NIPH
Norwegian Institute of Public Health

REPORT

2021

# HEALTH TECHNOLOGY ASSESSMENT:
# Surgical Treatment of Carpal Tunnel Syndrome

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| **Institution** | Norwegian Institute of Public Health (NIPH)<br>Division for Health Services |
| **Title** | Surgical Treatment of Carpal Tunnel Syndrome: A Health Technology Assessment |
| **Norwegian title** | Kirurgi ved karpaltunnelsyndrom: en fullstendig metodevurdering |
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| **ISBN** | 978-82-8406-238-9 |
| **Project number** | ID2020_022 |
| **Publication type** | Health technology assessment (Fullstendig metodevurdering) |
| **Number of pages** | 72 (123 including supplementary content) |
| **Client** | Commissioning Forum in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway |
| **Subject heading MeSH)** | Carpal Tunnel Syndrome; Median Neuropathy; Minor Surgical Procedures; Conservative Therapy; Systematic Review; Technology Assessment, Biomedical; Cost-benefit analysis. |
| **Citation** | Risstad H, Hamidi V, Espeland AL, Evensen LH, Berthelsen AL, Elvsaas IK. Surgical treatment of carpal tunnel syndrome: a health technology assessment [Kirurgi ved karpaltunnelsyndrom: en fullstendig metodevurdering] – 2021. Oslo: Norwegian Institute of Public Health, 2021. |

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# Key messages

Carpal tunnel syndrome is a compressive neuropathic disorder, leading to typical symptoms of numbness, tingling and pain in the hand. Surgical treatment with release of the transverse ligament of the wrist is an established treatment. In Norway, a geographic variation in the provision of surgery has been observed.

We conducted a health technology assessment of surgical treatment compared to non-surgical treatments with splinting, combinations of non-surgical treatments, local corticosteroid injection and physical therapy (including manual therapy). For evaluation of efficacy and safety, we included 10 randomized controlled trials. We found that:

- Surgery may slightly improve symptoms and hand function compared to splinting and combinations of non-surgical treatment in patients with mild to moderate carpal tunnel syndrome (low-certainty evidence).
- The efficacy of surgery compared to corticosteroid injection and surgery compared to manual therapy is uncertain due to very low-certainty evidence.
- No trials reported outcomes separately for subpopulations with mild, moderate or severe carpal tunnel syndrome.
- Overall, few adverse events were reported after the surgical and non-surgical treatments.
- Surgery in patients with mild to moderate carpal tunnel syndrome is the most costly treatment alternative at about Norwegian kroner (NOK) 11,200. Non-surgical treatment alternatives with splinting and local corticosteroid injection cost around NOK 3,100.
- Potential cost savings depend on the reduction of surgical procedures per health region. We estimated the potential cost savings at the national level to be between NOK 14.5 and 27.5 million over five years.

**Title**
Surgical Treatment of Carpal Tunnel Syndrome: A Health Technology Assessment

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**Publisher**
Norwegian Institute of Public Health (NIPH). Commission by the Commissioning Forum in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway.

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**Last search for studies**
December, 2020

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**Peer reviewers:**
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# Executive summary


### Background

Carpal tunnel syndrome is a clinical syndrome characterized by symptoms and signs of irritation or impairment of the median nerve at the level of the wrist. Typical symptoms are numbness, tingling and pain in the hand, sometimes also in the arm and shoulder. Although surgical treatment with release of the transverse carpal ligament is an established treatment, the relative benefits and risks compared with non-surgical treatments is unclear.

### Objective

The objective of this health technology assessment is to summarize the current knowledge on the efficacy and safety of decompression surgery for carpal tunnel syndrome compared to non-surgical treatments with wrist splinting, combinations of non-surgical treatments, local corticosteroid injection (steroid injection) and physical therapy (including manual therapy). We planned to analyse outcomes based on pre-treatment severity of carpal tunnel syndrome (mild, moderate, and severe) if reported, to evaluate whether some subpopulations seem to benefit more from surgery than others.

### Methods

We developed a project plan with input from the external experts and patient representatives. We searched for systematic reviews in the Cochrane Database of Systematic Reviews (Wiley), Epistemonikos (Epistemonikos Foundation), INAHTA (International Network of Agencies for Health Technology Assessment), MEDLINE (Ovid) and Embase (Ovid), and for randomized controlled trials (RCTs) in MEDLINE (Ovid), Embase (Ovid), and Cochrane Central (Wiley) up to December 2020. Additionally, we identified randomized controlled trials from the systematic reviews.

We included randomized controlled trials comparing surgery with the selected non-surgical treatments in individuals aged 18 years or older, regardless of other comorbidities or severity of carpal tunnel syndrome. Our primary outcomes were symptom severity including paraesthesia and pain, functional impairment, and health-related quality of life. Secondary outcomes included adverse events. Data from 6 months, 1 year, 2 years and 5 years were retrieved, and primary time point of interest was set at 1 year. Two researchers independently selected trials for inclusion and assessed risk of bias of the included randomized controlled trials according to the Cochrane Handbook for Systematic Reviews of Interventions (ROB1). One researcher extracted data, and one checked the accuracy of the data. We calculated measures of effect as mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes, and risk ratio (RR) with 95% CI for dichotomous outcomes. We

merged data into meta-analyses when possible, and we present data as forest plots if appropriate. We assessed certainty of evidence for the primary outcomes at 1 year with Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Due to great uncertainty in the estimates of the relative efficacy, we conducted a simplified assessment of economic consequences in the form of a cost analysis where the costs of the relevant non-surgical treatment alternatives in Norway, i.e., steroid injection and splinting, were estimated and compared to the costs of surgery for patients with mild to moderate carpal tunnel syndrome. In addition, we conducted a simple budget impact analysis to show possible cost savings.

**Results**

We included 10 randomized controlled trials (13 publications) with 960 patients or wrists with carpal tunnel syndrome. Mean age ranged from 41 to 53 years, and 51 to 100% of the participants were females. Seven trials excluded patients with severe carpal tunnel syndrome. All trials were at high risk of bias for at least two domains; lack of blinding of participants and assessors. Some trials had serious methodological concerns. None of the trials reported outcomes according to pre-treatment severity with mild, moderate, and severe carpal tunnel syndrome.

Three trials compared surgery with splinting. At 1 year, low-certainty evidence from one trial (downgraded for bias and imprecision) suggested a superior, but small, effect of surgery on symptom severity, daytime paraesthesia, and function. For symptoms, which was considered as the most important outcome by the patient representatives and the project's clinical experts, patients reported less severity after surgery than after splinting; the standardized mean difference between groups from the intention to treat (ITT) analyses was -0.47 (95% confidence intervals, CI -0.78 to -0.15). Notably, 38% of the patients allocated to splinting had undergone surgery at 1 year.

Three trials compared surgery with non-surgical treatments. At 1 year, low-certainty evidence from one trial (downgraded for bias and imprecision) suggested a superior, but small, effect of surgery on symptom severity and hand function, and little or no difference in effect on pain. Mean difference between groups in symptom severity was -0.33 points (95% CI -0.65 to -0.01). In this trial 44% of the patients allocated to non-surgical treatment had undergone surgery at 1 year. "As treated" analyses revealed a larger mean difference between groups; -0.84 (95% CI -0.55 to -1.13) points.

Two trials compared surgery with steroid injections and three trials compared surgery with manual therapy. We are uncertain of the efficacy of surgery compared to steroid injection and of surgery compared to manual therapy very low-certainty evidence (downgraded for bias and imprecision).

Overall, few serious adverse events were reported, but rare adverse events such as complex regional pain syndrome did occur after surgery.

The results of our economic evaluation showed that surgery is the most costly treatment at Norwegian kroner (NOK) 11,200 for treatment of patients with mild to moderate carpal tunnel syndrome. The non-surgical treatment alternatives splinting and local

steroid injection cost approximately NOK 3,100. We estimated potential cost savings at the national level to be between 14.5 and 27.5 million NOK kroner over five years.

## Discussion

Current evidence is insufficient to draw firm conclusions about the efficacy of surgery compared to non-surgical treatments. Low-certainty evidence demonstrated a superior effect of surgery compared to splinting and combinations of non-surgical treatments in patients with mild to moderate carpal tunnel syndrome, but the effect sizes were small, and the clinical relevance is therefore uncertain. An important finding from the trials was that a substantial proportion of patients allocated to non-surgical treatment had been treated with surgery at 1 year, suggesting that the patients were not satisfied with the conservative means. A planned Norwegian trial and other ongoing trials may further elucidate the relative efficacy of surgery to steroid injections. The trials of manual therapy were conducted at one single centre and other studies are needed to confirm the findings from these trials.

We have conducted a simple analysis of the costs associated with the treatments in the short term. Therefore, we have not included subsequent treatment after initial treatment. If more reliable evidence becomes available, the long-term effect of the different treatment alternatives should be evaluated in a model-based analysis.

There is moderate geographical variation in the provision of surgery for carpal tunnel syndrome in Norway. The need for surgery should be expected to be the same irrespective of geographic area. According to clinical experts, patients with mild to moderate carpal tunnel syndrome could initially have non-surgical treatments. We therefore performed a simple budget impact analysis to show possible cost-savings. However, there is uncertainty regarding this analysis. We did not have information about the distribution of disease severity in the surgically treated population in Norway and therefore we are uncertain about how many patients who could have been treated conservatively instead. This may have over- or underestimated the feasibility of the non-surgical treatments in the patient population used.

## Conclusion

Overall, low-certainty evidence suggests that decompression surgery is slightly more effective than splinting and combinations of non-surgical treatments at 1 year in patients with mild to moderate carpal tunnel syndrome. There is insufficient evidence regarding the efficacy of surgery compared to steroid injections and manual therapy. Overall, few serious adverse events were reported, but small randomized trials are not suitable to make reliable comparisons of adverse events. Surgery is the most costly treatment alternative for patients with mild to moderate carpal tunnel syndrome. An observed regional variation in the provision of surgery in Norway suggests a potential for cost-saving per health region and at the national level if patients with mild to moderate carpal tunnel syndrome are initially treated with the non-surgical alternatives.

# Hovedbudskap (Norwegian)

Karpaltunnelsyndrom er en vanlig tilstand der trange forhold for medianus-nerven i håndleddet fører til typiske symptomer som nummenhet, prikking og smerter i nervens forsyningsområde. Kirurgisk behandling med spalting av karpalligamentet er en etablert behandling. Bruk av prosedyren varierer mellom ulike opptaksområder i Norge.

Vi har utarbeidet en fullstendig metodevurdering av kirurgisk behandling sammenlignet med ikke-kirurgisk behandling med håndleddskinne, kombinasjoner av ikke-kirurgisk behandling, lokal kortikosteroid-injeksjon (steroidinjeksjon) og fysioterapi (inkludert manuellterapi). For effekt og sikkerhet inkluderte vi 10 randomiserte kontrollerte studier. Vi fant at:

- Kirurgi gir muligens bedring av symptomer og håndfunksjon sammenlignet med håndleddsskinne og kombinasjoner av ikke-kirurgisk behandling hos pasienter med mildt til moderat karpaltunnelsyndrom (lav tillit til resultatene).
- Vi er usikre på effekten av kirurgi sammenlignet med steroidinjeksjon og av kirurgi sammenlignet med manuellterapi fordi vi har svært lav tillit til resultatene.
- Ingen studier rapporterte resultater separat for subpopulasjoner med mildt, moderat og alvorlig karpaltunnelsyndrom.
- Få alvorlige komplikasjoner ble rapportert.
- Kirurgi er det mest kostbare alternativet på rundt 11 200 kroner for behandling av pasienter med mildt til moderat karpaltunnelsyndrom. Ikke-kirurgisk behandling med håndleddskinne eller steroidinjeksjon koster omtrent 3 100 kroner.
- Potensielle kostnadsbesparelser er avhengig av reduksjon i antall kirurgiske inngrep per helseregion. De potensielle kostnadsbesparelsene på nasjonalt nivå anslås til å være mellom 14,5 og 27,5 millioner kroner over fem år.

**Tittel:**
Kirurgi ved karpaltunnelsyndrom: en fullstendig metodevurdering

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**Utgiver:**
Folkehelseinstituttet utførte denne metodevurderingen på oppdrag fra Bestillerforum for Nye metoder

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**Oppdatert:**
Siste litteratursøk: Desember 2020

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Rasmus Thorkildsen, overlege i ortopedisk kirurgi, Oslo universitetssykehus

# Sammendrag (Norwegian)


**Introduksjon**

Karpaltunnelsyndrom er en tilstand hvor medianus-nerven kommer i klem i håndleddet. Typiske symptomer er nummenhet, prikking og smerte i hånden i nervens distribusjonsområde, men smerte i armen og skulderen kan også forekomme. Operasjon med spalting av karpalligamentet i håndleddet er en etablert behandling, men fordelene og ulempene av kirurgi sammenlignet med ikke-kirurgiske behandlingsmetoder er uklare.

**Mål**

Hensikten med denne metodevurderingen er å oppsummere eksisterende kunnskap om effekt og sikkerhet av operasjon for karpaltunnelsyndrom sammenlignet med ikke-kirurgisk behandling med håndledsskinne (skinne), kombinasjoner av ikke-kirurgiske tiltak, lokal kortikosteroid-injeksjon (steroidinjeksjon) og fysioterapi (inkludert manuellterapi). Vi planla å rapportere resultater basert på alvorlighet av tilstanden før behandling (mildt, moderat og alvorlig) for å undersøke om enkelte pasientpopulasjoner har mer nytte av behandlingen enn andre.

**Metode**

Vi utarbeidet en prosjektplan med innspill fra prosjektets eksterne fageksperter og pasientrepresentanter. Vi søkt etter systematiske oversikter i Cochrane Database of Systematic Reviews (Wiley), Epistemonikos (Epistemonikos Foundation), INAHTA (International Network of Agencies for Health Technology Assessment), MEDLINE (Ovid) og Embase (Ovid), og etter randomiserte kontrollerte studier i MEDLINE (Ovid), Embase (Ovid), and Cochrane Central (Wiley) fram til desember 2020. Videre identifiserte vi randomiserte kontrollerte studier fra de systematiske oversiktene.

Vi inkluderte randomiserte studier som sammenlignet kirurgi med de utvalgte ikke-kirurgiske behandlingene hos voksne pasienter (≥18 år) uavhengig av alvorlighetsgrad og tilstedeværelse av annen sykdom. Våre primære utfallsmål var symptomer inkludert parestesi (nummenhet) og smerte, funksjon og helserelatert livskvalitet. Sekundære utfallsmål inkluderte uønskede hendelser. Vi innhentet data fra 6 måneder, 1 år, 2 år og 5 år. Primært utfallsmål ble satt til 1 år. To forskere valgte ut studier for inklusjon og vurderte risiko for systematiske skjevheter ved hjelp av Cochranes *Risk of bias tool (ROB1)*. Én forsker hentet ut data og en annen kvalitetssjekket dataene. Vi kalkulerte effektmål som gjennomsnittlig forskjell (MD, *mean difference*, eller SMD, *standardized mean difference*) med 95 % konfidensintervall (KI) for kontinuerlige utfallsmål, *og risk ratio* (RR) med 95 % KI for dikotome utfallsmål. Vi sammenstilte effektdataene i metaanalyser der

det var mulig, og vi presenterte data som forest plots der vi anså det hensiktsmessig. For å vurdere tilliten til effektestimatene brukte vi *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) for hvert av de primære utfallsmålene ved 1 års oppfølging.

På grunn av stor usikkerhet rundt effektestimatene utførte vi en forenklet helseøkonomisk analyse i form av en kostnadsanalyse, hvor kostnadene knyttet til de aktuelle ikke-kirurgiske behandlingsalternativene i Norge, steroidinjeksjon og skinne, ble estimert og sammenlignet med kostnadene ved kirurgi hos pasienter med mildt til moderat karpaltunnelsyndrom. I tillegg utførte vi en forenklet budsjettkonsekvensanalyse for å belyse potensielle kostnadsbesparelser.

**Resultater**

Vi inkluderte 10 randomiserte kontrollerte studier (13 publikasjoner) med til sammen 960 pasienter eller håndledd med karpaltunnelsyndrom. Gjennomsnittlig alder i studiene var 41–53 år, og 51–100 % av deltakerne var kvinner. Syv studier ekskluderte pasienter med alvorlig karpaltunnelsyndrom. Alle studiene hadde høy risiko for systematiske skjevheter i minst to domener; mangel på blinding av deltakere og personell. Noen studier hadde alvorlige metodiske svakheter. Ingen av studiene rapporterte data basert på alvorlighet av karpaltunnelsyndrom før operasjon (mildt, moderat eller alvorlig).

Tre studier sammenlignet kirurgi med skinne. Ved ett år fant én studie at kirurgi ga større bedring i symptomer, parestesi (på dagtid) og funksjon sammenlignet med skinne (GRADE: liten tillit, nedgradert for systematisk skjevhet og presisjon). For symptomer, som var ansett som det viktigste utfallsmålet av pasientrepresentantene og av prosjektets kliniske eksperter, rapporterte gruppen som fikk kirurgi færre plager sammenlignet med gruppen som fikk skinnebehandling; gjennomsnittlig forskjell fra *intention to treat* (ITT) analysene var -0,47 (95 % KI -0,78 til -0,15) poeng på en skala fra 1–5. I denne studien hadde 38 % av pasientene som var randomisert til behandling med skinne gjennomgått kirurgi etter ett år.

Tre studier sammenlignet kirurgi med ulike kombinasjoner av ikke-kirurgisk behandling. Ved ett år fant én studie større bedring i symptomer og håndfunksjon, og liten eller ingen forskjell i smerte etter kirurgi sammenlignet med kontrollgruppen (GRADE: liten tillit, nedgradert for systematisk skjevhet og presisjon). Gjennomsnittlig forskjell mellom gruppene i symptomskår var på -0,33 (95 % KI -0,65 til -0,01) poeng på en skala fra 1–5. I denne studien hadde 47 % av pasientene som var randomisert til ikke-kirurgisk behandling gjennomgått kirurgi etter ett år. *"As treated"* analyser viste større bedring i symptomer etter kirurgi, med gjennomsnittlig forskjell i symptomskår på -0,84 (95 % KI -1,13 til -0,55) poeng.

To studier sammenlignet kirurgi med steroidinjeksjon og tre studier sammenlignet kirurgi med manuellterapi. Vi er usikre på effekten av kirurgi sammenlignet med disse behandlingene på grunn av svært liten tillit til resultatene (GRADE: svært liten tillit, nedgradert for systematisk skjevhet og presisjon).

Samlet sett ble det rapportert få alvorlige komplikasjoner, men sjeldne tilfeller som for eksempel refleksdystrofi ble observert etter kirurgi.

Resultatene fra den økonomiske evalueringen viste at kirurgi er det mest kostbare alternativet (11 200 kroner) for behandling av pasienter med mildt til moderat karpaltunnelsyndrom. De ikke-kirurgiske behandlingene skinne og steroidinjeksjon koster begge omtrent 3 100 kroner. Vi anslår potensielle kostnadsbesparelser ved å behandle flere av disse pasientene med ikke-kirurgiske alternativer til å være mellom 14,5 og 27,5 millioner kroner over fem år på nasjonalt nivå.

**Diskusjon**

Studier som sammenlignet kirurgi med skinne eller kombinasjoner av ikke-kirurgiske behandlingsmetoder viste at kirurgi var mer effektivt, men effektstørrelsene var små og den kliniske relevansen er usikker. Et viktig funn var at en betydelig andel av pasientene som ble randomisert til ikke-kirurgisk behandling hadde blitt operert etter ett år. Dette tyder på at disse pasientene var misfornøyde med den ikke-kirurgiske behandlingen. En planlagt norsk studie og andre pågående studier vil gi mer kunnskap om effekt av steroidinjeksjon sammenlignet med kirurgi. Studiene av manuellterapi var utført på ett senter og andre studier trengs for å bekrefte disse funnene.

Vi har utført en forenklet analyse av kostnadene forbundet med behandlingene på kort sikt, og har ikke inkludert kostnader for eventuell videre behandling. Dersom vi får mer pålitelig kunnskap, bør langsiktig effekt av de forskjellige behandlingsalternativene undersøkes i en modellbasert analyse.

Det er vist en moderat geografisk variasjon i omfanget av kirurgi for karpaltunnelsyndrom i Norge. Behovet for kirurgi forventes å være sammenlignbart i de ulike regionene. Ifølge prosjektets fageksperter kan pasienter med mildt til moderat karpaltunnelsyndrom i første omgang behandles med de minst invasive behandlingsmetodene. Vi har derfor utført en forenklet budsjettkonsekvensanalyse for å belyse potensielle kostnadsbesparelser på nasjonalt nivå. Det er imidlertid usikkerhet knyttet til våre analyser. Vi hadde ikke informasjon om fordeling av alvorlighetsgrad hos pasienter som behandles med kirurgi i Norge, og derfor er vi usikre på hvor mange pasienter som kunne blitt behandlet konservativt i stedet. Dette kan ha ført til en over- eller underestimering av antallet pasienter som kan være aktuelle for ikke-kirurgisk behandling.

**Konklusjon**

Samlet sett ser det ut til at kirurgi er en mer effektiv behandling enn skinne og kombinasjoner av ikke-kirurgisk behandling hos pasienter med mildt og moderat karpaltunnelsyndrom etter ett år, men effektstørrelsene er små og den kliniske relevansen usikker. Vi kan ikke si noe om effekten av kirurgi sammenlignet med lokal steroidinjeksjon og med fysioterapi, fordi vi har svært liten tillit til resultatene fra studiene som har undersøkt dette. Samlet sett ble det rapportert få alvorlige ønskede hendelser, men små randomiserte studier er ikke egnet til å evaluere dette. Kirurgi er det mest kostbare alternativet for behandling av pasienter med mildt til moderat karpaltunnelsyndrom. En regional variasjon i bruk av kirurgi i Norge tilsier at det er et potensiale for kostnadsbesparelser på nasjonalt nivå hvis pasienter i første omgang behandles med de konservative alternativene.

# Preface

The Norwegian Institute of Public Health (NIPH) has performed a health technology assessment (HTA) of decompression surgery for carpal tunnel syndrome on commission from The Ordering Forum of The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. The assignment was given in May 2020 and included efficacy and safety of surgical treatment compared to non-surgical treatments and was expanded to include a health economic evaluation in October 2020.

This report is part of a pilot project in a national program aiming to evaluate established surgical procedures in the specialist health care system in Norway. The intention of the assessment is to support sound decision making regarding to what extent certain surgical procedures should still be offered in the specialist health care, or if other treatment alternatives may be a better option for some patient groups.

