in conventional scores between the Boston and A-L scales was assessed with Lin's concordance correlation coefficient [19]. For assessing the difference in systematic error in measurement between the two scales, the Passing and Bablok regression analysis was used [20, 21].

IRT analyses: The IRT analyses were performed only on responses from the preoperative/short-term postoperative cohort. In the analyses of the Boston and A-L scales we used data from all hands with preoperative responses ($n = 329$), as well as data from the hands that had both preoperative and short-term postoperative responses ($n = 235$). In the analyses of the QuickDASH scale we included all hands with responses to at least 6 of the 11 items ($n = 231$).

In the development of the A-L scale [10] we used the partial credit model (PCM) as the item response model. However, based on the results of the development study we would expect the PCM to have a rather poor fit with the Boston scale items, and therefore, given the purpose of this study, we chose a more general model, the generalized partial credit model (GPCM) [22]. The PCM and GPCM are commonly used item response models for ordered polytomous data (ie, items that have multiple response options representing for example different levels of symptom severity). They model the probability of choosing the higher of two adjacent response options, conditional on the latent trait (symptom severity in this study). The GPCM also has a discrimination parameter that can be considered as an item weight; a larger discrimination parameter for a certain item implies a stronger association between the latent trait and the expected score on that item (ie, an item with a large discrimination parameter is better at distinguishing between lower and higher levels of symptom severity) (Appendix). We used the software ConQuest (version 4.0) for parameter estimation [23]. For parameter estimates in the GPCM we used weighted likelihood estimation (WLE) [24]. Parameter estimation was done in two steps. First, item parameters were estimated from the full preoperative data to maximize the amount of data in the item parameter estimation. In the second step, these pre-estimated item parameters were used to estimate preoperative and postoperative symptom severity for the hands that had both preoperative and postoperative responses. By following this procedure, we ensure that the item parameters are as robust as possible and that preoperative and postoperative symptom severity estimates are on the same scale. Item fit was evaluated using the infit and outfit statistics (Appendix). Expected values for both infit and outfit is 1, and it is desired that fit values should be approximately between 0.75 and 1.33, in accordance with Wilson [25].

Reliability: To analyze reliability we estimated the Cronbach alpha coefficient.

Responsiveness: We calculated the overall and sex-specific effect size for each scale in patients who had both preoperative and postoperative scores. As a measure of effects size we used Cohen's d (mean difference in preoperative and postoperative scores divided by the pooled SD) with 95% CI. This was calculated for both the conventional and the IRT-based scores, using STATA version 16.0 (Stata Corporation, College Station, TX). We then compared d for the Boston and A-L scales using the z-test.

Results

Conventional scoring

In all 3 cohorts the mean A-L score was marginally (0.1 to 0.2 score units) lower than the mean Boston score (Table 2). The percentage mean difference (Boston as reference) was −9.8% at the short-term, −5.1% at the mid-term and −6.1% at the long-term follow-up. The multivariate multiple linear regression analysis of change scores among patients with both preoperative and short-term postoperative scores showed that age, sex and time since surgery were not confounders in the difference of the change (preoperative to postoperative) scores between the Boston and A-L scales.

Score agreement

Lin's concordance correlation coefficients were high, ranging from 0.81 to 0.91 (Table 3). The Passing-Bablok regression analysis showed a statistically significant constant and proportional difference in all cohorts, except in Cohort 1 preoperative-to-postoperative change where it showed constant agreement but proportional disagreement.

IRT

All item infit and outfit values for the Boston and A-L scales were within the 0.75–1.33 range, indicating acceptable fit (Table 4). All QuickDASH items showed acceptable fit, with values ranging from 0.98 to 1.05. The mean Boston score was −0.12 (SD 1.02) preoperatively and −1.68 (SD 0.94)

Table 2 Scale scores (conventional scoring)

Scale	Preoperative mean (SD)	Short-term postoperative mean (SD)	Mid-term postoperative mean (SD)	Long-term postoperative mean (SD)
Boston	3.12 (0.76)	1.69 (0.75)	1.56 (0.66)	1.41 (0.65)
Atroshi-Lyrén	3.06 (0.84)	1.51 (0.72)	1.47 (0.66)	1.30 (0.55)
Score difference	−0.06 (0.40)	−0.19 (0.36)	−0.09 (0.28)	−0.11 (0.23)
QuickDASH	46 (22)	19 (20)	17 (20)	10 (16)

See Table 1 for number of hands in each cohort

Boston and Atroshi-Lyrén scale scores range from 1 (no symptoms) to 5 (most severe symptoms) and QuickDASH scale score ranges from 0 (no disability) to 100 (most severe disability)

Table 3 Concordance correlation and Passing-Bablok agreement between the Boston and Atroshi-Lyrén scales

	Preoperative	Short-term postoperative	Short-term change	Mid-term postoperative	Long-term postoperative
CCC	0.87 (0.85 to 0.89)	0.85 (0.82 to 0.89)	0.81 (0.77 to 0.86)	0.90 (0.87 to 0.94)	0.91 (0.89 to 0.94)
A	−0.33 (−0.58 to −0.19)	0.21 (0.06 to 0.29)	0.07 (−0.03 to 0.18)	0.08 (0.01 to 0.25)	0.31 (0.23 to 0.39)
B	1.10 (1.05 to 1.17)	0.77 (0.71 to 0.86)	1.10 (1.01 to 1.17)	0.92 (0.75 to 0.99)	0.69 (0.61 to 0.77)

Values within parentheses are 95% confidence intervals (CI)

A is the constant difference and B the proportional difference between the two scales, a CI including 0 or 1 implies constant or proportional agreement, respectively

CCC Lin's concordance correlation coefficient

Table 4 Infit and outfit values for average item locations in the Boston and Atroshi-Lyrén (A-L) scales in the item response theory (IRT)-based analyses