**Contributors**

The internal working group from The Norwegian Institute of Public Health consisted of:

- Hilde Risstad, team leader
- Ida-Kristin Ørjasæter Elvsaas, efficacy and safety
- Line Holtet Evensen, efficacy and safety
- Annette Vogt Flatby, efficacy and safety
- Vida Hamidi, health economics
- Anna Lien Espeland, health economics
- Anne-Lise Berthelsen, literature search
- Elisabet Hafstad, literature search
- Martin Lerner, department director

A group of external experts from all the regional health authorities was appointed by The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway and consisted of:

- John Håkon Williksen, MD, senior consultant in orthopedics and hand surgery, Oslo University Hospital, South-Eastern Norway Health Authority
- Cecilie Bendiksen Wold, MD, senior consultant in ortopedics, Nordland Hospital, Northern Norway Health Authority
- Gjermund Rø, MD, PhD, senior consultant in orthopedics, St. Olavs Hospital, Central Norway Health Authority
- Magnus Hjortås, MD, senior consultant in plastic surgery, Haukeland University Hospital, Western Norway Health Authority

- Kristian Bernhard Nilsen, MD, PhD, senior consultant in clinical neurophysiology, Oslo University Hospital, South-Eastern Norway Health Authority
- Hilde Berner Hammer, MD, PhD, senior consultant in rheumatology, Diakonhjemmet Hospital, South-Eastern Norway Health Authority

We would like to thank the external experts for their valuable contribution to the project plan and report. Warm thanks also to the four patient representatives for their input to the project plan and report, for sharing their experiences with carpal tunnel syndrome and for their reflections on the treatment options. Furthermore, we want to acknowledge Ulf Sundin, postdoctoral fellow and consultant in orthopaedics at Diakonhjemmet Hospital, and Rasmus Thorkildsen, senior consultant in orthopaedics, Oslo University Hospital, for external review of the report, and Hege Kornør, Department director at NIPH, for internal review of the project plan and report. Thanks to Trond Sand, senior consultant in clinical neurophysiology and neurology, St. Olavs Hospital, and Daniel Gregor Schultze, senior consultant in clinical neurophysiology, Oslo University Hospital, for valuable input on the complex field of electrodiagnostic tests. Finally, we would like to thank Ole-Mats Moskvil, physiotherapist at Fjellgata Fysioterapi, for valuable input concerning resource use for physical therapy treatment.

**Conflict of interests**

All authors, clinical experts, patient representatives and reviewers have declared their potential conflicts of interests (Appendix 1).

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|---|---|
| Health technology assessment (HTA) on efficacy and safety commissioned | 25.05.2020 |
| Project expanded to include health economic evaluation | 26.10.2020 |
| | |
| Recruitment of clinical experts initiated | 15.06.2020 |
| Recruitment of clinical experts completed | 12.10.2020 |
| First meeting with clinical experts – initiation of the HTA | 28.10.2020 |
| Project plan sent to clinical experts | 24.12.2020 |
| | |
| First attempt to recruit user representatives | 05.10.2020 |
| First contact with patient representative | 04.01.2021 |
| Recruitment of patient representatives completed | 22.03.2021 |
| Project plan sent patient representatives | 05.01.2021 |
| Project plan approved by NIPH | 23.03.2021 |
| | |
| Report sent internal and external reviewers | 20.09.2021 |
| Report sent Commissioning Forum | 26.10.2021 |
| | |
| Time from expanded commission to completion | 365 days |
| Time from first meeting with clinical experts to completion | 363 days |

**Limitations**

The systematic review did not demonstrate which patient groups benefit the most from surgery, and due to great uncertainty in the estimates of the relative efficacy, a cost-effectiveness analysis in the form of cost per quality-adjusted life-year (QALY) analysis was not conducted. Absolute shortfall and severity were consequently not estimated.

The Norwegian Institute of Public Health is solely responsible for the content of this report.

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| Kåre Birger Hagen<br>*Director reviews and health technology assessment* | Martin Lerner<br>*Department director* | Hilde Risstad<br>*Project leader* |

# Introduction

## Description of the condition

Carpal tunnel syndrome is a complex of symptoms and signs following irritation or impairment of the median nerve at the level of the wrist, where the nerve passes through a narrow anatomical canal. Typical symptoms are numbness, tingling and pain limited to the fingers innervated by the median nerve; the thumb, index, middle and radial half of the ring finger, but paraesthesia and pain can be localized to the wrist, the whole hand, the forearm and, in some cases, in the upper arm and shoulder (1). The symptoms often worsen at night and can disturb sleep. Pain is an important symptom but is not always present. In more severe cases, persistent sensory loss and motor involvement with muscle weakness and thenar atrophy can occur (2). Both hands may be affected.

Carpal tunnel syndrome is a common condition in the adult population and a common cause of work disability. A Swedish study reported a prevalence of 3.8 percent in the general population when using clinical criteria alone, and 2.7 percent when using clinical and electrodiagnostic criteria combined (3). The prevalence has been shown higher in women than men (4). Several conditions have been associated with a higher risk of carpal tunnel syndrome, including pregnancy, obesity, hypothyroidism, diabetes, rheumatic disease, and connective tissue disorders. Injuries, infections, and surgery in the wrist area are other known risk factors. The natural history of carpal tunnel syndrome varies. Prospective studies have shown that symptoms may remain stable, worsen, or resolve spontaneously without treatment (5;6).

### Diagnosis

Carpal tunnel syndrome is a clinical diagnosis, but there are no clear diagnostic criteria. Several other conditions may present with similar symptoms and are important to rule out. Clinical examination with provocative manoeuvres, such as the Tinel test and Phalen manoeuvre are easy to apply, but the utility is limited due to low sensitivity and specificity (7).

Electrodiagnostic tests can be a useful supplementary diagnostic tool. In nerve conduction studies, the presence and extent of nerve damage can be measured by functional measurements of conduction velocity and amplitude of sensory and motor responses in the nerves. The sensitivity and specificity vary between studies (8). One explanation for

the observed variation is that the examination is performed differently and that different cut-off values are used (9). In Norway, the Norwegian Association for Clinical Neurophysiology has developed a protocol in order to standardize the procedure for nerve conduction studies (10). The role of nerve conduction studies in carpal tunnel syndrome has been discussed for several years (11). Adding such examinations to the patient history and clinical examination have proved to increase the sensitivity and specificity of the diagnosis. Additionally, the test can be used as a prognostic tool and to support the treatment choice (8). Electromyography (EMG) is sometimes used together with nerve conduction studies, primarily in patients with severe symptoms and when there is a need to exclude other conditions.

Other relevant diagnostic tools are neuromuscular ultrasound and magnetic resonance imaging (MRI) (12). MRI is rarely used as a diagnostic tool for carpal tunnel syndrome but can be used in case of suspected structural lesions in the wrist area. Neuromuscular ultrasound can be used to measure the cross-sectional area of the median nerve, and to detect other structural lesions (13;14). In carpal tunnel syndrome, the cross-sectional area of the median nerve increases proximal to the carpal tunnel (15). However, the optimal cut-off values for the cross-sectional area of the nerve in the diagnosis of carpal tunnel syndrome is uncertain, and the sensitivity and specificity of diagnostic ultrasound differ across studies.

### Severity of carpal tunnel syndrome

Carpal tunnel syndrome is often classified by severity. Table 1 shows clinical grading of severity based on UpToDate (16), with minor modifications made in collaboration with the project's clinical experts. Findings from nerve conduction studies is also often used to classify severity (17;18).

***Table 1**. Clinical severity grading of carpal tunnel syndrome modified from UpToDate (16)*

| Severity | Clinical symptoms |
|---|---|
| Mild | Numbness, tingling or discomfort in the hand and/or arm. Symptoms occur occasionally. No sensory loss or weakness. Normal hand function. Nocturnal symptoms may be present. |
| Moderate | Numbness, tingling or discomfort in the hand and/or arm. Sensory loss and/or pain may slightly influence hand function, but the patient is able to sustain daily activities. Nocturnal symptoms are common. |
| Severe | Numbness, tingling or discomfort in the hand and/or arm. Sensory loss, weakness or thenar atrophy. Hand function is deteriorated, nocturnal symptoms disrupt sleep. Pain may be severe but may also be absent. |

## Description of the intervention

In surgical treatment, the transverse ligament of the wrist is transected to reduce pressure on the median nerve. The procedure can be performed open or endoscopic. According to the project's clinical experts, open surgery under local anaesthesia is most common in Norway. Complications after decompression surgery include swelling, hematoma, infection, nerve injury, wrist stiffness, hypertrophic scarring, pain, and complex regional pain syndrome. In a large cohort from England, 0.08 percent of patients had complications requiring hospital admission within 90 days after surgery (19).

A wide range of non-surgical treatments have been proposed, including systemic steroid treatment, diuretics, non-steroidal anti-inflammatory drugs, laser, acupuncture, massage, weight reduction, cognitive therapy, and yoga (20). Most of these interventions have little or no evidence of efficacy. In this review, we focus on splinting, local corticosteroid injection (steroid injection), combinations of non-surgical treatments and physical therapy (including manual therapy). Splinting is an established treatment particularly in patients with mild to moderate carpal tunnel syndrome (21;22). Splinting creates immobility of the wrist joint by a custom made or prefabricated device that is worn over the wrist. Steroid injection is also an established treatment (21). Corticosteroids, sometimes with the addition of local anaesthetic, are injected close to the median nerve in the wrist. The project's clinical expert who is providing treatment with steroid injections does the procedure with the aid of ultrasound-guidance. Physical therapy (including manual therapy) is occasionally attempted for the treatment of carpal tunnel syndrome (21).

According to the project's clinical experts, a rehabilitation period with sick leave from a few days up to four weeks is common after surgery. Sick leave is not routinely prescribed after steroid injection and other non-surgical options. However, the symptoms of carpal tunnel syndrome may interfere with work ability and lead to work absence.

In studies evaluating the effectiveness of treatments for carpal tunnel syndrome, a wide range of outcome measurements have been reported. The Boston Carpal Tunnel Questionnaire (BCTQ) is a patient-reported outcome measure that has been developed specifically for patients with carpal tunnel syndrome (23). It has two distinct scales, the Symptom Severity scale containing 8 items, and the Functional Status Scale containing 5 items, both ranging from 1–5, where a higher score indicates more impairment. The BCTQ has undergone extensive testing for validity, reliability and responsiveness (24). A minimum difference of 0.8–1.05 points has been suggested as clinically important difference for the Symptom Status Score, and 0.5–1.13 for the Functional Status Score (24;25).

## Why is it important to do this health technology assessment?

Carpal tunnel syndrome is a common condition that has substantial quality of life implications for the patients and economic implications for the health care system. In 2017, around 7,500 patients had surgery for carpal tunnel syndrome in Norway (26). A regional variation in the provision of surgery has been shown. The proportion of patients

having surgery was 2.5 times higher in some regions than others in 2017. The need for surgery is expected to be the same irrespective of geographic region. Possible explanations for the variation may be differences in referral practice, differences in the access to surgery, or differences in access to non-surgical treatment.

The Ordering Forum of The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway commissioned an evaluation of the efficacy and safety of surgical treatment compared to non-surgical treatments for carpal tunnel syndrome. This is part of a pilot project where established surgical procedures will be assessed to ensure that there is sufficient evidence of efficacy, and to evaluate whether some patient groups may benefit more from the treatment than others.

## Objectives

The objective was to evaluate the efficacy and safety of surgical treatment of carpal tunnel syndrome compared to non-surgical treatments with splinting, combinations of non-surgical treatments, steroid injection, and physical therapy (including manual therapy). Moreover, we have conducted a cost analysis and a simple budget impact analysis.

In more detail, we have sought evidence to answer the following research questions:

- How effective is decompression surgery compared to non-surgical treatment to relieve symptoms, improve hand function and health-related quality of life (HRQoL)?
- How is the safety profile, and the results from nerve conduction studies after surgery compared to the non-surgical treatments?
- Do subpopulations with mild, moderate or severe carpal tunnel syndrome benefit more from surgery than non-surgical treatments?
- What are the economic consequences of the different treatment alternatives?

We developed a project plan with input from the external experts and patient representatives. The project plan was written in Norwegian with an English summary and was published at the Norwegian Institute of Public Health (NIPH) web pages (27) and the International HTA Database (INAHTA Database) (28) prior to the initiation of this report.

# Methods - efficacy and safety

## Inclusion criteria

We used the following inclusion criteria:

| | |
|---|---|
| **Study design** | 1. Systematic reviews (moderate or high quality)<br>2. Randomized controlled trials |
| **Population** | Adults (≥18 years) diagnosed with carpal tunnel syndrome, regardless of diagnostic criteria and whether the diagnosis was confirmed with electrodiagnostic testing.<br><br>We planned to present results from subpopulations with mild, moderate, and severe carpal tunnel syndrome if reported, regardless of methods used to categorize severity. |
| **Intervention** | Surgical release of carpal tunnel syndrome (all types of open and endoscopic procedures) |
| **Comparison** | Non-surgical treatment:<br>• Splinting (all types of wrist immobilisation)<br>• Combinations of non-surgical interventions (two or more interventions combined)<br>• Local corticosteroid injection (one or more injections, all dose regimens)<br>• Physical therapy (including manual therapy) |
| | Time points for outcome measurement:<br>• 6 months (>3 months and <9 months)<br>• 1 year (≥9 months and <18 months)<br>• 2 years (≥18 months and <36 months)<br>• 5 years (≥48 months and <72 months)<br>The primary time point was set at 1 year.<br><br>Primary end points:<br>• Patient-reported symptom severity. If outcomes from several questionnaires were reported, we used the most commonly applied and validated instruments. We included assessments of paraesthesia or pain as separate outcomes.<br>• Patient-reported hand function. If outcomes from several questionnaires were reported, we used the most commonly applied and validated instruments. |

| | |
|---|---|
| | • Health-related quality of life (generic instruments such as Short Form-36, SF-12, EQ-5D etc., and condition-specific instruments)<br><br>Secondary end points:<br>• Proportion of patients with "treatment success", as defined by the authors (for example patients considered to have clinically relevant improvement)<br>• Adverse events (including death, hospitalizations, all types of surgical and medical complications and unwanted effects as reported in the trials)<br>• Surgery (primary procedure in patients allocated to non-surgical treatment and secondary procedure in patients allocated to decompression surgery)<br>• Results from nerve conduction studies<br>• Work status |
| **Publication year** | Systematic reviews: January 2015 and later<br>Randomized controlled trials: January 2016 and later |
| **Country/context** | No restrictions |
| **Language** | We limited study languages to Norwegian, English, German, French, Danish and Swedish. |

### Exclusion criteria

We excluded trials that compared surgical procedures or techniques.

## Literature search

### Database search

An information specialist (Anne-Lise Berthelsen) prepared the search strategy in accordance with the project plan. The literature search was performed in a two-step process. First, we searched for systematic reviews. We restricted the search to systematic reviews published in 2015 or later to ensure that we identified the most updated reviews. We performed searches in the Cochrane Database of Systematic Reviews (Wiley), Epistemonikos (Epistemonikos Foundation), INAHTA (International Network of Agencies for Health Technology Assessment), MEDLINE (Ovid) and Embase (Ovid). Moreover, we searched for relevant health technology assessments on the websites of Canadian Agency for Drugs and Technologies in Health (CADTH), National Institute for Health and Care Excellence (NICE) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU).

Our next step was to search for primary studies, covering the time frame from the most current search date in identified systematic reviews until December 2020. Therefore, we searched for randomized controlled trials (RCTs) published between January 1, 2016 and December 18, 2020. These searches were performed in MEDLINE (Ovid), Embase (Ovid), and Cochrane Central (Wiley).

Customized search strategies for each database were used and combined MESH terms and text words for carpal tunnel syndrome and surgical procedures. In MEDLINE and Embase we used filters for the specific study designs (29;30). The detailed search strategies are documented in Appendix 2. Information specialist Elisabet Hafstad reviewed the search strategy. The results were imported to the reference tool EndNote after removal of duplicates in Ovid (Medline and Embase). Further duplicates were removed in EndNote (31).

### Search in other sources

We searched for ongoing studies in NIH Clinical Trials and WHO international Clinical trials Registry Platform (ICTRP) (Appendix 2).

## Study selection

Two researchers (Hilde Risstad and Line Evensen) independently reviewed abstracts and full-text articles in two steps; first systematic reviews and then RCTs. Disagreements were resolved by discussion. We used the Covidence software in the study selection process (32).

## Quality assessment and assessment of risk of bias

Three researchers (Hilde Risstad, Line Evensen and Ida-Kristin Ø. Elvsaas) assessed the quality of systematic reviews deemed potentially relevant for inclusion. We used a 9-point checklist for systematic reviews from our methodology handbook (33). Disagreements were resolved by discussion. If the systematic reviews were not considered medium or high quality, they were only used to identify RCTs published before January 2016.

Two researchers (Hilde Risstad and Line Evensen) independently assessed risk of bias of the included RCTs according to the Cochrane Handbook for Systematic Reviews of Interventions (RoB1) (34). We used the Review Manager version 5.4.1 (REVMan 5) software (35). The following methodological domains were evaluated: a) sequence generation, b) allocation concealment, c) blinding of participants, d) blinding of outcome assessment, e) incomplete outcome data, f) selective reporting, g) other potential sources of bias. Each item was judged as “low risk”, “unclear risk”, or “high risk” of bias. The assessments were performed on study level. If there were more than one publication from a study, we assessed the main publication. Disagreements were resolved by discussion or consulting a third researcher (Ida-Kristin Ø. Elvsaas).

## Data extraction

One researcher (Hilde Risstad) extracted data from the included trials and a second researcher (Line Evensen or Annette Vogt Flatby) checked the accuracy of the data. Data was extracted to Excel after pilot testing. We extracted the first author’s last name, publication year, interventions, duration of follow-up and outcomes as specified in the study protocol. When additional data or clarifications were needed, we attempted to

contact the corresponding authors of the included trials. Additionally, we extracted a comprehensive summary of each included study, i.e., study characteristics including publication year, setting, country, study design, inclusion period, timing of outcome assessments, study registration, interventions, number of participants, patient characteristics including age, sex, severity of carpal tunnel syndrome, eligibility criteria, statistical analyses used, power calculations, patient follow-up, and outcome data.

We used the following a priori defined decision rules to select data from trials:

- When outcome data were analysed based on the intention to treat (ITT) principle and other principles such as per protocol analyses, we extracted ITT-analysed data.
- Where final values and change from baseline values were reported for the same outcome, we extracted the final values.

For nerve conduction assessments, many outcomes were reported. We consulted our clinical experts and decided to extract data on sensory conduction velocity, distal sensory latency, and distal motor latency.

## Analyses

We compiled results from included trials in meta-analyses where possible. That is, the trials had to be sufficiently homogeneous in terms of study design, participants, intervention, comparison, and outcome measures.

### Effect estimates

We performed meta-analyses using the REVMan 5 software. For continuous outcomes, such as patient-reported symptom severity, we expressed the results as mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI). For dichotomous outcomes, such as treatment success, we calculated relative risk (RR) with 95% CI. We presented data as forest plots if possible, even if meta-analyses could not pe performed. As we could not expect populations, interventions, and outcomes to be identical in the included trials, we used the random effect model in the analyses. Generally, this gives somewhat wider confidence intervals compared to the fixed effect model. We calculated $I^2$ to assess statistical heterogeneity between trials. A high value ($I^2$ >50–60) indicates substantial heterogeneity between trials and affects our confidence in the overall results (36).

We did not assess risk of publication bias by visual inspection of funnel plots as outlined in the protocol, because few trials were included for each comparison. Hence, the power is probably too low to distinguish chance from real asymmetry (37).

## Grading the certainty of evidence

To assess certainty of evidence we used the GRADE-approach (Grading of Recommendations Assessment, Development and Evaluation) (38) and the software GRADEpro (39). GRADE assessment is a structured way to consider key factors that may increase

or decrease our confidence in the synthesized findings. Although the quality of evidence represents a continuum, it is categorized as described below in GRADE:

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

Certainty of evidence was assessed for the primary outcomes at 1 year: symptom severity, function, paraesthesia, and pain. Two researchers (Hilde Risstad and Line Evensen) independently assessed certainty of evidence using the five GRADE considerations; risk of bias, inconsistency, imprecision, indirectness, and publication bias. Disagreements were resolved through discussion and by consulting a third researcher (Ida-Kristin Ø. Elvsaas). We created summary of findings tables using the GRADEpro software.

## Patient involvement

The patient perspective was considered important in this reassessment project. We strived to recruit patient representatives in line with the NIPH's routines. First, we searched for patient organizations, but we did not identify any relevant organizations for patients with carpal tunnel syndrome. Next, we contacted central patient committees or patient councils at hospitals treating carpal tunnel syndrome, but we still failed. Finally, we requested the clinical experts to assist with recruitment of patients. The patients received oral and written information about the project before we asked if they were willing participate as patient representatives.

Four patients (two women and two men) were recruited to the project, of whom three had bilateral carpal tunnel syndrome. Three patients had undergone decompression surgery and one patient had been treated with steroid injection. Two of the patients had previously been treated with splinting and exercises, and all of them had been treated with some type of oral medication (non-steroid anti-inflammatory drugs, paracetamol, prednisolone).

We organized individual digital meetings with each patient representative between January 2021 and March 2021. The meetings were arranged as interviews with questions from a survey for patient involvement from Health Technology Assessment International (HTAi) (40) and translated into Norwegian by NIPH. The patients' experiences with carpal tunnel syndrome, including impact on quality of life and their surroundings

or relatives, experiences with different types of treatments, and their personal reflections on surgical and non-surgical treatments were elucidated. All patients were given the opportunity to comment on the project plan and the report. The patients considered symptoms as the most important outcome. As a result of this discussion, we added pain and paraesthesia as separate primary outcomes in addition to overall assessment of symptom severity.

## Other considerations/assessments

Ethical, organizational, and legal aspects were not part of the commission and are therefore not included in this review.

# Results – efficacy and safety

## Literature search and selection of studies

We performed the literature search in a two-step process, where we first searched for systematic reviews and then for primary studies. We identified 531 publications in the search for systematic reviews. After removal of duplicates, we screened 356 publications (Figure 1). Sixteen systematic reviews were reviewed in full text. Four systematic reviews, including 69 primary studies, were considered possibly relevant and quality assessed. In the search for RCTs, we identified 938 publications and screened 678 publications after removal of duplicates (Figure 1). In total, we assessed 23 primary studies in full text, identified from the search for systematic reviews and RCTs. Finally, we included 13 publications from 10 studies. Excluded publications reviewed in full text are listed in Appendix 3, Table 1.

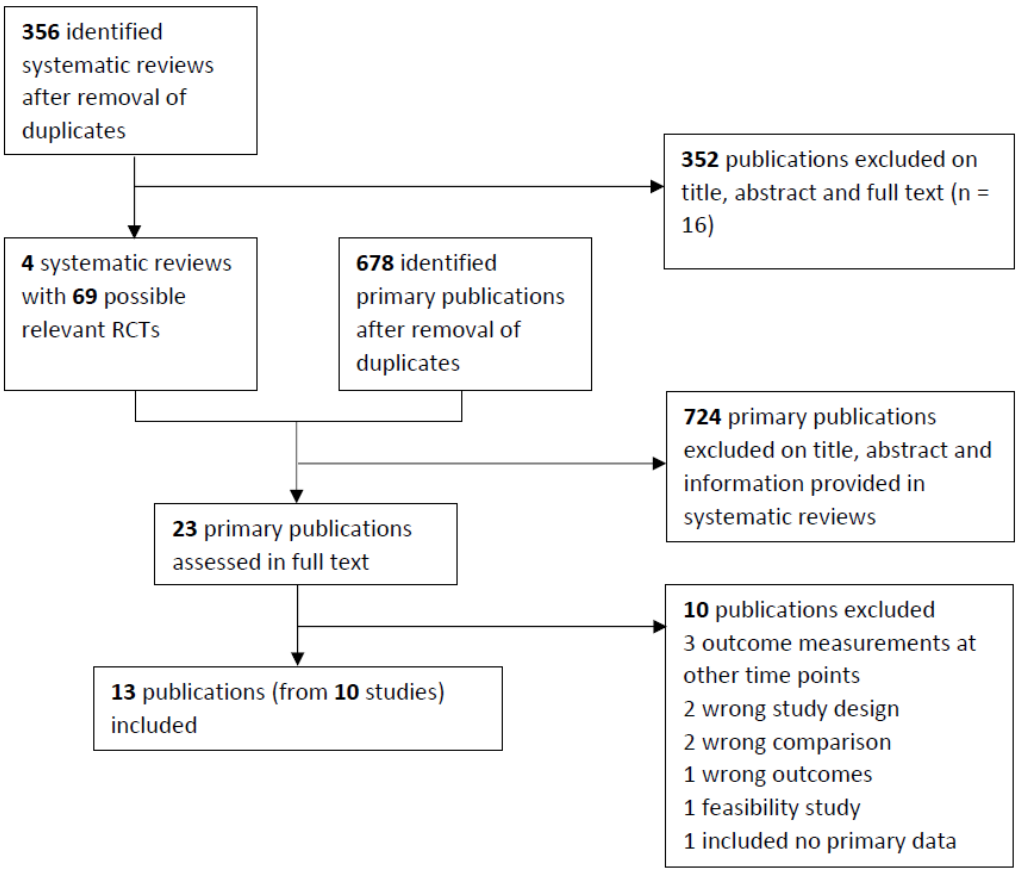


***Figure 1**. Flow-chart of study selection*

We assessed the quality of the four systematic reviews considered possibly relevant. A summary of the checklist is shown in Table 2. We judged the overall quality of the systematic reviews to be of low quality. Consequently, we conducted a systematic review of primary studies as outlined in the project plan. Included primary studies that were identified from the systematic reviews are shown in Appendix 4, Table 1.

***Table 2**. Quality assessment of potential relevant systematic reviews*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Overall quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Shi 2020 (41) | Yes | Yes | Yes | Yes | Yes | Partial | Yes | No | No | **Low** |
| Huisstede 2018 (42) | Yes | Partial | Yes | Yes | Partial | No | Yes | No | No | **Low** |
| Klokkari 2018 (43) | Yes | No | Yes | Partial | Yes | Yes | No | No | No | **Low** |
| D'Angelo 2015 (44) | Yes | Partial | Yes | Yes | Partial | Partial | Partial | No | No | **Low** |

*1) Do the authors clearly describe the methods used to identify the primary studies? 2) Was the literature search performed satisfactorily? 3) Do the authors describe the criteria used to determine study inclusion (study design, participants, interventions, outcomes)? 4) Was bias avoided in the selection of studies? (explicit selection criteria, independent assessments by several people) 5) Are criteria for assessing internal validity clearly described? 6) Is the internal validity for all studies referred to in the text assessed with relevant criteria? 7) Are methods used to summarize results clearly described? 8) Are the results from the studies summarized properly considering the purpose of the overview? 9) Are the authors' conclusions supported by data and analyses described or reported in the review? 10) How do you rate the overall quality of the review?*

## Description of included studies

We included 10 RCTs (13 publications) (Table 3). The trials included between 22 and 176 patients or wrists. In one trial (Jarvik et al.), the gender distribution was balanced (53% women) (45), while in the other trials, participants were predominantly women (81-100%) (46-54). In three trials (four publications), all by Fernández-de-las-Peñas et al., all patients were women (46;48-50). Diagnosis was made based on clinical judgement supplied with electrodiagnostic testing in all trials. Pathological findings on electrodiagnostic testing were an inclusion criterion in all trials except from one (De Kleermaeker et al.), where normal findings on electrodiagnostic testing was an inclusion criterion (47). All trials, except from the trials comparing surgery with manual therapy (Fernández-de-las-Peñas et al.) (48;50), excluded patients with severe carpal tunnel syndrome or thenar atrophy. Symptom duration before inclusion was around 1 year in four trials (Gerritsen et al., de Kleermaeker et al., Ucan et al., Hui et al.) (47;52-54), 3 years in five trials (Jarvik et al., Ly-Pen et al. and the trials by Fernández-de-las-Peñas et al.) (45;48-51), and from 1 month to 20 years in one trial (Garland et al.) (46).

Duration of follow-up was from 6 months to 4 years. None of the trials were double blinded, and none included placebo surgery. Three trials (Gerritsen et al., Garland et al., Ucan et al.) compared decompression surgery with wrist splinting (46;53;54). Three trials (Jarvik et al., De Kleermaeker et al., Ucan et al.) compared decompression surgery with combinations of non-surgical treatment (45;47;53). Two trials (Ly-Pen et al., Ucan et al.) compared decompression surgery with steroid injection (51;52), and three trials (all by Fernández-de-las-Peñas et al.) compared decompression surgery with manual therapy (48-50). One trial (Hui et al.) had three study arms and compared surgery with i) splinting, and ii) splinting and steroid injection. The last study arm was compared to surgery and analysed in the "combinations of non-surgical treatments" group. In two trials (Ly-Pen et al., Ucan et al.), wrists, not patients, were allocated to treatment (51;53). Table 4 gives an overview of the outcomes of interest in this review that were reported in each of the included trials. For a more detailed description of each included trial, see Appendix 5, Table 1.

***Table 3****. Brief description of included trials (N=10)*

| **Study author Country** | **Non-surgical study arm(s)** | **Outcomes**[a] i. **Primary** ii. **Secondary** | **Partici-pants (surgery + non-surgical treat-ment)** | **Follow-up** |
|---|---|---|---|---|
| **Surgery vs. splinting** | | | | |
| Gerritsen 2002 (54) Netherlands | Wrist splinting | i. Symptom severity, function<br>ii. Success rate, adverse events, surgery[b], results from nerve conduction studies | 87 + 89 | 6 m<br>12 m<br>18 m[c] |
| Garland 1964 England (46) | Wrist splinting | ii. Successful outcome, adverse events | 22 | 6 m |
| Ucan 2006[d] (53) Turkey | Wrist splinting | i. Symptom severity and function<br>ii. Adverse events, nerve conduction tests | 11 + 23 | 6 m |
| **Surgery vs. combinations of non-surgical treatment** | | | | |
| Jarvik 2009 (45) United States of America | NSAIDS, hand ther-apy, wrist splinting, therapeutic ultra-sound | i. Symptom severity, function, pain, HRQoL<br>ii. Successful outcome, adverse events, surgery[b], work status | 57 + 59 | 6 m<br>1 year |

| | | | | |
|---|---|---|---|---|
| De Kleermaeker 2017 (47) Netherlands | Steroid injection or nocturnal wrist splint | i. Symptom severity, function<br>ii. Adverse events | 39 + 18 | 6 m |
| Ucan 2006[d,e] (53) Turkey | Splinting + steroid injection | i. Symptom severity, function<br>ii. Adverse events, nerve conduction tests | 11 + 23 | 6 m |
| **Surgery vs. local steroid injection** | | | | |
| Ly-Pen 2005 [e] +2012 Andreu 2014 (51;55;56) Spain | Steroid injection, with a second dose after 2 weeks if deemed necessary | i. Paresthesia, pain, hand function<br>ii. Adverse events, surgery[b] | 80 + 83[e] | 6 m<br>1 year<br>2 years |
| Hui 2005 (52) | 1 steroid injection | i. Symptom severity<br>ii. Adverse events, nerve conduction studies | 25 + 25 | 20 weeks |
| **Surgery vs. manual therapy** | | | | |
| Fernández-de-las-Peñas 2017 (50) Spain | Manual therapy for 3 weeks + home exercises | i. Symptom severity, function<br>ii. Adverse events, surgery[b] | 50 + 50 | 6 m<br>1 year |
| Fernández-de-las-Peñas 2017 (49) Spain | Manual therapy for 3 weeks + home exercises for 1 month | i. Pain<br>ii. Adverse events, surgery[b] | 50 + 50 | 6 m<br>1 year |
| Fernández-de-las-Peñas 2015 + 2020 (48;57) Spain | Manual therapy for 3 weeks + home exercises | i. Symptom severity, function, pain<br>ii. Adverse events, surgery[b] | 60 + 60 | 6 m<br>1 year<br>4 years |

*Abbreviations: NSAIDS, non-steroidal anti-inflammatory drugs; HRQOL, health-related quality of life; m, months*

[a]*Primary and secondary outcomes as defined in this review, not in the primary study. The primary studies may also include other endpoints than reported here.*

[b]*Surgery refers to patients allocated to non-surgical treatments who received surgery during the study period, or patients allocated to surgery who received a second surgical procedure during the study period.*

[c]*Analysed as 2-year data according to our inclusion criteria*

[d]*The trial had two control groups: i) splinting, ii) splinting + steroid injection*

[e]*Hands, and not patients, were allocated to treatment*

***Table 4**. Primary and secondary outcomes reported in the included trials*

| | Symptoms | Function | Paraesthesia | Pain | HRQoL | Treatment success | Adverse events | Surgery | Nerve conduction tests | Work status |
|---|---|---|---|---|---|---|---|---|---|---|
| De Kleermaeker 2017 | x | x | - | - | - | - | - | - | - | - |
| Fernández-de-las-Peñas 2017 (pain) | | | | x | - | - | x | x | - | - |
| Fernández-de-las-Peñas 2017 (function) | x | x | - | x | - | - | x | x | - | - |
| Fernández-de-las-Peñas 2015 + 2020 | x | x | - | - | - | x | x | x | - | - |
| Garland 1964 | - | - | - | - | - | - | x | x | - | - |
| Gerritsen 2002 | x | x | x | - | - | - | x | x | x | - |
| Hui 2005 | x | - | - | - | - | - | x | - | x | - |
| Jarvik 2009 | x | x | - | x | x | x | x | x | - | x |
| Ly-Pen 2005 + 2012 + 2014 | - | x | x | x | - | - | x | x | x | - |
| Ucan 2006 | x | x | - | - | - | - | x | - | x | - |

*Abbreviations: HRQoL, health-related quality of life. Surgery refers to patients allocated to non-surgical treatment who had surgery, and patients who were allocated to surgery who had a second procedure.*

### Excluded studies

We excluded 10 primary studies after full text review. A table of the excluded studies and the reason for exclusion is provided in Appendix 3, Table 1.

### Ongoing studies

We screened 347 publications in our search for ongoing studies after removal of duplicates. Twelve were assessed in more detail, whereof 5 were ongoing RCTs comparing surgery with non-surgical treatments. A brief description of each trial is given in Appendix 6, Table 1. All trials compared surgery with steroid injection. All trials were small, except from one trial from The Netherlands which aims to include 940 patients and will report outcomes up to 18 months after the intervention. The trial was initiated in 2021 and is currently recruiting patients.

## Risk of bias in included trials

A summary of the risk of bias-assessment for each included trial is presented in Figure 2, and details by domain is provided in the Characteristics of included studies (Appendix 5, Table 1–10). We judged two of the trials (Gerritsen et al., Jarvik et al.) as having

no serious risk of bias except from lack of blinding (45;48-50;54). In the three trials by Fernández-de-las-Peñas, no patients eligible for study inclusion accepted to participate. This seems unlikely in a clinical setting and rises question about the recruitment process. Three of the trials (De Kleermaeker et al., Garland et al., Ucan et al.) had serious methodological concerns (46;47;53). Hui et al. had possible concerns with the allocation concealment that was insufficiently described, and with possible selective reporting due to lack of study registration (52). Ly-Pen et al. had concerns with incomplete outcome data and possible selective reporting due to lack of study registration (51).

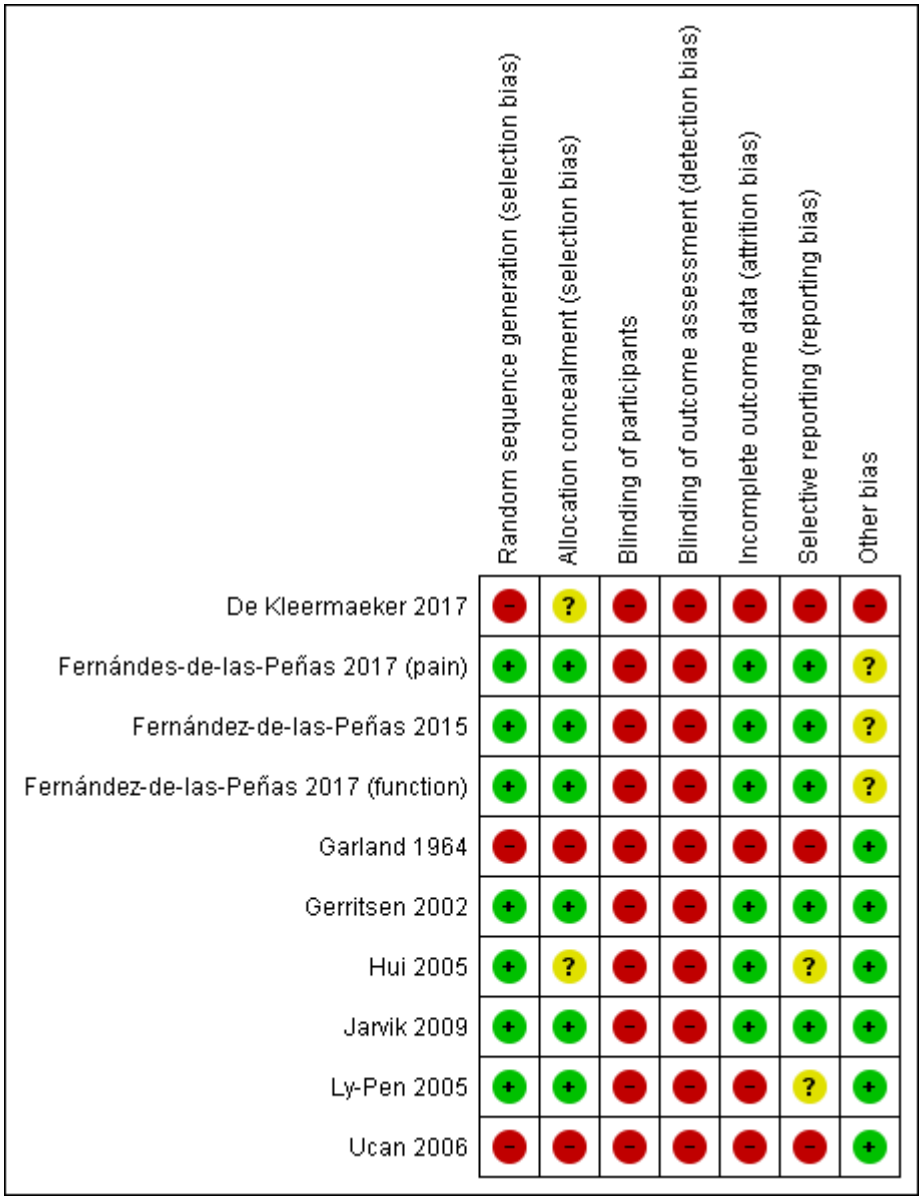


***Figure 2**. Risk of bias assessment by domain for the included trials*

## Efficacy of interventions

### Surgery versus splinting

A multicenter trial (Gerritsen et al.) reported data comparing surgery with splinting at 6 months, 1 year and 18 months (54). Data from 18 months were analysed as 2-year

data as defined in the protocol. A 3-armed trial (Ucan et al.) compared surgery with splinting at 6 months (53). A study from 1964 (Garland et al). presented data from 6 months (46), but no data from this study could be included in meta-analyses or forest plots.

***Symptoms reported at 6 months, 1 year and 2 years***

Symptoms were evaluated with the symptom severity scale of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) (23) in two trials (Gerritsen et al, Ucan et al.). Scores range from 1–5, where a higher score indicates more severe symptoms. Gerritsen et al. reported mean values of change from baseline, while Ucan et al. reported mean values at 6 months.

Low-certainty evidence from one trial (Gerritsen et al.) indicated that surgery may slightly improve symptom severity at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 1).

At 6 months, the standardized mean difference between groups was -0.48 (95% CI -0.77 to 0.20) points in favour of surgery (Figure 3). At 1 and 2 years, the standardized mean difference between groups was -0.47 (95% CI -0.78 to –0.15) points and -0.47 (95% CI -0.79 to -0.14) points, respectively.

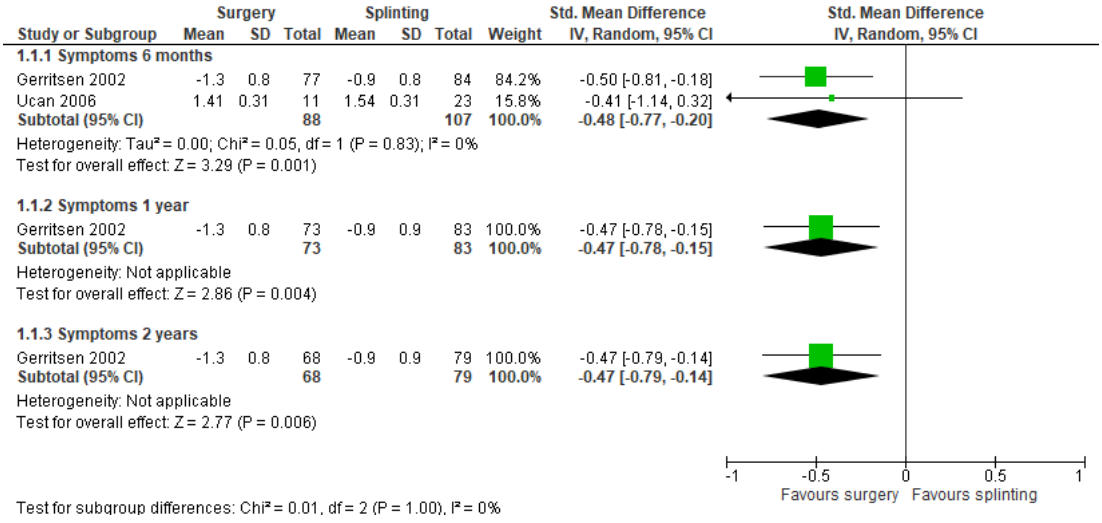


***Figure 3****. Symptom severity comparing surgery with splinting at 6 months, 1 year, and 2 years*

*Outcomes are from the symptom severity scale of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) and represent standardized mean difference of mean score (Ucan et al.) or mean change score from baseline (Gerritsen et al.). Data from 18 months (Gerritsen et al.) are analysed as 2-year data as defined in the protocol.*

*Abbreviations: SD, standard deviation; CI, confidence intervals*

***Paraesthesia reported at 6 months, 1 year and 2 years***

Paraesthesia was reported by Gerritsen et al. as perceived daytime and night-time paraesthesia measured on a scale ranging from 0–10, where a higher score indicates more severe paraesthesia. The outcomes were reported as mean change values from baseline.

Low-certainty evidence from one trial (Gerritsen et al.), indicated that surgery may slightly improve daytime paraesthesia at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 1).

At 6 months, daytime paraesthesia was reduced by mean (SD) 5.5 (2.9) points after surgery and 3.7 (3.2) points after splinting, difference in mean change score between groups was -1.80 (95% CI -2.74 to -0.86) points in favour of surgery (Figure 4). At 1 and 2 years, the mean between group change was -1.50 (95% CI -2.49 to -0.51) points and -1.30 (95% CI -2.37 to -0.23) points, respectively.

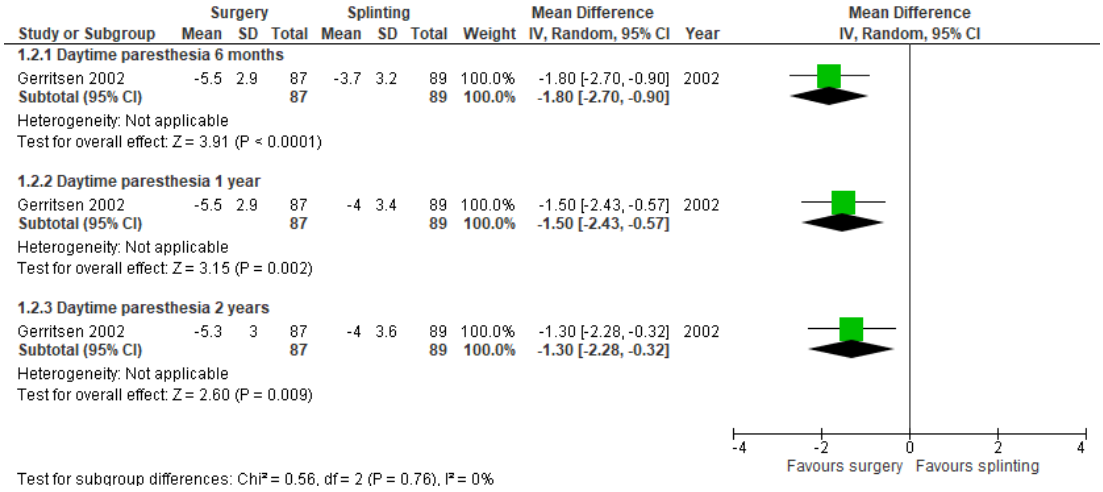


***Figure 4****. Daytime paraesthesia comparing surgery and splinting at 6 months, 1 year, and 2 years*
*Outcomes are change score from baseline on a symptom scale ranging from 0–10. Data from 18 months (Gerritsen et al.) are analysed as 2-year data as defined in the protocol. Abbreviations: SD, standard deviation; CI, confidence intervals*

Low-certainty evidence from one trial (Gerritsen et al.) indicated that surgery may make little or no difference to night-time paraesthesia compared to splinting at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 1).