		Boston				A-L	
		Preoperative				Preoperative	
Item		Infit	Outfit	Item		Infit	Outfit
1	Pain—night, severity	1.02	1.01	1	Pain—night, severity	0.97	0.94
2	Pain—wakening, frequency	1.00	0.97	2	Pain—daytime, severity	1.00	0.99
3	Pain—daytime, severity	1.02	1.01	3	Numbness/tingling—night, severity	0.99	0.96
4	Pain—daytime, frequency	1.01	1.01	4	Numbness/tingling—daytime, severity	0.99	0.99
5	Pain—daytime, duration	1.03	1.10	5	Pain—wakening, frequency	1.02	1.02
6	Numbness—severity	1.03	1.04	6	Numbness/tingling—wakening, frequency	1.00	0.98
7	Weakness—severity	1.01	1.01				
8	Tingling—severity	1.01	1.01				
9	Numbness/tingling—night, severity	1.03	1.01				
10	Numbness/tingling—wakening, frequency	1.02	1.00				
11	Gripping small objects	0.99	1.02				

postoperatively, and the mean A-L score was −0.03 (SD 1.02) preoperatively and −2.33 (SD 1.24) postoperatively.

Reliability

The Cronbach alpha estimates were high for all scales. The preoperative and postoperative alpha for the Boston scale were 0.88 and 0.93, for the Atroshi-Lyrén scale 0.89 and 0.91 and for the QuickDASH 0.91 and 0.94.

Responsiveness

Cohen's d was large for all scales (> 1.3 for the CTS scales and > 0.9 for the QuickDASH) with both conventional and IRT-based scoring (Table 5). The A-L scale had larger overall and sex-specific d values than the Boston scale with both conventional and IRT-based scoring; the A-L scale's larger IRT-based d values were statistically significant ($p < 0.001$). For all scales d was smaller among men than among women.

Discussion

Our study shows that in patients with CTS the mean conventional scores for the A-L scale were consistently lower than the Boston scale by 0.1 to 0.2 score units before and after surgery. However, this small difference is not considered clinically relevant. Thus, in pre-post intervention study design the mean change scores for both scales are expected to be near to equivalent. In a previous study, high agreement was found between these scales with an intraclass correlation coefficient of 0.80 [10]. Agreement analysis in this study demonstrated that, despite a high absolute agreement by Lin's CCC (0.81–0.91), the Passing-Bablok analyses showed constant and proportional differences in almost all comparisons. However, there was constant agreement between the two scales in the change in scores from baseline to short-term postoperatively, and the proportional difference was only marginally statistically significant.

The A-L scale has previously demonstrated good construct validity and reliability for measuring symptoms severity in CTS, both after surgical treatment [10, 14] and after steroid injection [12]. This was also the case in our present study (Cronbach alpha estimates 0.89–0.91). A study that used IRT (Rasch model) to compare the A-L and Boston scales in patients with surgically treated CTS suggested that the A-L scale had better psychometric properties based on analysis of item thresholds and differential item functioning [14].

In the present study all the Boston items had good infit when estimated from the preoperative data, which was not the case when the A-L scale was developed. However, this

Table 5 Overall and sex-specific responsiveness of the scales

Scale	Conventional scoring			IRT scoring		
	Preoperative mean (SD)	Postoperative mean (SD)	d (95% CI)	Preoperative mean (SD)	Postoperative mean (SD)	d (95% CI)
All hands ($n = 235$)						
Boston	3.03 (0.72)	1.68 (0.73)	1.86 (1.64–2.08)	−0.12 (1.02)	−1.68 (0.94)	1.59 (1.38–1.80)
A-L	2.98 (0.82)	1.47 (0.68)	2.00 (1.77–2.21)	−0.03 (1.02)	−2.33 (1.24)	2.02 (1.79–2.24)[d]
QuickDASH[a]	44 (22)	18 (19)	1.25 (1.04–1.45)	−0.15 (1.24)	−1.82 (1.55)	1.19 (1.00–1.39)
Women ($n = 141$)[b]						
Boston	3.05 (0.71)	1.59 (0.65)	2.14 (1.84–2.43)	−0.10 (1.01)	−1.76 (0.86)	1.77 (1.49–2.04)
A-L	3.01 (0.81)	1.40 (0.62)	2.22 (1.93–2.52)	−0.01 (1.03)	−2.46 (1.17)	2.22 (1.92–2.52)[d]
QuickDASH[a]	47 (22)	17 (19)	1.47 (1.19–1.74)	0.05 (1.21)	−1.78 (1.49)	1.35 (1.09–1.61)
Men ($n = 94$)[c]						
Boston	3.0 (0.74)	1.82 (0.81)	1.52 (1.20–1.85)	−0.15 (1.04)	−1.55 (1.03)	1.36 (1.04–1.67)
A-L	2.94 (0.84)	1.58 (0.76)	1.70 (1.37–2.04)	−0.06 (1.01)	−2.12 (1.33)	1.74 (1.41–2.08)[d]
QuickDASH[a]	39 (21)	19 (20)	0.95 (0.65–1.26)	−0.44 (1.24)	−1.89 (1.64)	0.99 (0.69–1.30)

Boston and Atroshi-Lyrén (A-L) scale scores range from 1 (no symptoms) to 5 (most severe) and the QuickDASH from 0 (no disability) to 100 (most severe)

Cohen's d values shown as absolute values

[a]No conventional QuickDASH scores because of ≥ 2 missing items in 11 women hands (5 preoperative and 6 postoperative) and 3 men hands (2 preoperative and 1 postoperative); 4 hands (3 women and 1 man) with ≥ 5 missing QuickDASH items were not included in the IRT analyses

[b]Right hand operated on in 82 (58%), mean time (weeks) from surgery 30.7 (SD 15.5)

[c]Right hand operated on in 54 (57%), mean time (weeks) from surgery 30.6 (SD 15.2)

[d]$p < 0.001$ (A-L vs Boston)

is not surprising given that we use a more general model in this study. In that development work, the starting point was the Boston scale items estimated on preoperative data. However, in that work two items were removed from the Boston scale before item parameter estimation (based on factor analysis), and that might have altered the scale enough to explain the difference in fit patterns. Another surprising finding was the coefficient alpha estimates being higher for the postoperative data than the preoperative data for all scales. This is counterintuitive as the spread (SD) is smaller in the postoperative measures. However, the results may be due to the presence of outliers, as it has been found that coefficient alpha estimates can be severely inflated by outliers in rating scale item responses [26].

If the two scales are not equivalent, which one should be used for measuring symptoms severity related to CTS? A scale may be highly reliable and valid but with low responsiveness [21]. We believe that it would be advantageous to use the scale that has demonstrated higher responsiveness. Our study showed that the A-L scale had higher responsiveness than the Boston scale especially when using IRT-based scoring. The fact that many Boston items did not fit the PCM in the original study [10] may be indicative of "noise", which could be a plausible explanation to its lower responsiveness. Another advantage of the IRT-based scoring is that it can use data even from patients with more missing responses than allowed with conventional scoring. Considering that responsiveness of the A-L was high with both scoring methods, conventional scoring would be more feasible in clinical practice.

There was a statistically significant difference in both overall and sex-specific responsiveness between the A-L and Boston scales when using IRT-based scoring. Previous studies of both scales have shown no differential item functioning with regard to sex [10, 27]. In this study the QuickDASH had similar responsiveness with both conventional and IRT-based scoring. It is important to note that even though the QuickDASH had good item fit and reliability, that is, the scale meets some of the criteria to measure an intended construct, it is not specifically intended to measure CTS symptoms severity. A previous study has also shown higher responsiveness of the A-L scale than the QuickDASH, probably because the former is a disease-specific measure of symptoms [11].

One limitation is that our study only involved patients whose symptoms severity required surgical treatment. Thus, our results are generalizable mainly to surgically treated patients.

In conclusion, our study shows good agreement between the A-L 6-item CTS symptoms scale and the Boston 11-item symptom severity scale in measuring symptoms severity related to CTS. When using IRT-based scoring, the A-L scale demonstrated significantly higher responsiveness than the Boston scale. As the more responsive and efficient measure, the A-L scale would be the preferable measure when evaluating symptoms severity in CTS.

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Author contributions RSR, PEL and IA contributed to the study conception and design. KM, RSR, PEL and IA contributed to material preparation, data collection and analysis and writing of the manuscript. The final manuscript has been read and approved by all authors.

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Data availability The datasets generated and/or analyzed during the current study are not publicly available due to that individual patient privacy could be compromised but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors of this manuscript declare that they have no financial or non-financial competing interests.

Ethical approval The studies that generated the data were approved by the Regional Ethical Review Board of Lund University, Lund, Sweden (reference numbers 2008/119, 2013/307 and 2015/906).

Consent to participate Informed consent was obtained from all participants.

Consent for publication Informed consent was obtained.

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Paper IV

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Trials

STUDY PROTOCOL Open Access

Treatment of carpal tunnel syndrome with wrist splinting: study protocol for a randomized placebo-controlled trial

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Abstract

Background: Carpal tunnel syndrome (CTS) is a common cause of pain, weakness, sensory loss, and activity limitations. Currently, the most common initial treatment is use of a rigid splint immobilizing the wrist, usually during night-time, for several weeks. Evidence regarding the efficacy and effect durability of wrist splinting is weak. The treatment is associated with costs and may cause discomfort and limit daily and work activities. No placebo-controlled trials have been performed.

Methods: This is a randomized controlled trial designed to assess the efficacy of a rigid wrist splint compared with soft wrist bandage (placebo) in patients with primary idiopathic CTS. The trial will be conducted at an orthopedic department. Patients, 25 to 65 years old, who seek primary health-care with symptoms of CTS will be screened, and potentially eligible patients will be referred to the study center. Patients who fulfill the trial's eligibility criteria will be invited to participate. A total of 112 patients who provide informed consent will be randomly assigned to treatment with either a rigid wrist splint or a soft bandage to be used initially for 6 weeks at night and, if possible, during the day. The splints and bandages will be fitted with a temperature-monitoring device to measure the total time during which they have actually been worn. The trial participants will complete a questionnaire that includes the 6-item CTS symptoms scale (CTS-6); the 11-item disabilities of the arm, shoulder, and hand (*Quick*DASH) scale; and the EuroQol 5-dimension (EQ-5D) health status and quality-of-life measure at baseline and at 6, 12, 24, and 52 weeks after treatment start. The participants will undergo physical examination and nerve conduction testing at baseline and at 52 weeks. The trial's primary outcomes are the change in the CTS-6 score from baseline to 12 weeks and the rate of carpal tunnel release surgery at 52 weeks.

Discussion: This is the first placebo-controlled randomized trial with electronic monitoring of actual splint use and will provide evidence regarding the efficacy of wrist splinting in patients with CTS.

Trial registration: ISRCTN Registry, ISRCTN81836603. Registered on May 5, 2018.

Keywords: Carpal tunnel syndrome, CTS, Median nerve, Wrist, Non-surgical treatment, Splinting, Randomized trial, RCT

Background

Carpal tunnel syndrome (CTS) is a very common cause of hand pain, weakness, and loss of sensation leading to limitations in daily activities, work disability, and worsening quality of life [1]. The prevalences in the adult general population are about 5% among women and 2% among men [2]. The goal of treating CTS is to relieve symptoms and improve hand function. Currently, the most common non-surgical treatment across the world is splinting the wrist with a rigid splint, usually at night, sometimes combined with other treatments [3]. There is some evidence that wrist splinting may be effective in the short term [4–6], but the evidence is generally weak, the optimal duration of treatment is unclear, and the long-term efficacy has not been established [7, 8]. Treatment benefit of wrist splinting itself has often been small and of short duration, but in trials that compared splinting with surgery [5, 9], the benefit

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has often been augmented by large cross-over to surgery [10]. The rationale behind wrist splinting is that it prevents wrist flexion, known to increase pressure in the carpal tunnel [11]. However, the duration of splinting currently used in clinical practice (4 to 6 weeks) is not based on clear evidence [7]. The long-term effect of splinting the wrist for this short time on the pathophysiological factors involved in the causation of CTS may not be large. It is unclear why the benefit from wrist splinting in idiopathic CTS can persist after cessation of splinting.