At 6 months, the mean (SD) night-time paraesthesia was reduced by 5.4 (3.5) points after surgery and 4.1 (3.7) points after splinting, mean between group change was -1.30 (95% CI -2.41 to -0.19) points (Figure 5). At 1 year and 2 years, the mean between group change was -0.40 (95% CI -0.67 to -0.13) and -0.40 (95% CI -0.67 to -0.13) points, respectively.

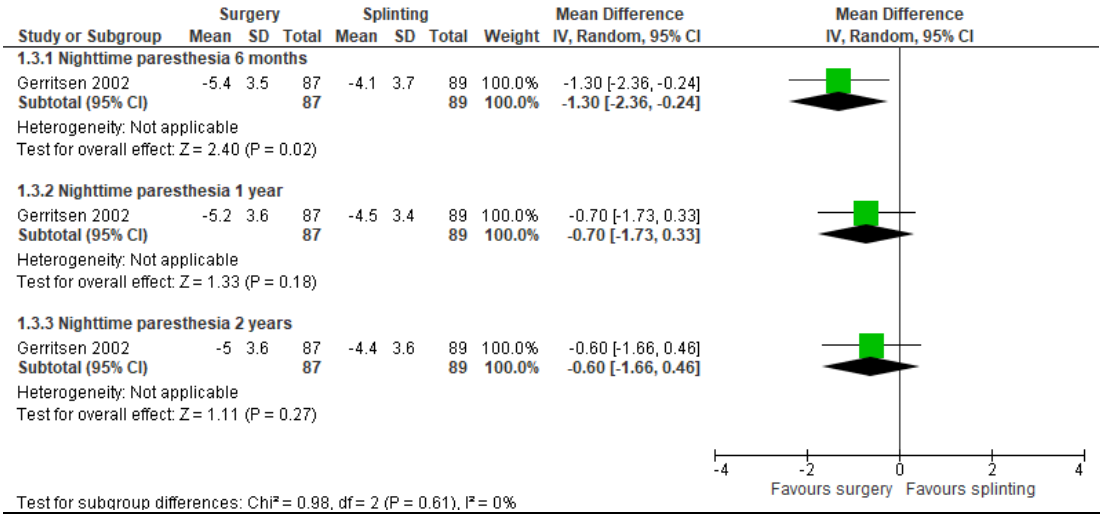


***Figure 5**. Night-time paraesthesia comparing surgery and splinting at 6 months, 1 year, and 2 years*
*Outcomes are change score from baseline on a symptom scale ranging from 0–10. Data from 18 months (Gerritsen et al.) are analysed as 2-year data as defined in the protocol. Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Function reported at 6 months, 1 year and 2 years*

Gerritsen et al. and Ucan et al. both evaluated function with the function scale of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) (23). Scores range from 1–5, where a higher score indicates more functional impairment.

Low-certainty evidence from one trial (Gerritsen et al.) indicated that surgery may slightly improve function at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 1).

At 6 months, the standardized mean difference between groups was -0.61 (95% CI -0.89 to -0.33) points in favour of surgery (Figure 6). At 1 and 2 years, the mean difference between groups was -0.35 (95% CI -0.65 to -0.05) points and -0.23 (95% CI -0.53 to 0.06) points, respectively.

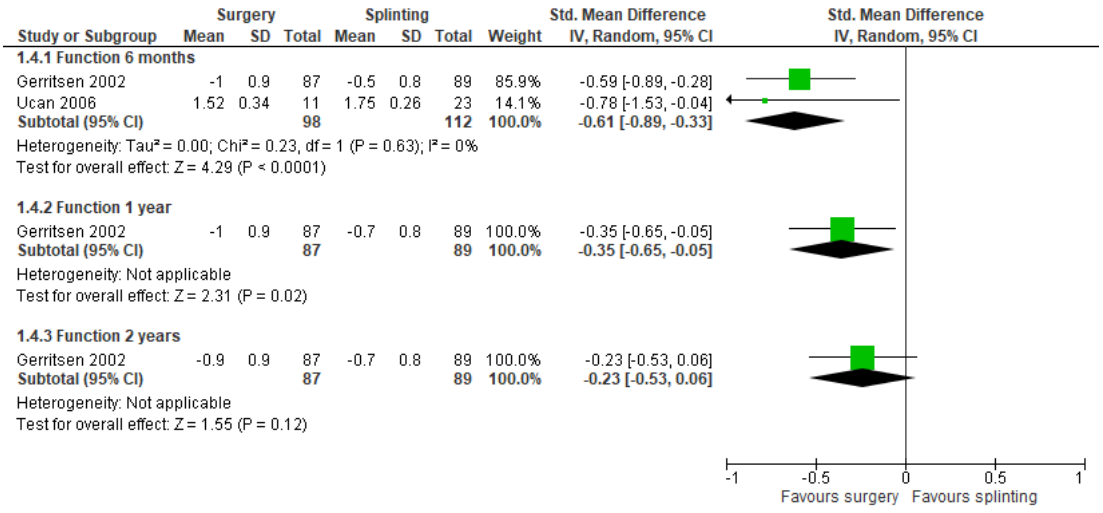


***Figure 6**. Reported function comparing surgery with splinting at 6 months, 1 year, and 2 years*

*Outcomes are from the function scale of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) and represent standardized mean difference of mean score (Ucan et al.) or mean change score from baseline (Gerritsen et al). Data from 18 months (Gerritsen et al.) are analysed as 2-year data as defined in the protocol.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Treatment success reported at 6 months, 1 year and 2 years*

Gerritsen et al. reported patient-perceived general improvement on a 6-point scale, ranging from "completely recovered" to "much worse" (58). Treatment success was defined as "completely recovered or "much improved". At 6 months 72 (94%) patients in the surgery group and 57 (68%) patients in the splinting group were considered as being treated successfully; RR 1.38 (95% 1.18 to 1.61) (Figure 7). At 1 year, 67 (92%) patients in the surgery group and 60 (83%) patients in the control group were considered as being treated successfully; RR 1.27 (95% CI 1.09 to 1.47). At 2 years, the corresponding numbers were 61 (90%) and 59 (75%), respectively; RR 1.20 (95% CI 1.03 to 1.40). Garland et al. reported treatment success narratively as judged by the surgeon/author and reported that all surgical patients were treated successfully. Narrative data from the control group was incompletely reported.

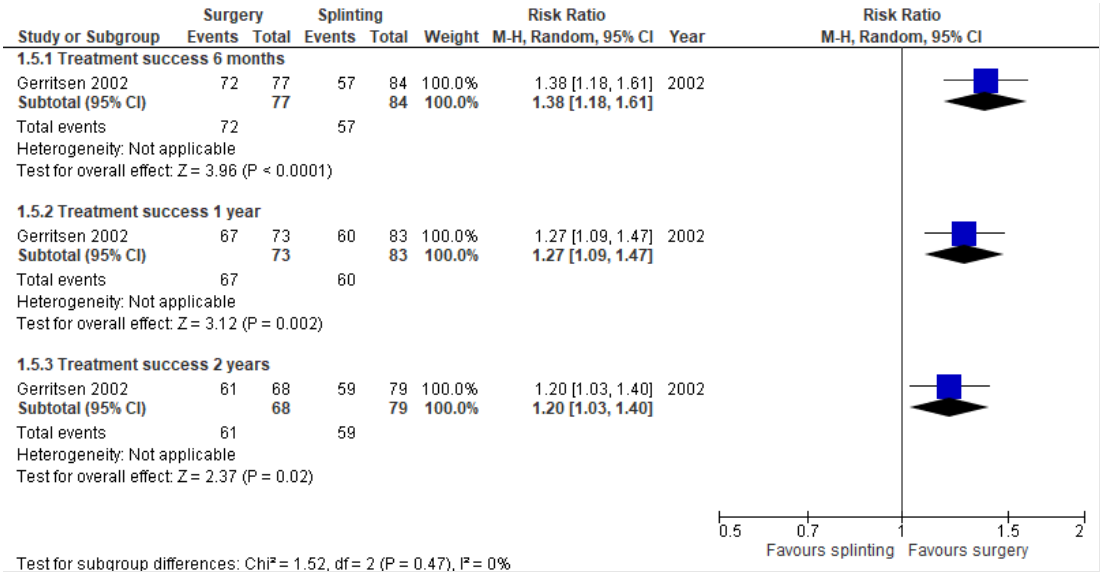


***Figure 7****. Treatment success comparing surgery and splinting at 6 months, 1 year and 2 years*
*Number of events represents successful outcome. Data from 18 months (Gerrtsen et al.) are analysed as 2-year data as defined in the protocol.*
*Abbreviations: CI, confidence intervals*

### *Adverse events*

Gerritsen et al. recorded adverse events regardless of severity, and results at 18 months were presented in a table. The total number of adverse events during follow-up in the surgery group was 58 (85%) and in the splinting group 46 (58%), RR 1.46 (95% CI 1.19 to 1.81) (Figure 8). The most common adverse event after surgery was painful or hypertrophic scarring, while the most common adverse event after splinting was stiffness of the wrist, hand, or fingers. There was 1 patient with complex regional pain syndrome after surgery. Ucan et al. reported complications in 2 (18%) patients in the

surgery group; one patient with complex regional pain syndrome and one patient with scar tenderness. Garland et al. reported "no surgical failures".

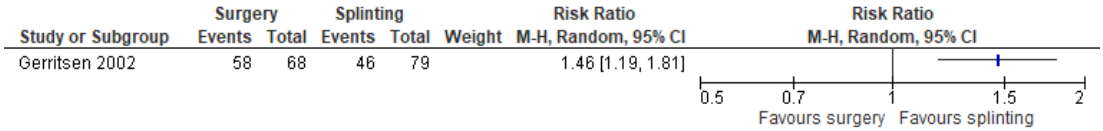


***Figure 8**. Adverse events comparing surgery and splinting*
*Data from 18 months (Gerritsen et al.) are analysed as 2-year data as defined in the protocol.*
*Abbreviations: CI, confidence intervals*

### *New surgical procedure or surgery after non-surgical treatment*

In Gerritsen et al., patients allocated to splinting were evaluated by a neurologist 6 weeks after initiation of treatment, and the need for other treatments including surgery was discussed with the patients. The decision to undergo surgery could also be made later at any stage. Of patients allocated to splinting, 31% had surgery at 6 months, 39% at 1 year and 41% at 18 months. One patient allocated to surgery had complex regional pain syndrome and underwent a second surgical procedure. In Garland et al., 8 patients allocated to the non-surgical group had undergone surgery at 6 months, but the total number of patients allocated to splinting was unclear.

### *Nerve conduction assessments*

Two trials reported outcomes from nerve conduction assessments. Ucan et al. reported sensory conduction velocity and distal motor latency at 6 months, and Gerritsen et al. reported change in distal sensory latency and distal motor latency at 1 year. Higher latency indicates more severe nerve impairment.

At 6 months, the mean (SD) sensory conduction velocity was 39.6 (2.5) milliseconds (ms) after surgery and 37.8 (4.7) after splinting. Mean difference between groups was 1.8 (95% CI -0.62 to 4.22) ms (Figure 9).

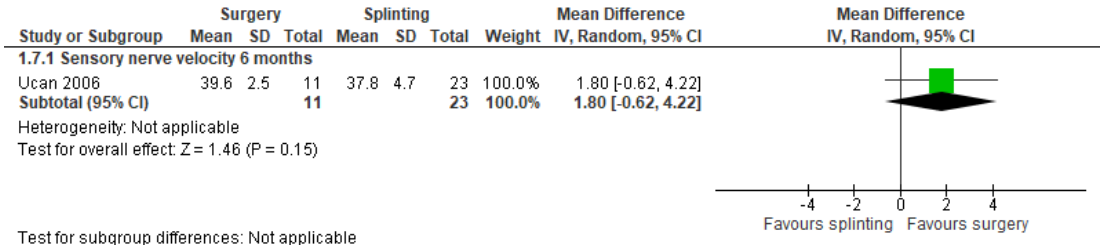


***Figure 9**. Sensory nerve velocity measured in milliseconds from nerve conduction examination comparing surgery with splinting at 6 months*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

Gerritsen et al. reported change in distal sensory latency at 1 year. The mean (SD) reduction was 1.1 (1.2) ms after surgery and 0.7 (1.2) ms after splinting. Difference in mean change between groups was 0.4 (95% CI -0.08 to 0.88) ms (Figure 10).

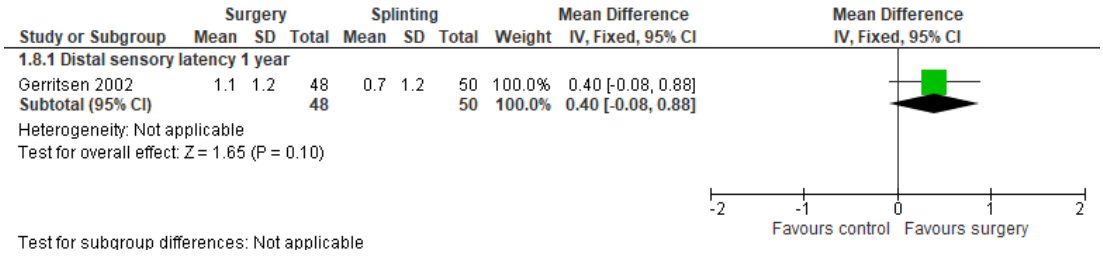


***Figure 10**. Change in distal sensory latency measured in milliseconds from nerve conduction examination comparing surgery with splinting at 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

At 6 months, Ucan et al. reported distal motor latency of mean (SD) 3.57 (0.35) ms after surgery and 3.72 (0.40) ms after splinting. Mean difference between groups was 0.15 (95% CI -0.41 to 0.11) ms (Figure 11). At 1 year, Gerritsen et al. reported change in distal motor latency from baseline. The reduction was mean (SD) 1.3 (1.5) ms after surgery and 1.0 (1.5) ms after splinting. Difference in mean change between groups was 0.3 (95% CI -0.21 to 0.81) ms (Figure 12).

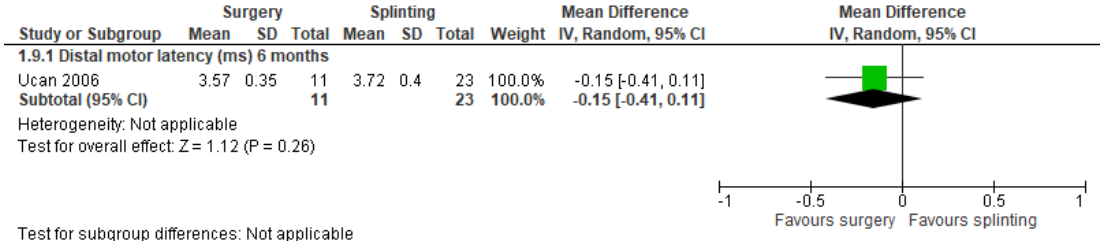


***Figure 11**. Distal motor latency measured in milliseconds from nerve conduction examination comparing surgery with splinting at 6 months*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

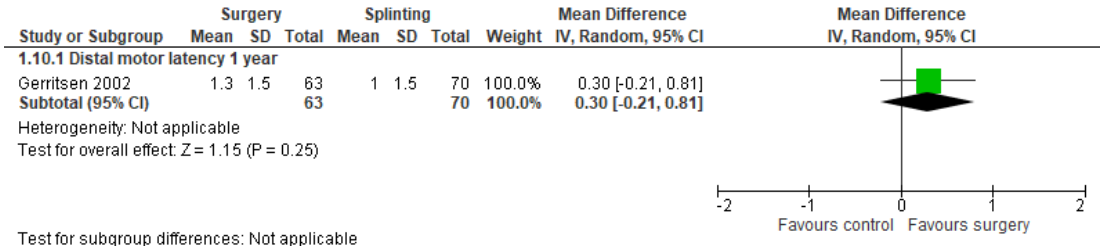


***Figure 12**. Distal motor latency measured in milliseconds from nerve conduction examination comparing surgery with splinting at 1 year*
*Data are change values from baseline.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Other outcomes*

Outcomes regarding pain, health-related quality of life (HRQoL) and work status were not reported in any of the trials. None of the trials reported results from subpopulations with mild, moderate, or severe carpal tunnel syndrome.

## Surgery versus combinations of non-surgical treatments

Three trials compared surgery with various combinations of non-surgical treatments (Jarvik et al., De Kleermaeker et al., Ucan et al.) (45;47;53). Jarvik et al. compared surgery with non-steroidal anti-inflammatory drugs (NSAIDs), hand therapy and splinting in a multicenter trial, and reported data from 6 months and 1 year (45). In this trial, 23 (44%) of the patients allocated to non-surgical treatment had received surgery at 1 year (the publication is unclear about these data; thus, the correct number is retrieved after personal communication with the author). We therefore decided to report "as treated" analyses from this trial in addition to the ITT analyses, even though it was not predefined in the protocol. De Kleermaeker et al. explored outcome of surgery in patients with *normal* nerve conduction studies, in contrast to the other included in this review (47). The control group received local steroid injection, splinting or no treatment. They reported data from 6 months. A 3-armed trial by Ucan et al. compared surgery with i) splinting and ii) splinting and steroid injection combined and reported data from 6 months (53). Data from surgery versus splinting and steroid injection combined were included in this comparison. In this trial, some of the outcomes were presented in figures. We attempted to retrieve the data by contacting the author, but we did not receive any response.

### *Symptom severity reported at 6 months and 1 year*

Three trials (Jarvik et al., De Kleermaeker et al., Ucan et al.) reported on symptom severity at 6 months (45;47;53), and Jarvik et al. reported on symptom severity at 1 year (45). The tool used to measure symptoms was the symptom severity scale of the Boston Carpal Tunnel Syndrome Questionnaire (BTCQ) (23). The score ranges from 1–5, where a higher score indicates more severe symptoms.

At 1 year, low-certainty evidence suggests that surgery may slightly improve symptom severity compared to combinations of non-surgical treatments at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 2).

At 6 months, the mean difference between groups was -0.54 (95% CI -0.76 to -0.32) points in favour of surgery (Figure 13). At 1 year, the mean difference between groups was -0.33 (95% CI -0.65 to -0.01) points. The "as treated" analyses from Jarvik et al. at 1 year showed larger difference in score between groups; -0.84 (95% CI -1.13 to -0.55) points (Figure 14).

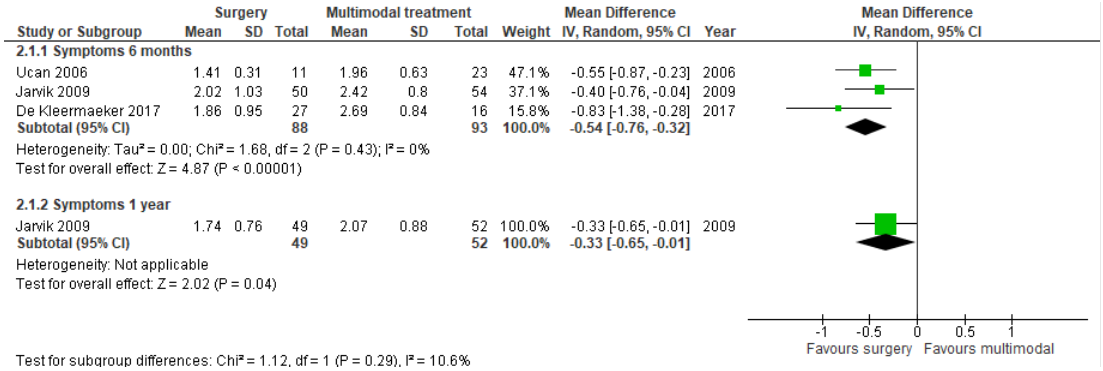


***Figure 13**. Reported symptom severity comparing surgery with combinations of non-surgical treatment from intention to treat analyses at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

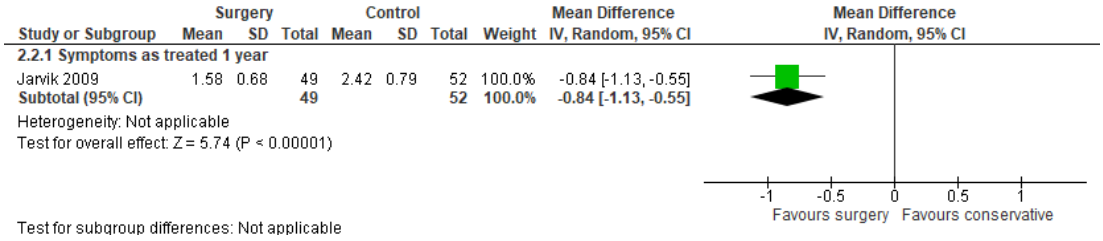


***Figure 14**. Reported symptom severity comparing surgery with combinations of non-surgical treatment from "as treated" analyses at 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Pain at 6 months and 1 year*

Jarvik et al. reported pain at 6 months and 1 year (45). The tool used was a visual analogue scale (VAS) from 0–10, where a higher score indicates more pain.

At 1 year, low-certainty evidence suggests that surgery may make little or no difference on pain compared to combinations of non-surgical treatments at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 2). The difference between groups were -1.00 (95% CI -2.21 to -0.21) points at 6 months and -0.80 (-2.03 to 0.43) points at 1 year (Figure 15).

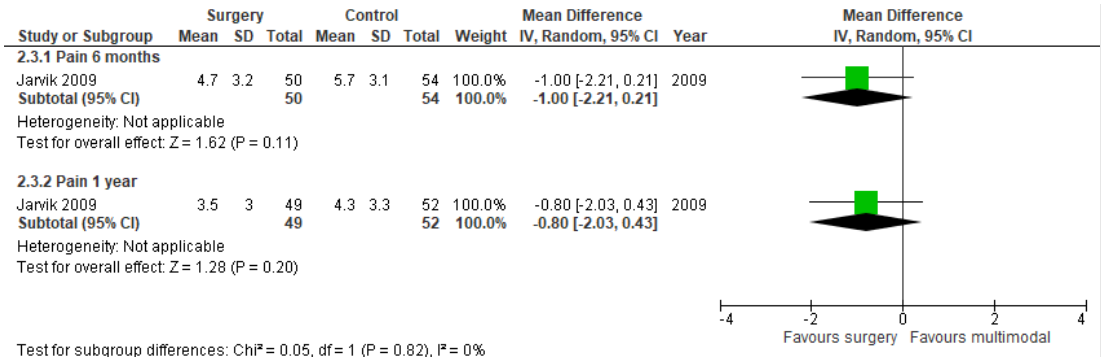


***Figure 15**. Reported pain comparing surgery with combinations of non-surgical treatments at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Function reported at 6 months and 1 year*

Function was reported by Jarvik et al. and De Kleermaeker et al. at 6 months (45;47) and by Jarvik et al. at 1 year (45). The tool used to measure function was the function score from the Boston Carpal Tunnel Syndrome Questionnaire (BTCQ) (23). Scores range from 1–5, where a higher score indicates more severe impairment.

At 1 year, low-certainty evidence suggests that surgery may slightly improve function compared to combinations of non-surgical treatments at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 2).

At 6 months, the mean difference between groups was -0.35 (95% CI -0.62 to -0.09) points in favour of surgery (Figure 16). At 1 year, the mean difference between groups was -0.43 (95% CI -0.77 to -0.09) points. "As treated" analyses showed a larger mean difference between groups; -0.67 (95% CI -1.01 to -0.33) points (Figure 17).

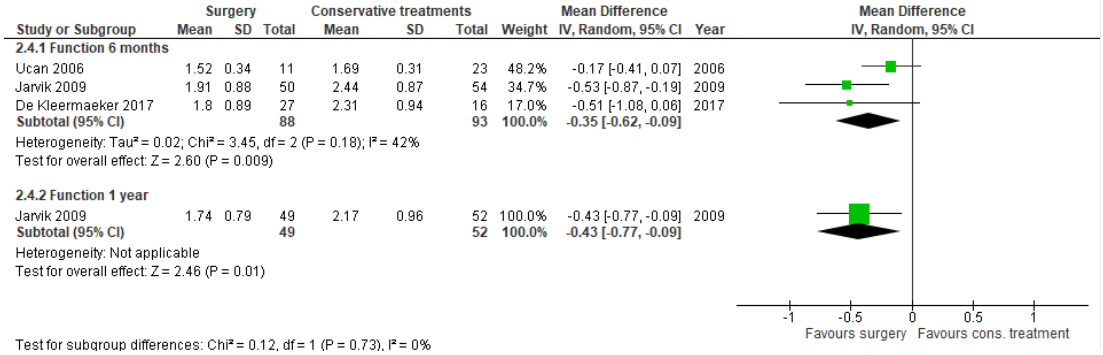


***Figure 16****. Function comparing surgery with combinations of non-surgical treatments from intention to treat analyses at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

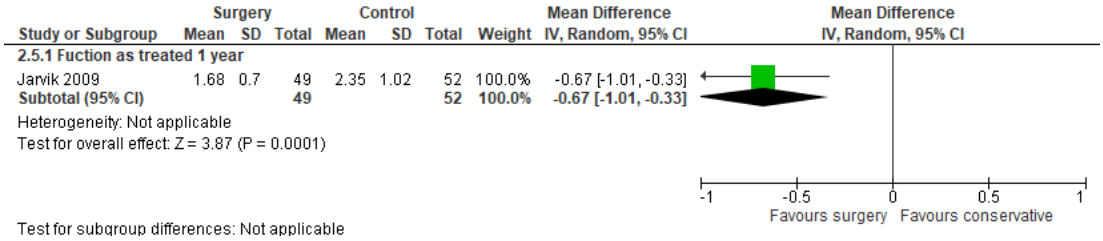


***Figure 17****. Function comparing surgery with combinations of non-surgical treatments from "as treated" analyses at 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Health-related quality of life*

Jarvik et al. reported data on HRQoL at 6 months and 1 year (45). The tool used was Short-Form 36, and data were presented as physical and mental summary score. Scores range from 0–100, where a higher score indicate more impaired HRQoL.

Low-certainty evidence suggests that surgery may make little or no difference on HRQoL compared to combinations of non-surgical treatments at 1 year. Certainty of evidence was downgraded one level for risk of bias and one level for imprecision (Appendix 7, Table 2).

As shown in Figure 18, there was no difference between groups in any of the domains.

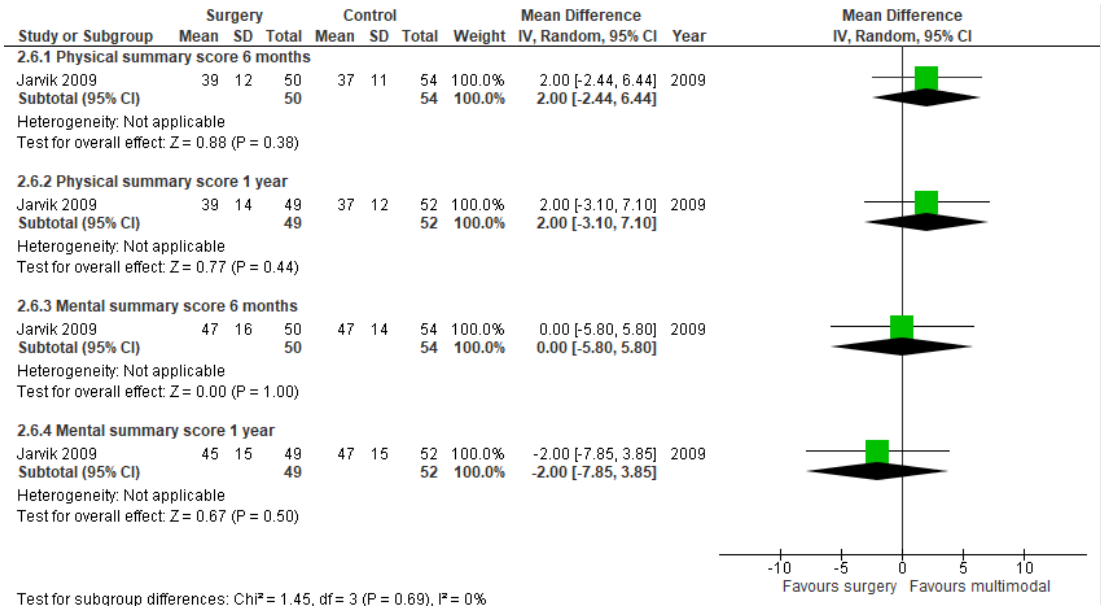


***Figure 18**. Generic health-related quality of life comparing surgery with combinations of non-surgical treatments at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Treatment success at 6 months and 1 year*

Jarvik et al. reported on treatment success (45). Treatment success was defined according to specific scores on three different questionnaires measuring functional outcomes, symptoms and pain interference with work and housework. At 6 months, 17 (34%) patients in the surgery group and 9 (17%) patients in the control group were considered as being treated successfully; RR 2.04 (95% CI 1.00 to 4.15) (Figure 19). At 1 year, 22 (46%) patients in the surgery group and 14 (27%) patients in the control group were considered as being treated successfully; RR 1.67 (95% CI 0.97 to 2.88). From the "as treated" analyses at 6 months, 16 (32%) patients were considered as being treated successfully in the surgery group and 10 (19%) in the control group; RR 1.73 (95% CI 0.87 to 3.45), and at 1 year the numbers were 29 (59%) and 5 (10%); RR 6.16 (95% CI 2.59 to 14.62) (Figure 20).

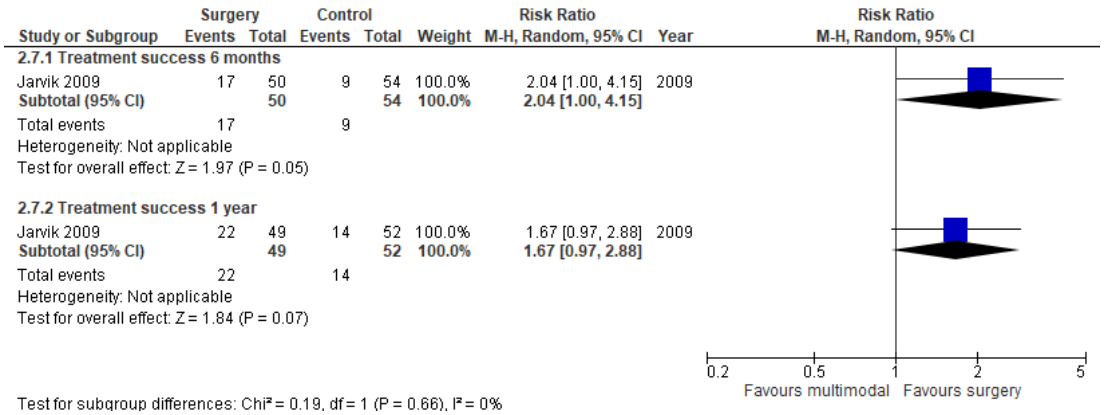


***Figure 19**. Proportion of patients with successful outcome comparing surgery with combinations of non-surgical treatment from intention to treat analyses at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

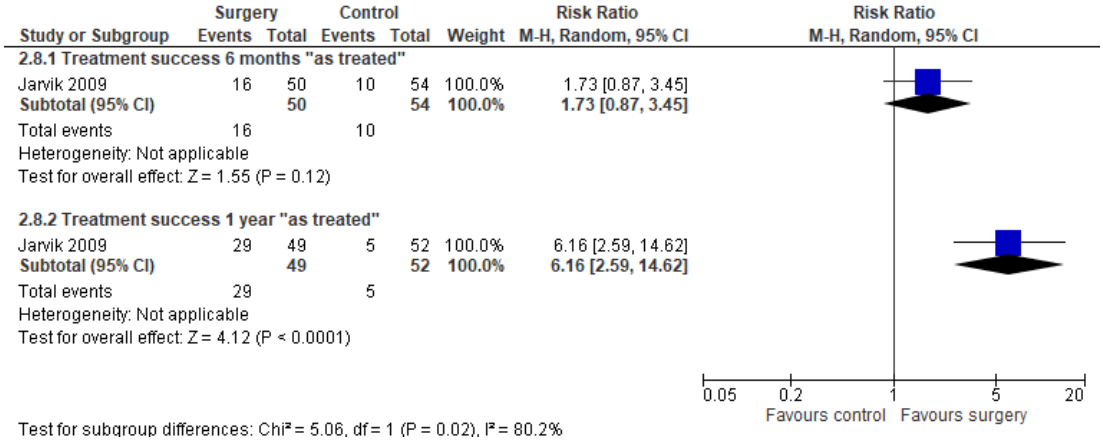


***Figure 20**. Proportion of patients with successful outcome comparing surgery with combinations of non-surgical treatment from "as treated" analyses at 6 months and 1 year Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Adverse events at 6 months and 1 year*

Three trials presented data on adverse events; De Kleermaeker et al. and Ucan et al. at 6 months (47;53) and Jarvik et al. at 1 year (45). De Kleermaeker et al. reported one patient having complex regional pain syndrome. However, it is unclear whether information on adverse events was registered systematically. Ucan et al. observed adverse events in 2 wrists (18%) in the surgery group; 1 wrist with complex regional pain syndrome and 1 wrist with scar tenderness that resolved spontaneously shortly after surgery. No complications were reported in the control group. Jarvik et al. reported no surgical complications and no clinically important adverse events in any of the groups at 1 year.

### *New surgical procedure or surgery after non-surgical treatment*

Jarvik et al. reported data on patients allocated to non-surgical treatment who had surgery. At 1 year, 23 (44%) patients allocated to non-surgical treatment had been treated with surgery. No patients who were allocated to surgery had a second procedure at 1 year.

### *Work status at 6 months and 1 year*

Jarvik et al. reported days of lost work during the past month. At 6 months, mean difference between groups was -2.10 (95% CI -4.57 to 0.37) days (Figure 21). At 1 year, the mean difference between groups was -1.50 (95% CI -3.09 to 0.09) days.

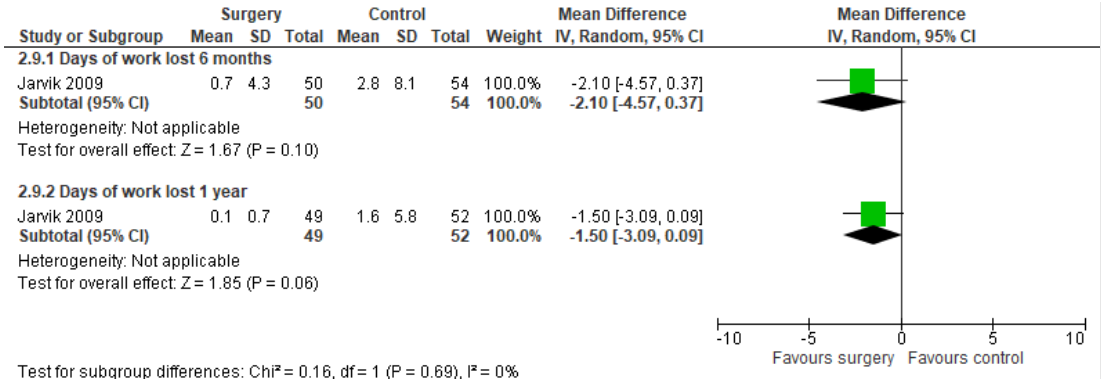


***Figure 21**. Days of work lost during the last month comparing surgery with combinations of non-surgical treatments at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Nerve conduction assessments*

Ucan et al. reported sensory conduction velocity and distal motor latency from nerve conduction assessments at 6 months. A lower velocity and a higher latency may indicate more severe nerve impairment. Sensory conduction velocity was mean (SD) 39.6 (2.5) ms in the surgery group and 36.3 (6.8) ms in the control group. Mean difference between groups was 3.30 (95% CI 0.15 to 6.45) ms (Figure 22).

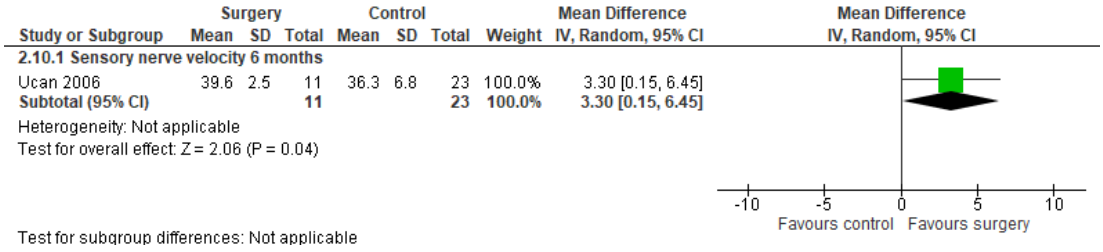


***Figure 22**. Sensory conduction velocity measured in milliseconds from nerve conduction assessment comparing surgery with splinting at 6 months*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

Mean (SD) distal motor latency was 3.6 (0.4) ms in the surgery group and 3.7 (0.5) ms in the control group. The mean difference between groups was -0.15 (95% CI -0.44 to 0.14) ms (Figure 23).

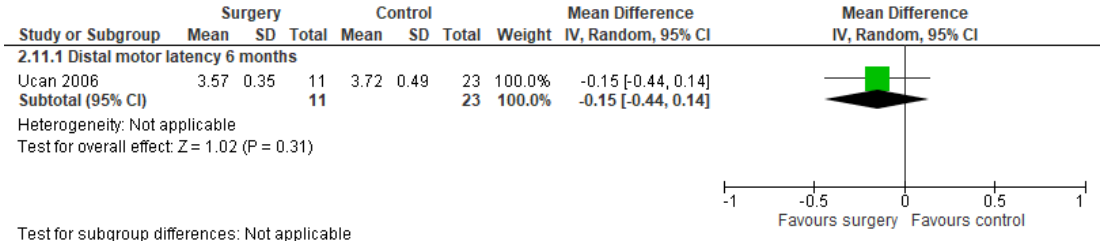


***Figure 23**. Distal motor latency measured in milliseconds from nerve conduction examination comparing surgery with splinting at 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Other outcomes*

None of the trials reported results from subpopulations with mild, moderate, or severe carpal tunnel syndrome.

## Surgery versus steroid injection

Two trials (four publications) reported data comparing surgery with steroid injection (51;52). Hui et al. measured outcomes at 20 weeks. These data were analysed as 6-month data in our review (52). Ly-Pen et al. reported data from 6 months (51), 1 year (51;56), and 2 years (55). In this trial, wrists, not patients, were randomized to treatment.

### *Symptom severity at 6 months*

Hui et al. reported data on symptom severity comparing surgery with steroid injection (52). The Global Symptom Scale (GSS) questionnaire was used to measure symptom severity (59). In GSS, five symptom measures are rated on a scale from 0–10, where a higher score indicates more severe symptoms. Scores from all symptom measures are summed up, and maximum score is 50 points.

For symptom severity, we are uncertain whether surgery results in greater improvement compared to steroid injection due to very low-certainty evidence. The evidence was downgraded one level for risk of bias and two levels for imprecision (Appendix 7, Table 3).

At 6 months, the mean (SD) score in the surgery group was 4.3 (5.6) points and 16.6 (12.3) points in the steroid injection group, mean difference between groups was -12.3 (-17.6 to -7.0) points (Figure 24).

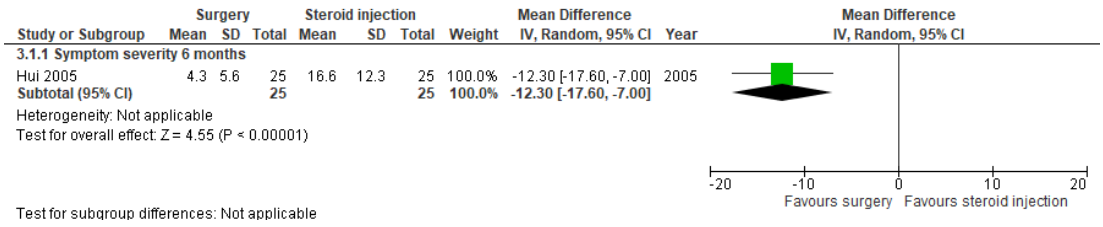


***Figure 24****. Symptom severity comparing surgery with local steroid injection at 6 months*
*Mean scores are from Global Symptom Scale (0–10), where a higher score indicates more severe symptoms.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Paraesthesia at 6 months, 1 year and 2 years*

Ly-Pen et al. reported outcomes at 6 months, 1 year and 2 years in two publications (51;55). Nocturnal paraesthesia was assessed on a VAS scale with score 0–100, where a higher score indicates more paraesthesia. Data were reported as proportion of hands reaching 20%, 50% and 70% improvement. We extracted data on 20% improvement, as this was set as the minimal clinically important difference in the trial, and calculated risk ratio.

For nocturnal paraesthesia, we are uncertain whether surgery results in greater improvement compared to steroid injection due to very low-certainty evidence. The evidence was downgraded one level for risk of bias and twice for imprecision (Appendix 7, Table 3).

At 6 months, the risk ratio was 0.89 (95% CI 0.77 to 1.04) (Figure 25). At 1 and 2 years, the risk ratio was 1.07 (95% CI 0.89 to 1.30) and 1.14 (0.91 to 1.43), respectively.

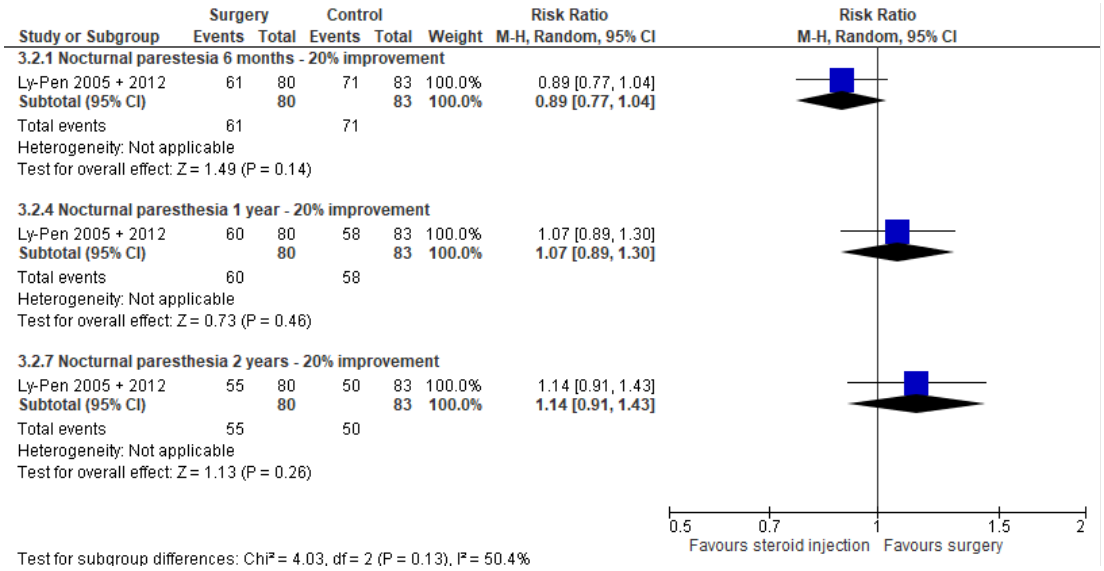


***Figure 25****. Nocturnal paraesthesia comparing surgery and steroid injection at 6 months, 1 year, and 2 years*
*Numbers represent hands reaching 20% improvement measured on a VAS scale from 0–100, where a higher score indicates more impairment.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Pain at 6 months, 1 year and 2 years*

Ly-Pen et al. reported outcomes at 6 months, 1 year and 2 years (51;55). Diurnal pain was assessed on a VAS scale with score 0–100, where a higher score indicates more severe pain. Data was reported as proportion of hands reaching 20%, 50% and 70% improvement. We extracted data on 20% improvement, as this was set as the minimal clinically important difference, and calculated risk ratio.

For diurnal pain, we are uncertain whether surgery results in greater improvement compared to steroid injection due to very low-certainty evidence. The evidence was downgraded one level for risk of bias and twice for imprecision (Appendix 7, Table 3).

At 6 months, the risk ratio was 0.93 (95% CI 0.78 to 1.10) (Figure 26). At 1 and 2 years, the risk ratio was 1.07 (95% CI 0.88 to 1.31) and 1.19 (95% CI 0.94 to 1.52).