In previous randomized studies, treatment of CTS with wrist splint has been compared with surgery [5] or other non-surgical treatments, such as steroid injection or exercises [7, 12]. Of the non-surgical treatments, only local steroid injection has strong evidence from placebo-controlled trials supporting short-term efficacy [12]. However, it is still an invasive procedure not routinely available in primary care and thus may require referral to specialists. The few randomized studies that evaluated wrist splinting in the treatment of patients with CTS were not placebo-controlled and therefore the reported improvement may have been related to non-specific effects or the natural course of the disease. Compliance in wearing the splint was often not evaluated or was assessed by asking patients to register data in a diary, a method with uncertain reliability. A previous study has shown that patients tend to overestimate their splint use [13].

Although splinting is a simple and safe treatment, it has some disadvantages. Patients may find that wearing a splint is uncomfortable and limits them in some work or daily activities or both. The costs of the splint and therapy visits may be high [14]. There is a need for a randomized placebo-controlled trial assessing the efficacy of wrist splinting in the treatment of patients with CTS.

Trial objective

The objective of the trial is to evaluate the placebo-controlled treatment efficacy and effect durability of wrist splinting in patients with primary idiopathic CTS up to 12 months after treatment start. Our hypothesis is that, in patients with CTS, wearing a rigid wrist splint at night and, if possible, during the day for 6 weeks is more effective than wearing a soft wrist bandage in reducing symptoms and subsequent need for surgery.

Methods

Trial design and setting

The study is a prospective randomized parallel-group superiority clinical trial conducted at one university health-care orthopedic department (Department of Orthopedics, Hässleholm-Kristianstad-Ystad) in collaboration with several primary care centers in the region of Northeastern Skåne in southern Sweden (population of 300,000). The department is the only referral facility for patients with CTS in that region. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided as an Additional file 1.

Inclusion criteria

- Primary, idiopathic CTS
- Age 25–65 years, either sex
- Symptoms of classic or probable CTS according to the criteria in the Katz hand diagram [15]
- Two surgeons (specialists in orthopedic or hand surgery) independently diagnose the patient's CTS
- Symptom duration of at least 1 month

Exclusion criteria

- CTS classified as severe (thenar muscle atrophy or 2-point discrimination exceeding 8 mm in at least one finger)
- Treatment of the study hand with a wrist splint in the past 12 months
- Previous steroid injection for CTS in the study hand
- Inflammatory joint disease
- Vibration-induced neuropathy
- Polyneuropathy
- Current pregnancy
- Trauma to the study hand in the past 12 months
- Previous CTS surgery in the study hand
- Inability to complete questionnaires because of language difficulties or cognitive disorder
- Severe medical illness
- Known abuse of drugs or alcohol or both

Screening

Patients consulting a primary care physician or referred to occupational therapists at primary health-care centers for symptoms suggestive of CTS will be screened. Potentially eligible patients are referred to the orthopedic department and scheduled for assessment by two surgeons in the research team (a senior hand surgeon and an orthopedic specialist) within 1 to 2 weeks of referral. Both surgeons will be present when a full history is taken, but the following physical examination will be carried out by the orthopedic specialist only. Patients judged to fulfill the eligibility criteria are then given, by the orthopedic specialist, full verbal and written information about the aims and conduct of the trial as well as the potential advantages and disadvantages of participation. Patients who accept participation will provide written informed consent. Participants will undergo the baseline assessment immediately and nerve conduction testing

as soon as possible but no later than 2 weeks after enrolment. Only one hand will be included in the trial (in bilateral symptoms, the hand with the worse score on the 6-item CTS symptoms scale (CTS-6) will be included). Each patient will be allowed to enter the trial only once.

Randomization

Patients will be randomly assigned in accordance with a computer-generated randomization list (ratio of 1:1) [16]. The randomization will be stratified in accordance with patient sex and carried out in random blocks of various sizes (4, 6, and 8). An administrative assistant, not involved in the trial, will prepare sequentially numbered sealed opaque envelopes containing the group allocation. After providing written informed consent and undergoing the baseline assessment by a study investigator (orthopedic surgeon), the enrolled patient will proceed to the hand therapist, who will open the envelope with the lowest number and provide the patient with either a wrist splint with a metal bar or a soft bandage in accordance with treatment allocation (Fig. 1).

Interventions

Group A: Splint with metal bar

The patients will receive a standard splint (model Base, Catell AB, Hägersten, Sweden) with wrist in neutral position to be worn at night and, if possible, during the day (Fig. 2). No other instructions or treatments will be given. If after 6 weeks the patient reports large improvement, no further treatment will be given. If the patient reports small or no improvement, further treatment with the same splint will be given for 4 weeks. If the patient reports small or no improvement after 10-week splinting, the patient will be offered surgery. Patients who refuse further treatment with wrist splinting will be offered surgery. Surgery will not be performed before 12 weeks after treatment start.