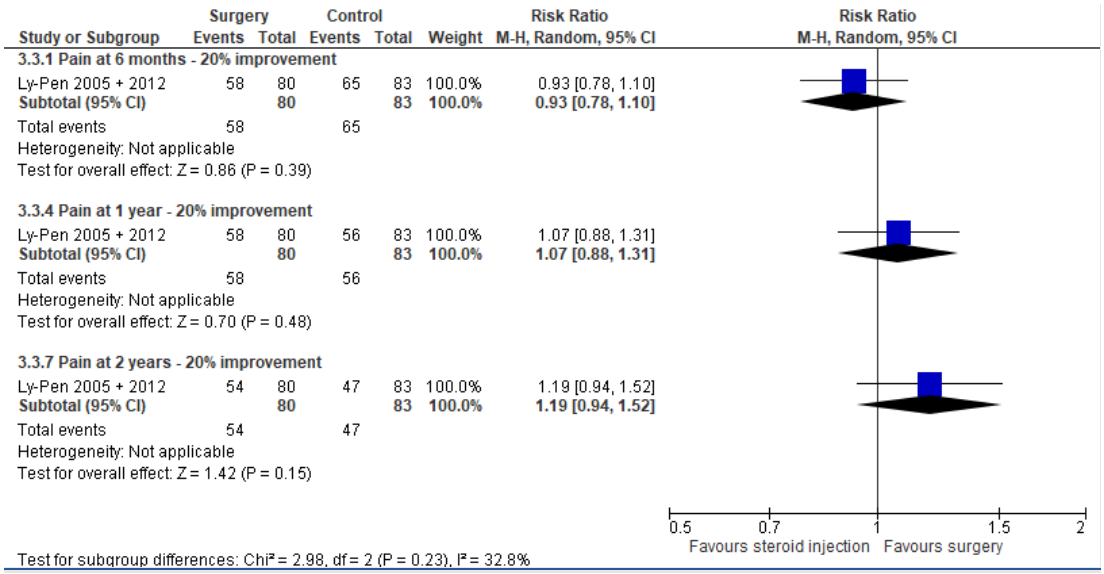


***Figure 26****. Diurnal pain comparing surgery and steroid injection at 6 months, 1 year, and 2 years*
*Numbers represent hands reaching 20% improvement in pain measured on a VAS-scale from 0–100, where a higher score indicate more severe pain.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

***Function reported at 6 months, 1 year and 2 years***

Ly-Pen et al. reported outcomes on hand function at 6 months, 1 year and 2 years (51;55). Functional impairment was assessed on a VAS scale with score from 0–100, where a higher score indicates more severe impairment. Data were reported as proportion of patients reaching 20%, 50% and 70% improvement. We extracted data on 20% improvement, as this was set as the minimal clinically important difference in the trial. As the percentage, and not the number of hands, were presented in the tables, we calculated the number of patients to be able to calculate risk ratio (Figure 27).

We are uncertain whether surgery results in greater improvement in function compared to steroid injection due to very low-certainty evidence. The evidence was downgraded one level for risk of bias and twice for imprecision (Appendix 7, Table 3).

At 6 months, the risk ratio was 0.94 (95% CI 0.79 to 1.12). At 1 and 2 years, the risk ratio was 1.04 (95% CI 0.85 to 1.26) and 1.25 (0.97 to 1.61).

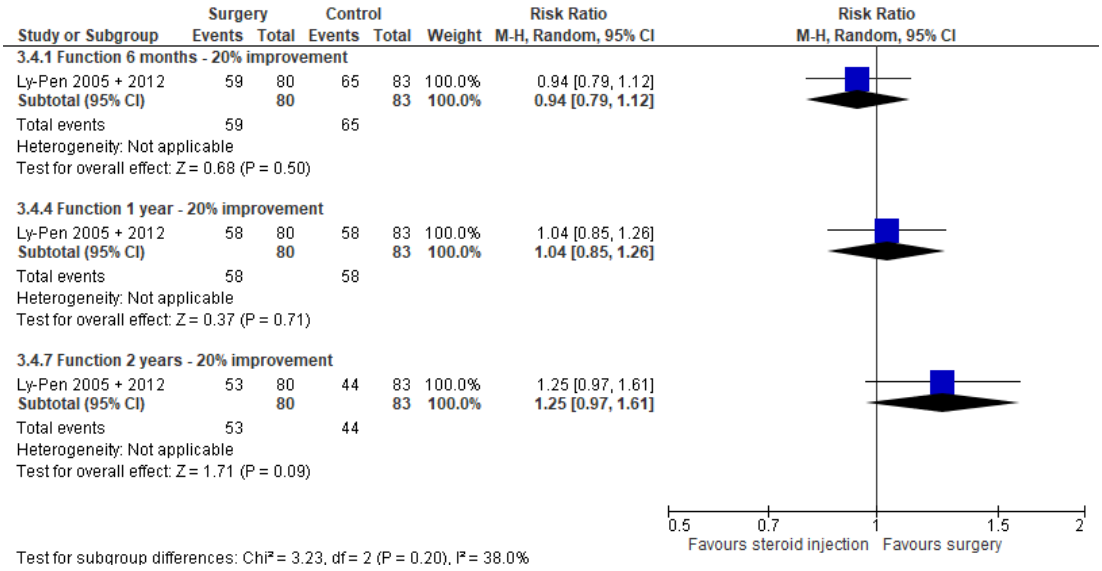


***Figure 27****. Hand function comparing surgery with local steroid injection at 6 months, 1 year, and 2 years*

*Events represents number of hands achieving 20% improvement in hand function on a VAS-scale from 0–100, where a higher core indicates more impairment.*

### *Adverse events at 6 months and 1 year*

Adverse events were not predefined outcomes in any of the trials, but were reported by Hui et al. at 6 months (52) and Ly-Pen et al. at 1 year (51). No severe treatment-related adverse events were reported in the trials. In the trial by Hui et al., one (4%) patient who had steroid injection developed cellulitis and was treated with antibiotics, and four patients (16%) reported pain at the injection site. Two (8%) patients who had surgery developed wound hematoma and nine (36%) had mild to moderate wound pain after surgery that resolved within 6 weeks. All the observed adverse events were considered as minor. In the trial by Ly-Pen et al., one patient in the surgery group died of hepato-carcinoma and two patients in the steroid injection group had a wrist fracture. None of these events was considered related to the study treatment.

### *New surgical procedure or surgery after non-surgical treatment*

In the trial by Ly-Pen et al., patients considered as treatment failures were offered alternative treatment, with limited incision surgery for hands in the steroid injection group, and wide-incision decompression surgery for wrists in the surgery group. At 2 years, nine wrists in the surgery group and 26 wrists in the steroid injection group were considered treatment failures. Ten (15%) wrists allocated to steroid injection had surgery. The number of patients in the surgical group who had a second procedure was not reported.

### *Nerve conduction assessments*

Outcomes from nerve conduction assessments were reported in two trials. Sensory conduction velocity and distal motor latency was reported by Hui et al. at 6 months (52), and by Andreu et al. at 1 year (56). Andreu et al. presented outcomes from nerve conduction assessments performed in the RCT by Ly-Pen et al. A lower velocity or higher latency may indicate more severe nerve impairment.

At 6 months, sensory conduction velocity was mean (SD) 42.2 (8.0) ms after surgery and 40.5 (6.3) ms after steroid injection. Mean difference between groups was 1.7 (95% -2.3 to 5.7) ms (Figure 28). At 1 year, the mean difference between groups was 6.8 (2.9 to 10.7) ms.

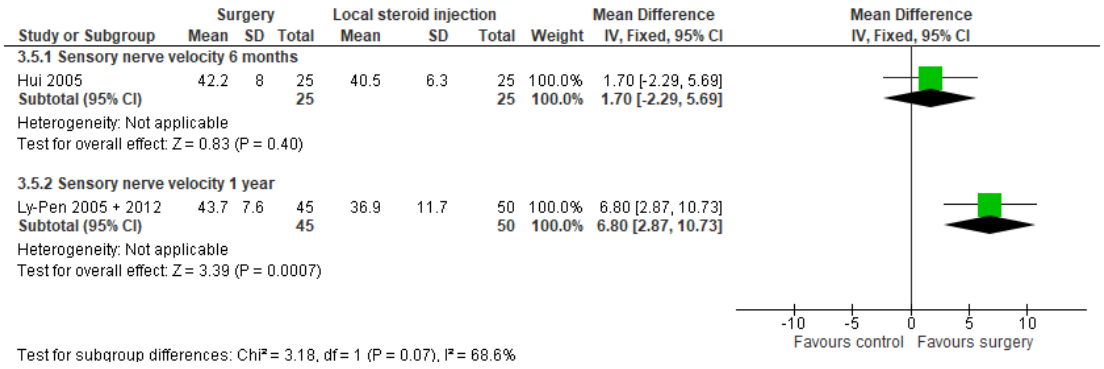


***Figure 28****. Sensory conduction velocity measured in milliseconds from nerve conduction assessments comparing surgery with steroid injection at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

At 6 months, the mean (SD) distal motor latency was 4.2 (0.9) ms in the surgery group and 4.4 (0.9) ms in the steroid injection group. The mean difference between groups was -0.2 (95% CI -0.7 to 0.3) ms. At 1 year, the mean (SD) distal motor latency was 4.7 (1.3) ms in the surgery group and 5.3 (1.7) ms in the steroid injection group. The mean difference between groups was -0.60 (95% CI -1.21 to -0.01) ms (Figure 29).

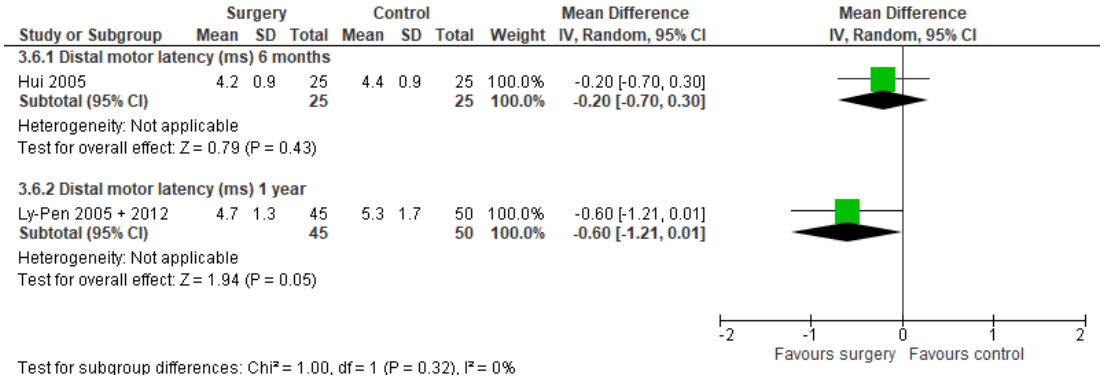


***Figure 29****. Distal motor latency measured in milliseconds from nerve conduction assessments comparing surgery with steroid injection at 6 months and 1 year*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

***Other outcomes***

Health-related quality of life (HRQoL) was not measured in any of the trials. None of the trials reported results from subpopulations with mild, moderate, or severe carpal tunnel syndrome.

## Surgery versus physical therapy

Three trials by Fernández-de-las-Peñas et al. reported data comparing surgery with manual therapy (48-50), and one publication by the same author reported extended

follow-up data at 4 years (57). The 4-year data were analysed as 5-year data in this review according to the protocol. All trials included 50–60 patients in each group, and all participants were women.

### *Symptoms reported at 6 months, 1 year and 5 years*

Two trials by Fernández-de-las-Peñas et al. reported symptom severity at 6 months and 1 year (48;50), and one of these trials reported extended data at 4 years (57). The tool used to measure symptom severity was the symptom severity scale of the Boston Carpal Tunnel Syndrome Questionnaire (BTCQ) in both trials (23). Symptom scores range from 1–5, where a higher score indicates more severe symptoms.

For symptom severity, we are uncertain about the relative efficacy of surgery to manual therapy due to very low-certainty evidence. Certainty of evidence was downgraded one level for risk of bias and twice for risk of imprecision (Appendix 7, Table 4).

At 6 months, the mean difference between groups was -0.15 (95% CI -0.29 to 0.00) (Figure 30). At 1 and 5 years, the mean difference between groups was -0.09 (95% CI -0.29 to 0.10) points and -0.20 (95% CI-0.54 to 0.14) points, respectively.

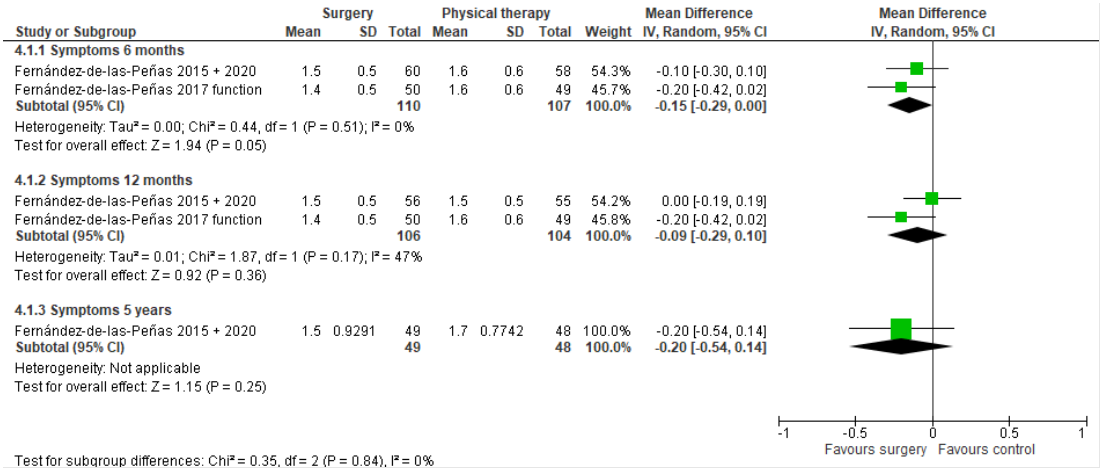


***Figure 30****. Symptom severity comparing surgery with manual therapy at 6 months, 1 year and 5 years*
*Outcomes are mean scores from the function scale of the Boston Carpal tunnel Syndrome Questionnaire (BCTQ). Scores range from 1–5, and a higher score indicates more severe symptoms.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Pain reported at 6 months, 1 year and 5 years*

Three trials by Fernández-de-las-Peñas et al. reported pain at 6 months and 1 year (48-50). One of these trials reported extended data at 4 years and was analysed as 5-year data as defined in the protocol (57). The tool used to evaluate pain was the Numerical Pain Rating Scale (NPRS) for current pain (preceding week), and worst and lowest experienced pain (preceding week) (60). Score ranges from 0–10, where a higher score indicates more severe pain. One of the publications reported current pain and worst pain separately (48). We included current pain in the analyses. One publication presented data on pain in a figure (49). Exact data from this figure was obtained after contact with the author.

We are uncertain about the relative efficacy of surgery to manual therapy due to very low-certainty evidence. Certainty of evidence was downgraded one level for risk of bias and twice for risk of imprecision (Appendix 7, Table 4).

At 6 months, the mean difference between groups was 0.66 (95% CI 0.09 to 1.22) points (Figure 31). At 1 and 5 years, the mean difference between groups was 0.05 (95% CI -0.45 to 0.55) and -0.10 (95% CI -1.00 to 0.08), respectively.

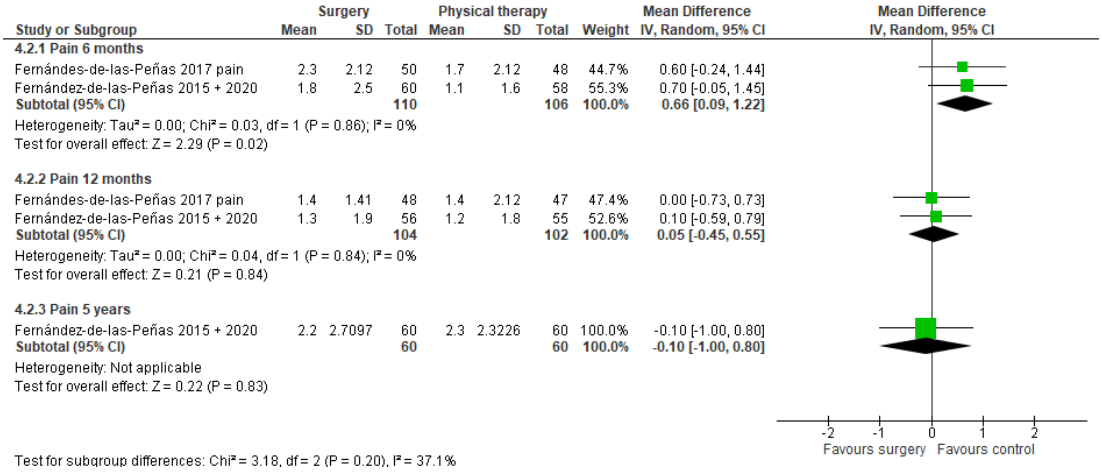


***Figure 31****. Pain reported at 6 months, 1 year and 5 years comparing surgery and manual therapy*
*Outcomes are mean score from current pain on a 0-10 scale, where a higher score indicates more severe pain.*
*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Function reported at 6 months, 1 year and 5 years*

Two trials by Fernández-de-las-Peñas et al. reported hand function at 6 months and 1 year (48;50), and one of these trials reported extended data at four years (57). The functional status scale from the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) was used in all trials (23). Scores range from 1–5, where a higher score indicates more severe impairment.

For function, we are uncertain about the relative efficacy of surgery to manual therapy due to very low-certainty evidence (downgraded one level for risk of bias and twice for imprecision (Appendix 7, Table 4).

At 6 months, the mean difference between groups was 0.05 points (95% CI -0.09 to 0.20) (Figure 32). At 1 and 5 years, the mean difference between groups was -0.04 (95% CI -0.20 to 0.11) points and -0.10 (-0.41 to 0.21) points, respectively.

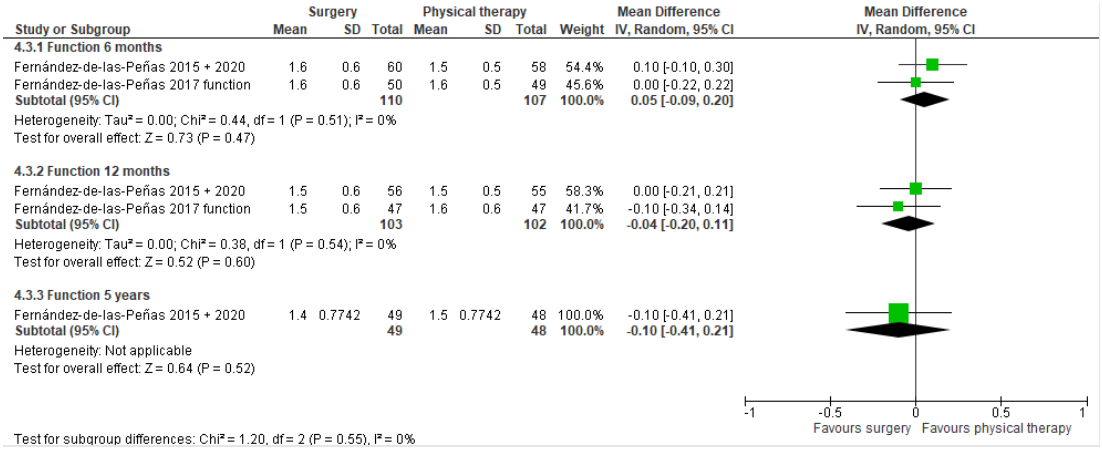


***Figure 32**. Hand function comparing surgery with manual therapy at 6 months, 1 year and 5 years*

*Outcomes are mean scores from the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), with score ranging from 1–5, where a higher score indicates more impaired function.*

*Abbreviations: SD, standard deviation; CI, confidence intervals*

### *Adverse events*

Three trials retrieved information on adverse events at 6 months and 1 year (48-50). None of the trials reported clinically important adverse events in any of the treatment groups.

### *Treatment success*

Criteria for considering the treatment as successful was defined in one of the trials (48). Treatment success was based on specific threshold scores from three of the symptom questionnaires. At 6 months, 27 (45%) in the surgery group and 31 (53%) patients (53%) in the manual therapy group were considered to have successful outcome, RR 0.84 (95% CI 0.58 to 1.22) (Figure 33). At 1 year, the corresponding numbers were 31 (55%) and 32 (58%), respectively; RR 0.95 (95% CI 0.69 to 1.32).

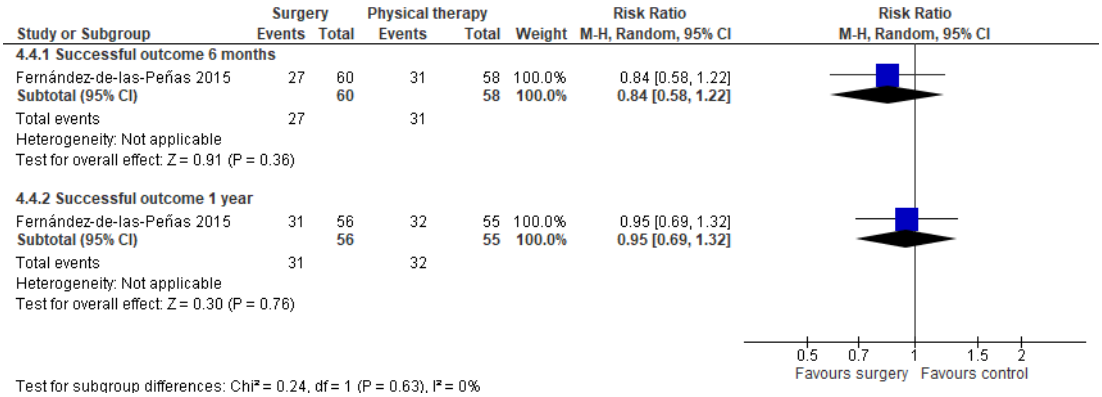


***Figure 33**. Treatment considered as successful at 6 months, 1 year and 5 years comparing surgery and manual therapy*

*Abbreviations: SD, standard deviation; CI, confidence intervals*

***New surgical procedure or surgery after non-surgical treatment***

The number of patients allocated to manual therapy who had surgery in the study period, and patients allocated to the surgical group who had a second surgical procedure in the study period, are presented in Table 5.

***Table 5****. Patients in the manual therapy group who had surgery for carpal tunnel syndrome during follow-up, and patients allocated to surgery who had a new surgical procedure during follow-up*

| Trial | Time point | Patients allocated to manual therapy who had surgery n (%) | Patients allocated to surgery who had a new surgical procedure n (%) |
|---|---|---|---|
| Fernández-de-las-Peñas 2015 + 2020 | 1 year<br>5 years | 3/55 (5.5%)<br>9/48 (19.0%) | 0/56 (0%)<br>8/49 (16.3%) |
| Fernández-de-las-Peñas 2017 (function) | 1 year | 3/47 (6.4%) | 0/47 (0%) |
| Fernández-de-las-Peñas 2017 (pain) | 1 year | 0/47 (0%) | 2/48 (4.2%) |

***Other outcomes***

None of the trials by Fernández-de-las-Peñas et al. reported data from HRQoL or nerve conduction testing, and none reported results from subpopulations with mild, moderate, or severe carpal tunnel syndrome.

# Health economic evaluation

## Introduction

The Norwegian regional health authorities have been commissioned by the Ministry of Health and Care Services to assess whether certain surgical procedures that are in use in the specialist health care services should not be routinely performed or only performed under specific and more clearly defined circumstances. There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion, the resource criterion, and the disease severity criterion (61). Decisions following reassessments of health technologies should also be based on the three priority-setting criteria. The priority-setting criteria are to be evaluated together and weighed against each other (61).

In practice, the three priority-setting criteria are considered by weighing costs against benefits in a health economic analysis. A health economic evaluation is a comparative analysis of treatment options where the health effects and costs of the treatment alternatives are measured and compared. Economic evaluation provides information to decision-makers for efficient use of available resources for maximizing health benefits. This is usually performed as a cost-effectiveness analysis based on a decision model. A model-based analysis is particularly appropriate when a health intervention is more effective and more costly than the relevant treatment alternatives or standard clinical practice. However, the choice of analysis method depends on the availability of appropriate and reliable data. For instance, if the evidence has shown that efficacy and safety profiles for the intervention and the comparator are approximately the same, a simpler assessment can be carried out, i.e., a cost minimisation analysis (62).

Due to great uncertainty in the estimate of the relative efficacy, and as there may be little or no difference between surgery and the relevant alternatives for the treatment of patients with mild to moderate carpal tunnel syndrome, we have conducted a simplified assessment of economic consequences in the form of a cost analysis. The costs of the relevant non-surgical treatment alternatives in Norway, i.e., local steroid injection and splinting, have been estimated and compared to surgery for patients with mild to moderate carpal tunnel syndrome. In addition, we have carried out a simple budget impact analysis to show possible cost savings.

## Methods

The cost estimation consists of three parts: identification, measurement, and valuation. Identification deals with which cost factors are to be included in the analyses. The measurement of resources used, in physical units, is made in the Norwegian health care context. Resources are valued based on the Norwegian unit prices.

We have calculated and compared costs associated with surgery for carpal tunnel syndrome and non-surgical treatment options. In consultation with the clinical experts, we have included local steroid injection and splinting as non-surgical treatment options.

The analysis was performed for patients with mild to moderate carpal tunnel syndrome. The analysis was carried out from a health service perspective in line with the guidelines in the Government white paper on priority setting in the Norwegian health care sector (61;63). The health service perspective includes the costs to the health care service, thus the costs related to production losses due to the disease are not included in the analysis. All costs are calculated in 2021 Norwegian kroner. All tariffs are multiplied by two based on the relevant national guidelines (62).

We included costs related to visiting physician, physical therapy, local steroid injection, splinting and examinations, as well as the surgical procedure. The average resource use per patient for each treatment alternative is presented in Table 6. The background for these estimates is discussed below.

***Table 6.*** *Assumed average resource use (n or %) per patient for the treatment options**

| Cost item | Surgery | Steroid injection | Splinting |
|---|---|---|---|
| Visiting medical doctor | 1 | 1 | 1 |
| Visiting specialist doctor* | 1 | 1.33† | 1 |
| Nerve conduction study (one per patient) | 100% | 50% | 50% |
| Surgery | 1 | - | - |
| Medical doctor visit for wound care and for stitch removal due to surgery | 1 | - | - |
| Steroid injection | - | 1.33† | - |
| Splint (one per patient) | 20% | 10% | 100% |
| Physical therapy visits | 5%‡ (ten visits) | - | 20% (five visits) |

**The estimates were made in consultation with the expert group.*
*†The first visit includes an examination. For local steroid injection, we assume that the specialist physician performs it. Moreover, we assume that two thirds of patients have one injection (and visit), while one third of patients have two injections (and visits).*
*‡Due to stiffness or other complaints after the surgery.*

### Visiting a medical doctor

We assumed that all patients visit their medical doctor once. For medical doctor visits, we assumed that half of medical doctors are specialists requiring an additional fee. We also assumed that patients treated with splinting, or surgery have one visit at a specialist doctor's office. The first visit includes a full clinical examination (the cost (tariff) of the diagnostics is mentioned in a separate paragraph). Steroid injection is usually given by a specialist doctor. According to one of the clinical experts, around two thirds of the patients need one injection, while one third need two injections. Therefore, we assumed 1.33 visits to specialist doctor for steroid injections. For the surgery patients, we assumed one additional visit to a general practitioner for wound care and stitch removal. We assumed that 80% of patients will get wound care and stich removal by a medical secretary, and that 20% of patients will need to be seen by a medical doctor. The costs for visiting a medical doctor are calculated based on the relevant tariff rates (Table 7).

***Table 7.*** *Unit costs for visiting medical doctor*

| Cost item | Unit cost (NOK) | Tariff code |
|---|---|---|
| Medical doctor visit* | 320 | 2ad |
| Additional fee for specialist doctor (general practice) | 198 | 2afdd |
| Wound care consumables | 190 | 10b |
| Visit at specialist doctor (incl. examination) | 1,390 | 3ad, 4a1 and 4e |
| Specialist doctor visit* | 750 | 3ad |

Source: (64)
*Visit to specialist doctor for streoid injections. The cost of streoid injection itself is presented under Drug treatment.

### Decompression surgery

The surgery is performed as outpatient care at the hospital. We have calculated the average cost of the surgery based on the diagnosis-related group reimbursement scheme (code 60) (65). This gives a reimbursement of NOK 8,383.

### Drug treatment

We assume that the use of non-steroidal anti-inflammatory drugs is similar for all treatment options, and that the cost is negligible. We have therefore excluded this cost from the analysis.

Steroid injection can be used and may relieve symptoms at least short-term (21). The steroid injection should be performed by ultrasound guidance. The treatment is usually given at a specialist doctor's office. According to one of the clinical experts, around 67% of patients need one injection, and 33% need two injections. This gives a weighted average number of steroid injections needed of 1.33 injections, which is what we have applied in our analysis. The cost of steroid injection is calculated based on the relevant tariff rate (rate 125b) (64), which is NOK 700. We have also included the cost related to visiting a physician for each injection.

### Splinting

Splinting can be used for mild to moderate carpal tunnel syndrome. According to the experts, patients may use a splint alone or as a complement to the other treatments. The estimates for the use of splint are based on input from the clinical experts. We have used an average price of splints of about NOK 450.

### Physical therapy

According to the expert group, some patients may need physical therapy after surgery, and some have it in addition to splinting. Our estimates are based on expert input.

According to a physiotherapist we have consulted, the use of physical therapy for patients with carpal tunnel syndrome is relatively low.

According to one of the clinical experts, very few patients who undergo surgery need physical therapy as part of the treatment afterwards, but for these patients, there may be several sessions needed. This may be due to stiffness or other complaints after the surgery. The number of physical therapy visits for these patients is usually between 10 and 15 in Norway (66). In our analysis, we assumed ten visits for patients having surgery (for 5% of the patients) and five visits for patients treated with splinting (for all patients), and no visits for patients treated with steroid injection. According to the physiotherapist, it is reasonable to assume that the clinical examinations are carried out during the first visit in addition to the therapy. Treatment may be performed by physiotherapists and manual therapists and there are different tariffs for these. We assumed that 80% is treated by a physiotherapist and that 20% is treated by a manual therapist based on input from the physiotherapist.

The unit costs for physical therapy are shown in Table 8. These tariffs are combined to get the costs for examination and treatment sessions and are based on input from the physiotherapist (66). Each treatment session by a physiotherapist amounts to NOK 530 (tariff A3a+A3b), and sessions by a manual therapist costs NOK 808 (tariff A8a+A8b). The costs related to examination at the first visit are estimated to be NOK 990 (tariff A1a+A1c).

***Table 8.*** *Unit costs of physical therapy*

| Cost item | Unit cost (NOK) | Tariff code |
|---|---|---|
| Examination | 666 | A1a |
| Additional fee for extra examination time | 162 | A1c |
| Treatment session by physiotherapist | 360 | A3a |
| Additional fee for extra treatment time for physiotherapist | 170 | A3b |
| Treatment session by manual therapist | 568 | A8a |
| Additional fee for extra treatment time for manual therapist | 240 | A8b |

Source: (67)

### Diagnostics

Carpal tunnel syndrome is primarily a clinical diagnosis. Nerve conduction studies are used as a supplement, especially before surgery. Based on input from the clinical experts, we have assumed that all patients considered for surgery have nerve conduction studies preoperatively, and that half of the patients having non-surgical treatment undergo nerve conduction studies.

The cost of diagnostics was calculated based on the relevant tariff (tariff 722) (64). This amounts to NOK 324. This cost only refers to the test itself. The full cost of the assessment of the patient (incl. cost of the test) does also include the cost of the specialist doctor visit which is estimated to be NOK 1,714.

### Complications

Based on our systematic literature review, there is probably a small risk of serious harm after the surgical and non-surgical treatment options. We have therefore excluded the cost of serious complications from our analysis.

## Results

### Costs of the treatment options

The average cost per patient for each treatment option for mild to moderate carpal tunnel syndrome is presented in Table 9.

***Table 9.*** *Average cost per patient associated with the treatment options*

| Cost item | Surgery | | Steroid injection | | Splinting | |
|---|---|---|---|---|---|---|
| | Units / % | Cost (NOK) | Units / % | Cost (NOK) | Units / % | Cost (NOK) |
| Medical doctor visit | 1 | 419 | 1 | 419 | 1 | 419 |
| Specialist doctor visit* | 1 | 1,262 | 1.33* | 1,512 | 1 | 1,262 |
| Nerve conduction study (one per patient) | 100% (one examination) | 324 | 50% (one examination) | 162 | 50% (one examination) | 162 |
| Surgery | 1 | 8,838 | - | - | - | - |
| Visit for wound care and stich removal | 1 | 332 | - | - | - | - |
| Steroid injection | - | - | 1.33* | 933 | - | |
| Splint | 20% (one splint) | 90 | 10% (one splint) | 45 | 100% (one splint) | 450 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Physical therapy† | 5% (ten visits) | 342 | - | - | 20% (five visits) | 784 |
| **Sum** | | **11,152** | | **3,071** | | **3,077** |

**The first visit includes an examination. For steroid injection, we assume that a specialist doctor performs it and that 67% of patients have one injection (and visit), while 33% of patients have two injections (and visits). This implies a weighted average of 1.33 visits. †80% treated by a physiotherapist and 20% by a manual therapist.*

Surgical decompression is the most costly treatment option, around NOK 11,200. The costs associated with the non-surgical treatment options are estimated to approximately NOK 3,100, both for steroid injection and for splinting.

**Budget impact analysis**

Based on the updated information we received from the Central Regional Health Authority (RHA), there were about 7,580 and 7,400 surgical procedures for treatment of carpal tunnel syndrome in 2017 and 2019, respectively (68).

The statistics showed that the number of surgical procedures per 100,000 inhabitants performed by the RHAs and at the national level seems to have remained relatively stable in the period 2017–2019. In 2019, the Central RHA had the highest number of surgeries per 100,000 inhabitants, while the Western RHA had the lowest number of surgeries per 100,000 inhabitants (68). The rates and number of surgical procedures per the RHAs for the period 2017–2019 is shown in Figure 34.

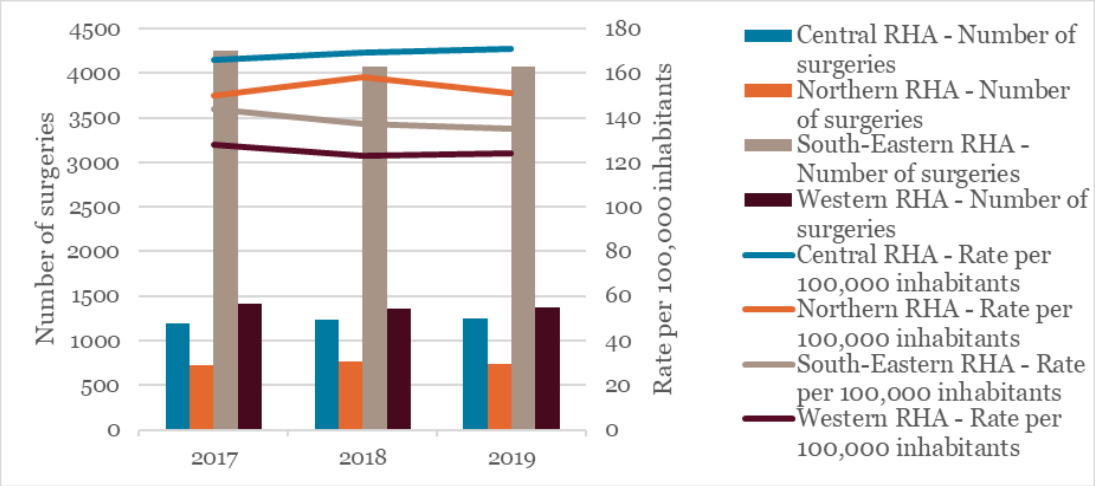


***Figure 34**. The rate per 100,000 inhabitants and total number of surgeries in each RHA in 2017, 2018, and 2019. Source: Data from NPR, reported by Central RHA (68)*

When looking at the number of surgical procedures per 100,000 inhabitants performed by each hospital trust (including the public hospitals and private treatment providers under contracts with the public specialist health service) in 2019, there was geographical variation between the hospital trusts and between the areas within each RHA. In 2019, Innlandet had the highest rate, and Oslo had the lowest rate, at 217 and 90 surgical procedures per 100,000 inhabitants, respectively. The four hospital trusts with the highest rates of surgeries per 100,000 inhabitants after Innlandet were Østfold (207),

Nordland (189), Møre og Romsdal (183) and Nord-Trøndelag (171). As it was previously calculated for the period 2015–2017 (26), this data showed that there is still moderate geographical variation between the areas regarding the number of surgeries for treatment of carpal tunnel syndrome. The number of surgical procedures per 100,000 inhabitants was approximately 2.4 times higher in the hospital referral area with the highest rate (Innlandet) compared to the one with the lowest rate (Oslo).

Due to geographical variation, we have estimated the potential cost saving if the rate of surgical procedures per 100,000 inhabitants for the other three RHAs comes down to the same level as the Western RHA (the RHA with the lowest rate) in 2019. Based on our assumptions, the potential cost savings at the national level could be between NOK 14.5 and 27.5 millions. More details about the budget impact analysis for each RHA can be found in Appendix 8. The limitations related to our assumptions are discussed in the discussion chapter of this report.

# Discussion

## Main findings efficacy and safety

We included 10 trials with 960 randomized patients or wrists comparing surgery with non-surgical treatments including splinting, combinations of non-surgical treatments, steroid injection, and manual therapy. In most trials, the patients had mild or moderate carpal tunnel syndrome. Overall, we found low-certainty evidence that surgery is more effective than splinting and combinations of non-surgical treatments at 1 year. We found very low-certainty evidence regarding the efficacy of surgery versus steroid injection and manual therapy.

Three trials compared surgery with splinting. Low-certainty evidence from one trial suggested a superior effect of surgery on several outcomes at 1 year. Evidence was from a multicenter trial with adequate methodology except for the lack of blinding. The effect sizes were, however, small, and close to what is considered as clinically important. Notably, the outcomes reported were from ITT analyses. In this trial, a substantial proportion (39%) of patients allocated to splinting had been treated with surgery at 1 year. This may have underestimated the efficacy of surgery. “As treated” analyses were not presented to confirm this, but subgroup-analyses from the trial support this assumption.

Three trials compared surgery with non-surgical treatments. At 1 year, low-certainty evidence from one trial suggested a superior effect of surgery on symptom severity and function. The evidence was from a multicenter trial with adequate methodology except from the lack of blinding. The outcomes reported were from ITT-analyses. In this trial, 44% of patients in the control group had been treated with surgery at 1 year. “As treated” analyses showed a more superior effect of surgery. Yet, the effect sizes with confidence intervals were still small and close to what is considered clinically important.

Two trials compared surgery with steroid injection and three trials compared surgery with manual therapy. We are uncertain about the efficacy of surgery compared to these treatment modalities due to very low-certainty evidence.

Complications were reported in most trials. Overall, few serious adverse events were reported both among patients having surgery and among patients having non-surgical treatments. Small RCTs are, however, not suitable to evaluate adverse events.

## Overall completeness and applicability of evidence

Despite carpal tunnel syndrome being a common condition and the fact that decompression surgery has been an established procedure in the health care system for decades, there are relatively few RCTs that have evaluated the efficacy of surgery. None of the included trials reported outcomes based on pre-treatment severity of the condition such as mild, moderate, and severe, which was one of our research questions. Most trials, however, excluded patients with severe carpal tunnel syndrome, which means that the findings in this report are generalizable to patients with mild to moderate carpal tunnel syndrome. The rationale for excluding patients with severe carpal tunnel syndrome is probably the broad acceptance that these patients do not respond to non-surgical treatment and that permanent nerve damage may occur if the condition is left untreated. Most of the trials in this review excluded patients with comorbid conditions such as metabolic disease (for example diabetes mellitus and thyroid disease), musculoskeletal disease and pregnancy. This means that the results may not be applicable to patients with such conditions.

## Quality of the evidence

The quality of the evidence is inherently limited by few and relatively small trials for each comparison. All outcomes were downgraded to low-certainty evidence or very low-certainty evidence due to risk of bias and imprecision. All trials had high risk of bias in at least two domains; blinding of participants and blinding of outcome assessors. Blinding in surgical trials is challenging. Some of the trials in this review attempted to blind outcome assessors, but such blinding is difficult to accomplish when the participants are not blinded. Additionally, all the primary outcomes were patient-reported data, so we considered risk of bias as high in the domains concerning blinding in all trials. Some of the trials had additional methodological concerns. The three trials by Fernández-de-las-Peñas et al. that compared surgery with manual therapy, were conducted by the same study group. In these trials, all patients who were eligible for study inclusion accepted to participate. This seems unlikely in a clinical setting, where patients often have a treatment preference. In contrast to the multicenter trials by Gerritsen et al. and Jarvik et al., few patients allocated to manual therapy had surgery during follow-up, even though the trials of manual therapy also included patients with severe carpal tunnel syndrome. Altogether, this raises questions about the generalizability of the results.

Certainty of evidence was downgraded due to imprecision in all trials because there were at most three trials for each outcome of interest at 1 year. The trials were relatively small, and the effect estimates were small with confidence intervals close to no effect or including no effect.

## Strengths and weaknesses of this systematic review

This review was conducted according to the published project plan (27). However, assessment of publication bias by visual inspection of funnel plots was not performed because of few included trials for each outcome. Our search strategy was comprehensive. As outlined in the protocol, we identified primary studies (RCTs) from identified systematic reviews. In this process, we searched all the systematic reviews considered possible for inclusion of primary studies as described in the results of the literature search. The literature search for primary studies was also comprehensive and covered the time after the searches in the systematic reviews were finalized.

The process of selection of studies, risk of bias assessments and assessments of certainty of evidence was performed independently by two researchers. We consider this process being performed adequately. A possible limitation, however, is that we assessed risk of bias on study level and not for each outcome of interest. This may have resulted in other judgements particularly in trials reporting extended data, because attrition rates were higher in these studies and could possibly result in risk of bias due to incomplete outcome data. In this review, one trial comparing surgery with steroid injection and one trial comparing surgery with manual therapy provided extended data, and the long-term (>1 year) results should therefore be interpreted with caution (57;69).

An important limitation with this review is the assessment of safety. RCTs are often too small to evaluate adverse events. Hence, in the design process of this review, we considered including non-randomized trials for the assessment of adverse events. In the early phase of the project, we identified large non-controlled studies that demonstrated low risk of adverse events (19), suggesting that safety after such procedures does not seem to be of great concern. Moreover, the main objective of this review was to evaluate the efficacy of surgery, and for this purpose a control group was considered essential due to the natural course of the condition with fluctuating symptoms. Altogether, with the addition of time and resource limits, we decided not to include non-randomized trials.

## Agreements and disagreements with other studies or reviews

Three of the systematic reviews identified in our literature search compared surgery to various non-surgical treatments (41-43). We assessed the methodological quality of the reviews to be low. In the review by Huisstede et al. (42), the authors found moderate-certainty evidence that surgery was superior to splinting and combinations of non-surgical treatments at >6 months of follow-up. Our results for the same comparisons were comparable to this review, but in contrast to us, the authors assessed several of the trials to have low risk of bias. In the reviews by Klokkari et al. and Shi et al. (41;43), the non-surgical treatments with splinting, steroid injection and physical therapy were pooled into one group. This makes the findings difficult to compare with our results. In both reviews the authors found evidence that symptom severity and function was superior after surgery compared to non-surgical treatments at 6 months, but they found no difference between the groups at 1 year.

## Health economics

The Government white paper on priority setting in the Norwegian health care sector recommends QALYs as a measure of the benefit, and cost-utility analysis as a standard analysis to assess the relation between costs and the health benefit of health interventions. Due to great uncertainty in the estimate of the relative efficacy and as there may be little or no difference between surgery and the relevant alternatives for the treatment of patients with mild to moderate carpal tunnel syndrome, we have conducted a simplified assessment of economic consequences in the form of a cost analysis where the costs of the relevant treatment alternatives in Norway were estimated and compared to each other. In addition, we have carried out a simple budget impact analysis to show possible cost savings. The results showed that surgery is the most costly treatment at NOK 11,200. The non-surgical treatment alternatives, which are steroid injection and splinting cost approximately NOK 3,100. Potential cost savings are estimated to be between NOK 14.5 and 27.5 million at the national level.

In the cost analysis, we have estimated the costs of surgery and the relevant non-surgical alternatives for the treatment of patients with mild to moderate carpal tunnel syndrome in Norway, i.e., steroid injection and splinting. Physical therapy seems to be used as a treatment for few patients, however according to the clinical experts it is not an effective treatment for most patients with carpal tunnel syndrome and these patients usually need other types of treatment as well. We have therefore not included physical therapy as monotherapy in our analysis. However, the cost of physical therapy is included in the analysis in combination with the other relevant treatment alternatives.