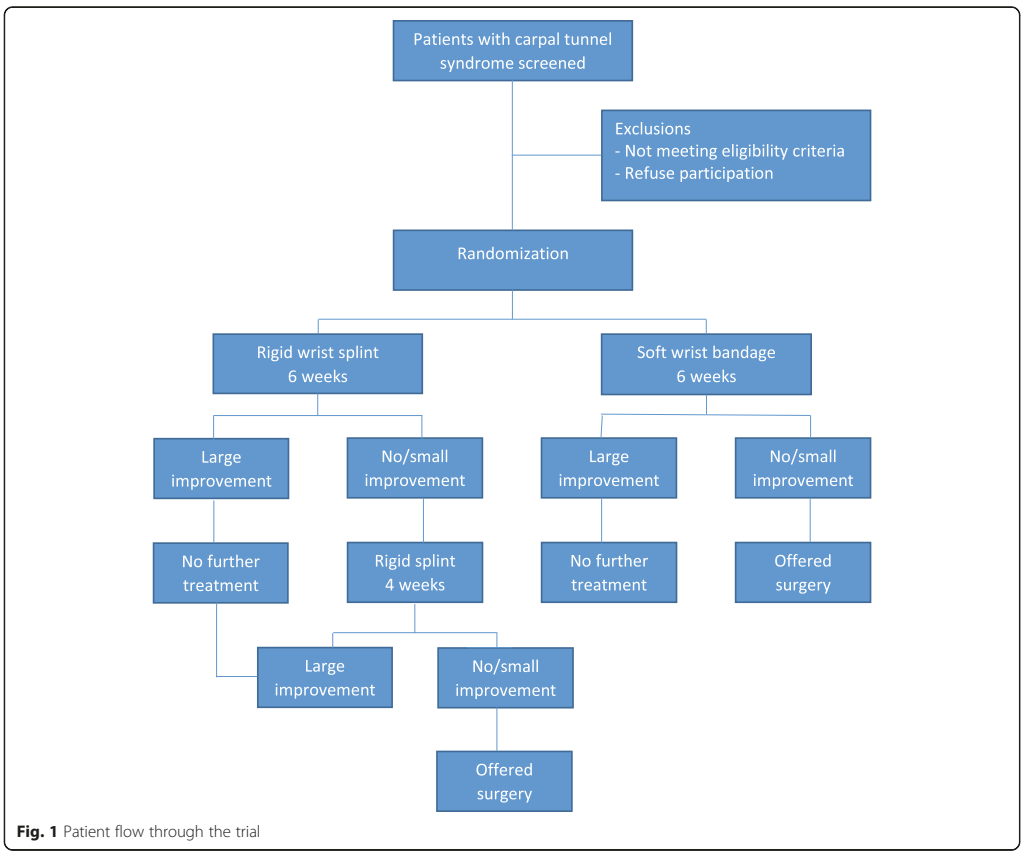

Fig. 1 Patient flow through the trial

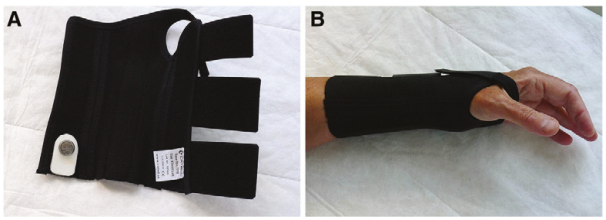

Fig. 2 Conventional splint containing a metal bar and a temperature-monitoring device (**a**), holding the wrist in neutral position (**b**)

If symptoms recur after improvement, the patients will be treated with 4 weeks of wrist splinting using the same type of splint. If after 4 weeks the patient reports small or no improvement, the patient will be offered surgery. Patients who refuse further treatment with wrist splinting will be offered surgery.

Group B: Soft bandage

The patients will receive a custom-made (neoprene) wrist bandage to be worn at night and, if possible, during the day (Fig. 3). No other instructions or treatments will be given. If after 6 weeks the patient reports large improvement, no further treatment will be given. If the patient reports small or no improvement, the patient will be offered surgery. Surgery will not be performed before 12 weeks after treatment start.

If symptoms recur after improvement, the patient will use the same type of bandage for 4 weeks. If after 4 weeks the patient reports small or no improvement, the patient will be offered surgery. Patients who refuse further treatment with the wrist bandage will be offered surgery.

Discontinuing/modifying allocated interventions

The trial interventions (wrist splint or soft bandage) are not expected to cause harms, but it is possible that a participant will experience discomfort using a splint or bandage. Participants will be asked to continue their allocated intervention if possible. The participants are informed that, in case of worsening of symptoms during intervention, they contact the trial therapist, who will discuss the case with the investigators. If the worsening is not experienced by the participant as severe, the participant will be asked to continue the allocated intervention in accordance with the protocol. If symptoms are severe or the participant declines to continue the allocated treatment, surgery will be offered. The participant will be asked to continue the allocated treatment until surgery.

Concomitant care

No other treatments will be prescribed during the trial interventions. The information provided to participants will not specify any prohibitions. Participants will be able to take non-prescription analgesics. Cross-over between the trial interventions is not allowed.

Follow-up procedures

Patients will complete a questionnaire consisting of disease-specific and generic patient-reported outcome measures at baseline and at 6, 12, 24, and 52 weeks after treatment start and will attend physical examination and nerve conduction testing at 52 weeks (Fig. 4). The trial coordinator (experienced research nurse) will monitor completeness of questionnaires and use telephone contact when necessary. Participants who choose to undergo surgery will be asked to complete the questionnaire shortly before surgery if the date of surgery precedes or is more than 2 weeks after the

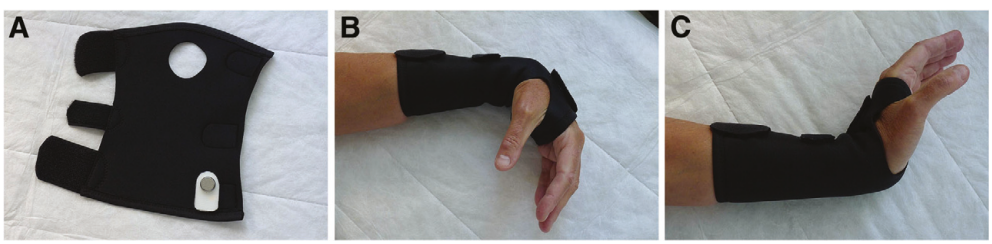

Fig. 3 Soft bandage (**a**) allowing full wrist flexion (**b**) and extension (**c**)

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	*0*	0	*6w*	*12w*	*24w*	*52w*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Demographics	X					
Allocation		X				
INTERVENTIONS:						
Splint with metal bar		←	→			
Soft bandage		←	→			
ASSESSMENTS:						
Two-point discrimination	X					X
Grip strength	X					X
Nerve conduction testing	X					X
Patient-reported outcomes measures	X		X	X	X	X
Data, temperature monitoring device			X			
Sick leave	X		X	X	X	X
Adverse events			X	X	X	X
Rate of surgery				X	X	X

Fig. 4 The schedule of enrolment, interventions, and assessments

scheduled follow-up dates. Participants will be informed, in writing and during examination/follow-up, about the importance of completing the intervention and the follow-up procedures. Patients who choose to discontinue intervention are asked to, if possible, respond to the outcome questionnaires at the intervals defined in the protocol and attend the 1-year follow-up.

Outcome measures

The CTS-6 is a validated questionnaire inquiring about severity, frequency, and duration of symptoms—including nocturnal and daytime pain and numbness or tingling—experienced by the patient in the past two weeks [17]. Each item has five possible response options, which range from 1 (no symptom) to 5 (most severe symptom). The symptom score is the mean of all answered items; higher scores (1 to 5) indicate worse symptoms. The *Quick*DASH is a short form of the disabilities of the arm, shoulder, and hand (DASH) questionnaire, a widely used outcome measure for upper extremity disorders, including CTS [18]. The *Quick*DASH consists of 11 items concerning difficulties in performing activities with five response options (from no difficulty to unable to perform an activity). Higher score (0 to 100) indicates worse activity limitations. The EuroQol 5-dimensions (EQ-5D) is a widely used measure of general health and quality of life; the EQ-5D-5 L version will be used [19]. The palmar pain scale is a two-item scale measuring pain in the palm and related activity limitations; higher score (0 to 100) indicates more pain and activity limitations [20]. Treatment satisfaction will be measured with a visual analog scale asking the patients to rate (on a scale of 0 to 100) their satisfaction with their current hand status with regard to symptoms and ability to use it in daily activities (higher score indicates higher satisfaction).

Physical examination

The physical examinations will be performed by an orthopedic specialist and will include measurement of 2-point discrimination (performed on the radial and ulnar aspects of each digit) and measuring grip strength with the Jamar dynamometer and pinch strength with the pinch gauge (three trials for each hand). The examiner will be blinded to group allocation, and at the 12-month follow-up, the palm will be covered to conceal possible surgical scars.

Nerve conduction tests

Median nerve conduction testing of the study hand will be carried out by a trained research nurse and interpreted by a neurophysiologist, both blinded to the clinical status. The measurements include median nerve distal motor latency and wrist-digit distal sensory latency in the index finger (median nerve), ring finger (median and ulnar nerves), and small finger (ulnar nerve). The results are classified as normal or as mild, moderate, or severe median neuropathy (Table 1) in accordance with standard neurophysiological criteria [21, 22].

Adherence

In written information before randomization and during all contacts with the research team, the trial participants will be informed about the importance of adhering to the allocated intervention.

Measurement of actual splint and bandage use

Both the rigid splint and the soft bandage will be fitted with a temperature-monitoring device that registers temperature variations according to whether the splint or bandage is in contact with the skin (Fig. 2). The Thermochron® iButton® device (Maxim Integrated, San Jose, CA, USA) is a small disk recording the temperature at predefined intervals and stores the results in a protected memory section. This type of temperature sensor is commonly used to monitor the cold chain of the food industry and also for pharmaceutical and medical products; a similar device has been previously used in clinical research [23, 24]. The device records temperature ranging from −40 °C to 85 °C with measurement accuracy of 1 °C. In this study, the recording intervals will be set at 40 min. After 6 weeks of splint use, the disc will be removed and the measurements will be uploaded to a computer. At the conclusion of the trial, the duration and pattern of wearing the splint will be computed and analyzed.

Surgery

The decision to choose to have surgery will be made by the patient, on the basis of the experienced severity of current symptoms and activity limitations, in consultation with an orthopedic surgeon not involved in the trial and blinded to the patient's group allocation. Surgery will be performed by specialists in orthopedics or hand surgery not involved in the trial, in accordance with usual practice at the department.

Assessments of efficacy

Primary endpoints (in rank order)

1. Change in the 6-item CTS symptoms score from baseline to 12 weeks
2. Rate of surgery at 52 weeks

Secondary endpoints

1. Change in the 6-item CTS symptoms score from baseline to 6 weeks and 52 weeks
2. Change in *Quick*DASH score from baseline to 12 weeks and 52 weeks
3. Change in patient satisfaction score at 12 weeks and 52 weeks
4. Change in EQ-5D index from baseline to 12 weeks and 52 weeks
5. Cost-effectiveness at 52 weeks
6. Palmar pain score at 52 weeks
7. Time to surgery within 52 weeks

Table 1 Classification of nerve conduction testing results

Grade	Motor latency[a]	Sensory latency[b]	
		Peak latency difference (index-small)[c]	Inter-peak latency (ring)
Normal	Normal	<0.6	Single peak
Mild	Normal	≥0.6	≥0.6
Moderate	Abnormal	>1.2	>1.0
Severe	Abnormal	Absent response	Absent response

All values are in milliseconds. A result is classified as abnormal if one or more criteria are present

[a]Distal motor latency values according to age-based reference limits. (For example, values of more than 4.2 ms for age of 30 years and of more than 4.3 ms for age of 50 years are considered abnormal.)

[b]Median-ulnar sensory latency difference

[c]Index finger peak latency values above 3.8 ms (women) and 4.0 ms (men) are considered abnormal

8. Duration of sick leave during 52 weeks
9. Change in grip strength from baseline to 52 weeks
10. Adverse events at 52 weeks

Assessment of safety

During the conduct of the trial, the investigator will report all adverse events. All adverse events will be followed up until resolved or as clinically required. Adverse events may be reported spontaneously by the patient or elicited through open questioning during and at the end of the trial. Participants will be informed to contact the trial therapists or coordinator whenever they wish to discuss or report any events during the intervention. In addition, they will be able to report adverse events at the 6-week follow-up and any subsequent follow-up. All reported or observed adverse events, including type, intensity, and duration, will be recorded in a standard protocol. Any serious adverse events will be promptly reported to the steering and data monitoring committees and the trial sponsor.

Assessment of costs

The costs of the rigid splint and soft bandage and the visits to therapist will be calculated. Cost for sick leave will be estimated by multiplying the number of days by the estimated mean income for the profession of that patient. In case of unemployment, a fixed rate will be used and for patients on maternity leave, cost will be calculated as for the working patients.

Staff information and documentation

All personnel involved with the trial will be informed orally and in writing about the trial procedures. Case report forms (CRFs) will be provided for recording of all data. Accuracy of the data on each CRF will be attested by the examiner's signature. If any assessments are omitted, the reasons will be noted on the CRFs. The patients' responses to questionnaires will be checked for completeness by the examiner or trial coordinator. All data will be stored in the department's databases accessed only by the trial researchers.

Monitoring and data management

The trial coordinator will keep all records related to randomly assigned participants at the research unit. The trial will be monitored by an independent three-member data monitoring committee (a senior orthopedic surgeon with experience in clinical research and two trained research nurses). A committee member will regularly (on a monthly basis) examine the records to ensure that the conduct of the trial and data collection is in accordance with the trial protocol. The steering committee will comprise the two on-site investigators, trial coordinator, and members of the data monitoring committee. The data management team will include the trial's principal investigator (IA), a co-investigator (KT), and a statistician (JR).

Withdrawals

Patients will be able to withdraw from the trial at any time without need to give reasons. Patients who do not wish to attend physical examination will be asked to complete the questionnaire.

Sample size

In a previous study, patients with idiopathic CTS improved on average by 1.6 points in the CTS-6 score (range of 1 to 5) at 12 weeks after surgery [20]. No previous data regarding change in CTS-6 score after use of wrist splinting or soft bandage are available. A score improvement of 0.7 corresponds to improvement by one severity level in four of the six items (i.e., from severe to moderate, moderate to mild, or mild to no symptoms, in more than half of the items). If the soft bandage is assumed to have no effect, it would correspond to "no treatment". A previous study found that the mean change in CTS-6 score in a group of patients who completed the CTS-6 on two occasions with 1–3 weeks' interval *without treatment* was 0.03 (95% confidence interval (CI) of −0.07 to 0.12) [17]. With 90% power, 5% significance level, two-sided tests, and mean changes (baseline to 12 weeks) in the CTS-6 score of 0.7 in the splint group (standard deviation of 0.9) and 0.1 in the soft-bandage group, a sample of 48 patients per group will be needed. To account for possible dropouts, we plan to recruit 112 patients.

Statistical analysis

For continuous endpoints (CTS-6, *Quick*DASH, patients satisfaction, palmar pain, EQ-5D index, grip strength, time to surgery, and sick leave duration), mean values and standard deviations will be calculated. For categorical variables (rate of surgery and adverse events), proportions will be calculated. Statistical tests will be performed in accordance with the intention-to-treat principle. An exploratory as-treated analysis will also be performed.

Both hypothesis-generating and confirmatory testing will be performed, the latter for the primary endpoints. Multiplicity issues will be addressed in compliance with the European Medicines Agency's Guideline on multiplicity issues in clinical trials. More specifically, the primary endpoints are ranked according to clinical relevance, and confirmatory claims will not be based on an endpoint with a rank lower than the variable whose null hypothesis was the first that could not be rejected. The subgroup analyses will be carried out in rank order.

Primary analyses

The change in CTS-6 score from baseline to 12 weeks (primary outcome) will be compared in the two groups by using mixed model analysis of repeated measures and adjusting for the baseline score. The rate of surgery at 52 weeks (co-primary outcome) will be compared by using Cox regression analysis with fixed follow-up time and the Huber–White estimator [25, 26] and adjusting for age, dominance of the study hand, and baseline CTS-6 score; relative risks with 95% CIs will be calculated. As supportive analysis the chi-squared test will also be performed.

Secondary analyses

Mean changes in *Quick*DASH score, EQ-5D index, and grip strength over time (from baseline to 52 weeks) will be compared by using mixed model analysis of repeated measures and adjusting for respective baseline values. Mean treatment satisfaction and palmar pain scores at 12 and 52 weeks will be compared between the groups by using the t test. Mean total duration of sick leave from treatment start to 52 weeks will be calculated and compared by using Satterthwaite's t test. Time to surgery (in days) will be analyzed by constructing Kaplan–Meier curves and comparing the groups with the log-rank test. Cost-effectiveness will be analyzed by using the incremental cost-effectiveness ratio. Three subgroup analyses will be carried out (in rank order): baseline CTS-6 score (≥3.0 versus < 3.0), baseline nerve conduction results (severe/moderate versus mild/normal), and symptom duration (≥6 versus < 6 months). Adverse events will be presented in tables. A P value of 0.05 will indicate statistical significance.

Missing values

For the patient-reported measures, missing item responses will be managed in accordance with the instructions specific to each scale. If the number of missing items precludes calculating a score, the missing score will not be replaced. Missing values for other variables will not be replaced.

Blinding

Blinding of patients to type of treatment is not possible. The primary outcome is a patient-reported outcome measure. Baseline and follow-up examinations, including nerve conduction tests, will be carried out by blinded assessors. Analysis of splint/bandage use data will be carried out by a blinded analyst. Discussions with patients about possible surgery and all possible surgical procedures will be performed by blinded surgeons. Interpretation of nerve conduction tests will be carried out by a blinded neurophysiologist. All statistical analyses will be carried out by a blinded statistician.

Ethics

The trial has been approved by the regional ethical review board (reference number: 2018/16; date: January 30, 2018). The trial will be conducted in accordance with the Declaration of Helsinki.

Recruitment strategy and timeline

Participants are recruited through referrals from primary care physicians and occupational therapists. Written information about the trial has been given (via e-mail) to all primary care units in the study region. To enhance recruitment, meetings with primary care therapists during which further information was given were held. Recruitment is expected to be completed in 2 to 3 years. If, during the trial, recruitment strengthening is deemed necessary, other strategies will be considered and discussed with the steering committee and approval from the ethical review board will be sought. No financial or non-financial incentives are provided to the trial participants (except for their contribution to the research's potential future benefit to patients with this condition).

Protocol modifications

Any important protocol modifications will first be presented to the ethical review board for approval and then communicated to relevant parties, including trial investigators, primary care physicians/occupational therapists, and involved participants.

Discussion

CTS is a very common condition affecting millions of people around the world [27]. Despite weak evidence, wrist splinting, alone or in combination with a variety of treatments, is currently the most common non-surgical treatment around the world.

A few previous studies have evaluated wrist splinting in the treatment of CTS by using the 11-item symptom severity scale (Boston CTS questionnaire), a scale that corresponds to the CTS-6, to measure symptoms [17]. A previous study that came closest to a placebo-controlled design compared two types of splints: a conventional rigid wrist splint ($n = 46$) and a soft splint ($n = 45$) that limits motion of the metacarpophalangeal joints but does not immobilize the wrist (although it is unclear whether full flexion was possible) [28]. The mean symptom severity score at baseline was 2.9 in both groups, and despite a small to moderate improvement at 3 months, the results at 9 months showed only a small mean score change (0.4 and 0.3, respectively), a difference of uncertain clinical importance.

In a study comparing steroid injection with 1-month night-time wrist splinting [29], the baseline mean symptom severity score in the splint group ($n = 25$) improved by 0.38 (standard deviation of 0.5) at 8 months (from a

relatively low mean baseline score of 2.0). In another study comparing platelet-rich plasma injection with 6-month night-time wrist splinting, the mean symptom severity scores in the splint group ($n = 60$) were 1.7 at baseline and 1.5 at 6 months [30]. In a randomized study that compared electroacupuncture with 4-month night-time wrist splinting [31], the mean symptom severity score in the splint group ($n = 91$) was 2.4 at baseline and had changed by only 0.09 at 4 months.

In a study comparing ultrasound-guided pulsed radiofrequency with 12-week night-time wrist splinting, the mean symptom severity score in the splint group ($n = 18$) improved from 3.0 at baseline to 2.0 at 12 weeks [32]. Thus, although the studies assessing wrist splinting alone have reported conflicting results, the majority have shown small changes in the symptom severity score even with splinting longer than the time used in clinical practice.

A previous study from the Netherlands suggested that surgery was more cost-effective than wrist splinting in the treatment of CTS [14]. Although it is well established that carpal tunnel release is effective in treating CTS with good long-term results [33], it has several disadvantages, including surgery-related pain and hand weakness that may last several months after surgery [34]. In addition, surgery is associated with direct costs as well as indirect costs related to work absence after surgery [35].

In the diagnosis of CTS, the history (including type and characteristics of the symptoms, their distribution in the hand, and presence or absence of other concurrent arm symptoms) is of the utmost importance. Clinical examination might be helpful but usually does not compensate when the history is not strongly indicative of CTS. Physical examination is important in establishing the presence of any exclusion criteria, such as thenar muscle atrophy and abnormal 2-point discrimination. The trial will not demand positive provocative tests (Tinel sign and Phalen test) for the diagnosis, although these will be part of the clinical examination. Two surgeons will be involved in the screening; if either judges that the history does not clearly suggest a CTS diagnosis, the patient will not be included. If the subsequent physical examination, performed by one of the surgeons, reveals the presence of any exclusion criteria, the patient will not be included. Besides, median nerve conduction tests will be performed at baseline, although inclusion will not require abnormal test results. However, baseline nerve conduction test results are important when the results of the trial are reported because they describe the characteristics of the trial participants in terms of disease severity. This trial has more stringent eligibility criteria than many previous clinical trials; this is important because an incorrect diagnosis compromises the assessment of the intervention's efficacy.

In a recent pragmatic primary care multicenter trial that compared wrist splinting with local steroid injection in CTS, the diagnosis was made by one of many different clinicians (doctors or therapists), and no nerve conduction tests were performed [36]. In the wrist-splinting group, the mean symptom severity score improved (from baseline) by 0.48 at 6 weeks and 0.73 at 6 months. The latter value is similar to the value considered a clinically important CTS-6 score change in the sample size calculation in our trial.

To our knowledge, this will be the first randomized placebo-controlled trial that evaluates the efficacy of wrist splinting in patients with CTS and the first to use an electronic monitoring device to measure time of active splint use. The evidence generated from this randomized trial can be expected to have large significance for patients and society.

Trial status

Recruitment started June 4, 2018, and is expected to conclude by the end of 2020.

Protocol version and date

This protocol is version 2.1 (dated July 31, 2019). No amendments have been made after the first patient was enrolled. Any subsequent amendment will be reported to the registry.

Dissemination

The trial results will be communicated to the participants and published in a scientific journal.

Additional file

Additional file 1: SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Checklist*. (DOC 122 kb)

Abbreviations

CI: Confidence interval; CRF: Case report form; CTS: Carpal tunnel syndrome; CTS-6: 6-item carpal tunnel syndrome symptom score; EQ-5D : EuroQol 5-dimensions; *Quick*DASH: 11-item disabilities of the arm, shoulder, and hand

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We thank research nurse Ingela Ranebo for coordinating the trial, occupational therapist Stina Brodén for designing the custom-made wrist bandage, orthotics specialist Paul Ipsen for managing the temperature-monitoring devices and software, and specialist nurse Pia Gunnarsson for performing the nerve conduction measurements. Catell AB (Hägersten, Sweden) provides the wrist splints, Aktiv Ortopedteknik (Kristianstad, Sweden) provides the custom-made soft bandages, and Mediracer Ltd. (Oulu, Finland) provides electrodes for nerve conduction tests.

Authors' contributions

IA (principal investigator) developed and planned this trial. KT and SM participated in design and planning. KT is responsible for data acquisition. IA and JR are responsible for the statistical plan. IA, KT, and JR contributed to protocol drafting. All authors read and approved the final manuscript.

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Availability of data and materials
The data will be available upon reasonable request.

Ethics approval and consent to participate
This trial was approved by the regional ethical review board (2018/16; date: January 30, 2018). All participants will provide written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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