We have conducted a simple analysis of the costs associated with the treatments in the short term. Therefore, we have not included subsequent treatment after the first treatment. This might be more relevant for the non-surgical treatment options where some patients may need surgery, or other conservative treatments at a later stage. Regarding the surgically treated patients, a few patients may need re-operation after the initial surgery, or additional conservative treatment. The long term effect of the different treatment alternatives should be investigated in a model-based analysis.

We have not included costs due to sick leave in our analyses according to the national guidelines. In Norway, health economic evaluations of treatments should be done from the health care perspective. Thus, production loss and sickness benefit are not to be included in the analyses (61;62). It should be mentioned that sick leave was defined as a secondary outcome in this HTA. Based on the results from one included trial (45), there may be little or no difference between surgery and non-surgical alternatives, regarding working days lost.

Lack of data makes it challenging to estimate the use of resources for the different treatments. This is more relevant for the conservative treatments and may underestimate or overestimate the costs. We sought to use the most relevant available sources for the calculations. Although the estimations were based on expert opinion, they may not completely reflect the reality of practice. Especially, there is uncertainty associated with the number of sessions needed for physical therapy. Further, the estimations of

the proportion of patients in the different treatment strategies that use or have used additional conservative treatment are based on input from the experts and are associated with uncertainty.

We have excluded the costs of drugs in the analyses. This may underestimate the total treatment costs. The experts agreed that it would be reasonable to assume the same use of pain-relieving drugs in the treatment strategies. In addition, anti-inflammatory drugs are to be used in the lowest possible dose for the shortest possible time. We can therefore expect that the use of these drugs would be approximately the same in all the treatment alternatives.

We have excluded the cost of complications in the analysis. Based on our systematic literature review, there is probably a small risk of serious complication after the surgical and non-surgical treatment options. Regarding the complications after surgery, a large cohort study support this finding (under 1% hospital admissions due to complications) (20). However, the exclusion of cost of complications after surgery may underestimate the total cost associated with the surgical treatment option.

There is uncertainty regarding the budget impact analysis. Mild cases are usually not treated surgically, and severe cases are usually not eligible for conservative treatment. We did not have information about the distribution of severity of CTS in the surgically treated population in Norway. This may have overestimated or underestimated the feasibility of the conservative treatments in the patient population used.

A report from Helseatlas, based on the data for the period 2015–2017 concluded that the difference in the rate of surgical procedures between the hospital referral areas were unlikely to be due to difference in morbidity or to coincidence (26). The need for surgery should be expected to be the same irrespective of geographic region. Therefore, in our analysis, we used the Western RHA (the one with the lowest rate) as a target rate for possible reductions in the surgery rate. However, it should be mentioned that it is difficult to suggest an “optimal” rate of surgeries per 100,000.

## Implications for practice

In this review we found that surgery may be superior to splinting and combinations of non-surgical treatments in patients with mild to moderate carpal tunnel syndrome. As demonstrated in some of the trials, a substantial proportion of patients having non-surgical treatment may not have adequate effect and end up having surgery. On the other hand, for many patients, surgery may not be necessary. Unfortunately, evidence from the included RCTs trials do not demonstrate which patients benefit the most from surgery.

Current treatment guidelines and clinical decision tools recommend attempting non-surgical treatment alternatives such as splinting and steroid injection before surgery in patients with mild to moderate carpal tunnel syndrome (21;70;71). A recent reassessment project in England updated the clinical criteria for treatment of carpal tunnel syndrome and recommend no treatment in cases with mild symptoms, non-surgical treatment with splinting or steroid injection in cases with moderate symptoms, and surgical

treatment in severe cases (72). These recommendations are based on knowledge from other trials showing that splinting may have a modest (but limited) effect compared to no treatment (73), and from trials of steroid injection that showed a superior effect short term (10 weeks) compared to placebo (74). The efficacy of steroid injection has been shown to be superior and more cost-effective than splinting (75). Splinting and steroid injection are treatments with low risk and low costs, and given the natural history of carpal tunnel syndrome, where some patients may improve with non-surgical treatment or with no treatment, guidelines suggest that the least invasive treatments may be attempted first. However, there is no consensus on the duration of non-surgical treatment before surgery should be offered, or whether steroid injection treatment should be repeated in patients with insufficient effect.

Patients with severe carpal tunnel syndrome were excluded in most of the RCTs in this review. Despite the efficacy of surgery in patients with severe symptoms has not been demonstrated in RCTs, there is a broad acceptance that surgery is the preferred treatment in severe cases with electrodiagnostic evidence of median nerve injury, as untreated cases may lead to prolonged symptom duration and irreversible nerve damage (76). Clinical guidelines (71;72) and decision tools (21;70) are consistent in the recommendations that surgery is the preferred treatment in severe cases.

There is a moderate regional variation in the provision of surgery in Norway. The need for surgery should be expected to be the same irrespective of geographic region. Since surgery is the most costly treatment alternative for patients with mild to moderate carpal tunnel syndrome, there is a potential for cost-savings if areas with high rates of surgery treat more patients (mild to moderate) conservatively instead. The potential cost-savings at the national level depend on the reduction in number of surgical procedures per health region.

Possible factors explaining the observed variation in provision of surgery can be difference in diagnostics, treatment indications, access to surgery and to non-surgical treatments. The diagnostics may be difficult, and several other conditions may mimic symptoms of carpal tunnel syndrome. In Norway, there are no clinical guidelines for the diagnostics and treatment of carpal tunnel syndrome. Standardizing diagnostics and implementing nerve conduction studies may be possible means to reduce unnecessary surgeries. In the reassessment project in England, early access to nerve conduction testing to confirm diagnosis and predict surgical outcome was pointed out as important. In the clinical decision tool UpToDate nerve conduction testing is recommended in patients being considered for surgery (16). In Norway, such examinations are available in all health regions. According to the project's clinical experts, waiting times have previously been long but are at present acceptable. The importance of nerve conduction studies was highlighted by the clinical experts and patient representatives in this project.

## Need for research

Research on the efficacy of steroid injection versus surgery is warranted, as the current evidence is insufficient. Trials of steroid injection versus placebo have shown that it

may be an effective treatment at least in the short term. A RCT of steroid injection versus surgery is planned at Diakonhjemmet Hospital in Norway and will start recruiting patients in 2022 (The Nor-Cactus trial). Other trials of surgery versus steroid injections are ongoing (Appendix 6, Table 1). These trials will hopefully answer questions regarding the efficacy, treatment duration, the presence of median nerve injury and need for repeated injections in patients with carpal tunnel syndrome. More research of physical therapy is also needed to confirm the findings from the trials included in this review, which were performed by one research group at a Spanish hospital.

The knowledge that a proportion of patients having non-surgical treatment may end up having surgery within one year (around 40% after 1 year in the two included multicenter trials comparing surgery with splinting or a combination of NSAIDs, hand therapy and splinting) (45;54), could help research groups in the planning of future trials. An adequate number of patients should be included to ensure sufficient power to reveal potential differences in outcomes between groups.

The results in this review mostly apply to patients with mild to moderate carpal tunnel syndrome. Studies that explore the efficacy of relevant treatments based on severity of the disease, i.e., patients with mild, moderate, or severe carpal tunnel syndrome, would help elucidate whether some patient groups benefit more from the specific treatments than others. If future research shows that some patient groups benefit more from one of the treatment alternatives, a model-based health economic evaluation should assess the use of resources in relation to health benefit of the different treatment alternatives.

# Conclusion

Although surgery for carpal tunnel syndrome has been an established procedure for decades, current evidence is insufficient to draw firm conclusions about the efficacy of surgery compared to non-surgical treatments. Low-certainty evidence from multicenter studies demonstrated a superior effect of surgery compared to splinting and combinations of non-surgical treatments (NSAIDs, physical therapy and splinting) in patients with mild to moderate carpal tunnel syndrome at 1 year. However, the effect sizes were small and close to what is considered clinically relevant. Unfortunately, the relative efficacy of surgery compared to local steroid injection and manual therapy remains unclear due to very low-certainty evidence from existing studies. Severe adverse events occurred occasionally after surgery, but small RCTs are not suitable to make reliable comparisons of adverse events. No trials explored the efficacy of surgery in subpopulations with mild, moderate, and severe carpal tunnel syndrome.

Surgery is the most costly alternative for the treatment of patients with mild to moderate carpal tunnel syndrome. An unexplained regional variation in the provision of surgery in Norway suggests that there is a potential for cost-saving per health region and at the national level if patients with mild to moderate carpal tunnel syndrome are initially treated with the non-surgical alternatives.

# References


1. Kleopa KA. In the Clinic. Carpal Tunnel Syndrome. Ann Intern Med 2015;163(5):Itc1.
2. Keir PJ, Rempel DM. Pathomechanics of peripheral nerve loading. Evidence in carpal tunnel syndrome. J Hand Ther 2005;18(2):259-69.
3. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of carpal tunnel syndrome in a general population. JAMA 1999;282(2):153-8.
4. Latinovic R, Gulliford MC, Hughes RA. Incidence of common compressive neuropathies in primary care. J Neurol Neurosurg Psychiatry 2006;77(2):263-5.
5. Ortiz-Corredor F, Enríquez F, Díaz-Ruíz J, Calambas N. Natural evolution of carpal tunnel syndrome in untreated patients. Clin Neurophysiol 2008;119(6):1373-8.
6. Padua L, Padua R, Aprile I, Pasqualetti P, Tonali P. Multiperspective follow-up of untreated carpal tunnel syndrome: a multicenter study. Neurology 2001;56(11):1459-66.
7. Mondelli M, Passero S, Giannini F. Provocative tests in different stages of carpal tunnel syndrome. Clin Neurol Neurosurg 2001;103(3):178-83.
8. Sonoo M, Menkes DL, Bland JDP, Burke D. Nerve conduction studies and EMG in carpal tunnel syndrome: Do they add value? Clinical neurophysiology practice 2018;3:78-88.
9. Nodera H, Herrmann DN, Holloway RG, Logigian EL. A Bayesian argument against rigid cut-offs in electrodiagnosis of median neuropathy at the wrist. Neurology 2003;60(3):458-64.
10. Retningslinjer for metoder i KNF [klinisk nevrofysiologi] [nettdokument]. [Oslo]: Norsk forening for klinisk nevrofysiologi, DNLF [updated 16.12.2014; cited 09.03.2021]. Available from: https://www.legeforeningen.no/foreningsledd/fagmed/norsk-forening-for-klinisk-nevrofysiologi/Faglige-ressurser/metoder-prosedyrer/retningslinjer-for-metoder-i-knf-/
11. Todnem K, Sand T. Nevrografi ved karpaltunnelsyndrom. Tidsskr Nor Laegeforen 2013;133(2):170-3.
12. Padua L, Coraci D, Erra C, Pazzaglia C, Paolasso I, Loreti C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. The Lancet Neurology 2016;15(12):1273-84.
13. Cartwright MS, Hobson-Webb LD, Boon AJ, Alter KE, Hunt CH, Flores VH, et al. Evidence-based guideline: neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome. Muscle Nerve 2012;46(2):287-93.
14. McDonagh C, Alexander M, Kane D. The role of ultrasound in the diagnosis and management of carpal tunnel syndrome: a new paradigm. Rheumatology (Oxford) 2015;54(1):9-19.
15. Moran L, Perez M, Esteban A, Bellon J, Arranz B, del Cerro M. Sonographic measurement of cross-sectional area of the median nerve in the diagnosis of

carpal tunnel syndrome: correlation with nerve conduction studies. J Clin Ultrasound 2009;37(3):125-31.
16. Kothari JM. Carpal tunnel syndrome: Clinical manifestations and diagnosis. UpToDate [database]. Waltham, MA: UpToDate, Inc [updated 18.06.2020; cited 16.09.2020]. Available from: https://www.uptodate.com/contents/carpal-tunnel-syndrome-clinical-manifestations-and-diagnosis
17. Bland JD. A neurophysiological grading scale for carpal tunnel syndrome. Muscle Nerve 2000;23(8):1280-3.
18. Padua L, Lo Monaco M, Padua R, Gregori B, Tonali P. Neurophysiological classification of carpal tunnel syndrome: assessment of 600 symptomatic hands. Ital J Neurol Sci 1997;18(3):145-50.
19. Lane JCE, Craig RS, Rees JL, Gardiner MD, Green J, Prieto-Alhambra D, et al. Serious postoperative complications and reoperation after carpal tunnel decompression surgery in England: a nationwide cohort analysis. Lancet Rheumatol 2021;3(1):e49-e57.
20. Carlson H, Colbert A, Frydl J, Arnall E, Elliot M, Carlson N. Current options for nonsurgical management of carpal tunnel syndrome. Int J Clin Rheumtol 2010;5(1):129-42.
21. Kothari JM. Carpal tunnel syndrome: Treatment and prognosis [database]. Waltham, MA: UpToDate [updated 18.06.2020; cited 09.03.2021]. Available from: https://www.uptodate.com/contents/carpal-tunnel-syndrome-treatment-and-prognosis
22. American Academy of Orthopaedic Surgeons. Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2016. Available from: https://www.aaos.org/globalassets/quality-and-practice-resources/carpal-tunnel/cts-cpg_4-25-19.pdf
23. Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, et al. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993;75(11):1585-92.
24. Leite JCdC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskelet Disord 2006;7(1):78.
25. Mehta SP, Weinstock-Zlotnick G, Akland KL, Hanna MM, Workman KJ. Using Carpal Tunnel Questionnaire in clinical practice: A systematic review of its measurement properties. J Hand Ther 2020;33(4):493-506.
26. Uleberg B, Mathisen S, Shu J, Balteskard L, Steindal AH, Byhring HS, et al. Dagkirurgi i Norge 2013-2017. Tromsø: Senter for klinisk dokumentasjon og evaluering; 2018. SKDE-rapport Nr. 2/2018. Available from: https://helseatlas.no/sites/default/files/dagkirurgi_2013-2017.pdf
27. Kirurgi ved karpaltunnelsyndrom - Prosjektplan for fullstendig metodevurdering. Oslo: Folkehelseinstituttet; 2020. Available from: https://www.fhi.no/cristin-prosjekter/aktiv/kirurgi-ved-karpaltunnelsyndrom----prosjektplan-for-fullstendig-metodevurde/
28. Risstad H, Elvsaas I, Evensen L, Hamidi V, Espeland A, Hafstad E, et al. Surgery for carpal tunnel syndrome: a health technology assessment. International HTA Database [database]. Oslo: Norwegian Institute of Public Health [cited 20.08.2020]. Available from: https://database.inahta.org/article/19553
29. Search Filters for MEDLINE in Ovid Syntax and the PubMed translation: McMaster University. [cited]. Available from: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx

30. Search Strategies for EMBASE in Ovid Syntax McMaster University [cited]. Available from: https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx
31. The EndNote Team. EndNote X9 [software]. Philadelphia, PA: Clarivate; 2013.
32. Covidence systematic review software [software]. Melbourne, Australia: Veritas Health Innovation.
33. Område for helsetjenester i Folkehelseinstituttet. Slik oppsummerer vi forskning. Håndbok for Folkehelseinstituttet. 4. reviderte ed. Oslo: Folkehelseinstituttet: 2018.
34. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
35. Review Manager. Version 1.22.0 [software]. The Cochrane Collaboration; 2020.
36. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions [nettdokument]. Cochrane; [updated September 2020; cited 07. desember 2020]. Available from: www.training.cochrane.org/handbook
37. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
38. GRADE handbook for grading quality of evidence and strength of recommendations: The GRADE Working Group [cited]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html
39. Evidence Prime. GRADEpro GDT: GRADEpro Guideline Development Tool [software]. McMaster University; 2020.
40. For Patient Groups and Individual Patients: Patient Group Submission Templates: Medicine's HTA [webpage]. Health Technology Assessment International (HTAi) [cited 20.08.2021]. Available from: https://htai.org/interest-groups/pcig/resources/for-patients-and-patient-groups/
41. Shi Q, Bobos P, Lalone EA, Warren L, MacDermid JC. Comparison of the Short-Term and Long-Term Effects of Surgery and Nonsurgical Intervention in Treating Carpal Tunnel Syndrome: A Systematic Review and Meta-Analysis. Hand (New York, NY) 2020;15(1):13-22.
42. Huisstede BM, van den Brink J, Randsdorp MS, Geelen SJ, Koes BW. Effectiveness of Surgical and Postsurgical Interventions for Carpal Tunnel Syndrome-A Systematic Review. Arch Phys Med Rehabil 2018;99(8):1660-80.e21.
43. Klokkari D, Mamais I. Effectiveness of surgical versus conservative treatment for carpal tunnel syndrome: A systematic review, meta-analysis and qualitative analysis. Hong Kong Physiother J 2018;38(2):91-114.
44. D'Angelo K, Sutton D, Cote P, Dion S, Wong JJ, Yu H, et al. The effectiveness of passive physical modalities for the management of soft tissue injuries and neuropathies of the wrist and hand: a systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) collaboration. J Manipulative Physiol Ther 2015;38(7):493-506.
45. Jarvik JG, Comstock BA, Kliot M, Turner JA, Chan L, Heagerty PJ, et al. Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial. Lancet 2009;374(9695):1074-81.
46. Garland H, Langworth EP, Taverner D, Clark JM. Surgical treatment for the carpal tunnel syndrome. Lancet 1964;1(7343):1129-30.
47. De Kleermaeker F, Meulstee J, Claes F, Kasius KM, Verhagen WIM. Treatment outcome in patients with clinically defined carpal tunnel syndrome but normal electrodiagnostic test results: a randomized controlled trial. J Neurol 2017;264(12):2394-400.
48. Fernández-de-Las Peñas C, Ortega-Santiago R, de la Llave-Rincón AI, Martínez-Perez A, Fahandezh-Saddi Díaz H, Martínez-Martín J, et al. Manual Physical

Therapy Versus Surgery for Carpal Tunnel Syndrome: A Randomized Parallel-Group Trial. J Pain 2015;16(11):1087-94.
49. Fernandez-de-Las-Penas C, Cleland J, Palacios-Cena M, Fuensalida-Novo S, Alonso-Blanco C, Pareja JA. Effectiveness of manual therapy versus surgery in pain processing due to carpal tunnel syndrome: a randomized clinical trial. Eur J Pain 2017.
50. Fernandez-de-Las-Penas C, Cleland J, Palacios-Cena M, Fuensalida-Novo S, Pareja JA, Alonso-Blanco C. The Effectiveness of Manual Therapy Versus Surgery on Self-reported Function, Cervical Range of Motion, and Pinch Grip Force in Carpal Tunnel Syndrome: A Randomized Clinical Trial. J Orthop Sports Phys Ther 2017;47(3):151-61.
51. Ly-Pen D, Andréu JL, de Blas G, Sánchez-Olaso A, Millán I. Surgical decompression versus local steroid injection in carpal tunnel syndrome: a one-year, prospective, randomized, open, controlled clinical trial. Arthritis Rheum 2005;52(2):612-9.
52. Hui AC, Wong S, Leung CH, Tong P, Mok V, Poon D, et al. A randomized controlled trial of surgery vs steroid injection for carpal tunnel syndrome. Neurology 2005;64(12):2074-8.
53. Ucan H, Yagci I, Yilmaz L, Yagmurlu F, Keskin D, Bodur H. Comparison of splinting, splinting plus local steroid injection and open carpal tunnel release outcomes in idiopathic carpal tunnel syndrome. Rheumatol Int 2006;27(1):45-51.
54. Gerritsen AA, de Vet HC, Scholten RJ, Bertelsmann FW, de Krom MC, Bouter LM. Splinting vs surgery in the treatment of carpal tunnel syndrome: a randomized controlled trial. JAMA 2002;288(10):1245-51.
55. Ly-Pen D, Andréu JL, Millán I, de Blas G, Sánchez-Olaso A. Comparison of surgical decompression and local steroid injection in the treatment of carpal tunnel syndrome: 2-year clinical results from a randomized trial. Rheumatology (Oxford) 2012;51(8):1447-54.
56. Andreu JL, Ly-Pen D, Millán I, de Blas G, Sánchez-Olaso A. Local injection versus surgery in carpal tunnel syndrome: neurophysiologic outcomes of a randomized clinical trial. Clin Neurophysiol 2014;125(7):1479-84.
57. Fernandez-de-Las-Penas C, Arias-Buria JL, Cleland JA, Pareja JA, Plaza-Manzano G, Ortega-Santiago R. Manual Therapy Versus Surgery for Carpal Tunnel Syndrome: 4-Year Follow-Up From a Randomized Controlled Trial. Phys Ther 2020;100(11):1987-96.
58. Gerritsen AAM, Scholten RJPM, Assendelft WJJ, Kuiper H, de Vet HCW, Bouter LM. Splinting or surgery for carpal tunnel syndrome? Design of a randomized controlled trial [ISRCTN18853827]. BMC Neurol 2001;1(1):8.
59. Herskovitz S, Berger AR, Lipton RB. Low-dose, short-term oral prednisone in the treatment of carpal tunnel syndrome. Neurology 1995;45(10):1923-5.
60. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149-58.
61. Helse- og omsorgsdepartementet. Verdier i pasientens helsetjeneste: Melding om prioritering. 2016. Meld. St. 34 (2015–2016). Available from: https://www.regjeringen.no/no/dokumenter/meld.-st.-34-20152016/id2502758/
62. Statens legemiddelverk. Retningslinjer for dokumentasjonsgrunnlag for hurtig metodevurdering av legemidler: Gyldig fra 01.01.2018. Oppdatert 20.05.2020. Oslo: Statens legemiddelverk; 2017. Available from: https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Dokumentasjon%20til%20metodevurdering/Retningslinjer%2020.05.2020.pdf

63. Helsedirektoratet. Økonomisk evaluering av helsetiltak: en veileder. Oslo: Helsedirektoratet; 2012. Veileder IS-1985. Available from: https://www.helsedirektoratet.no/veiledere/okonomisk-evaluering-av-helsetiltak/%C3%98konomisk%20evaluering%20av%20helsetiltak%20%E2%80%93%20Veileder.pdf
64. Den norske legeforening. Normaltariff for avtalespesialister 2020-2021. Oslo: Den norske legeforening. Available from: https://normaltariffen.legeforeningen.no/asset/pdf/Avtalespesialister-2020-2021.pdf
65. Helsedirektoratet. Innsatsstyrt finansiering 2021. Oslo: Helsedirektoratet; 2020. Regelverk IS-2966. Available from: https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet/innsatsstyrt-finansiering-isf/ISF-regelverket%202021.pdf
66. Moskvil O, Personal communication with physiotherapist. 03.08.2021.
67. Forskrift om stønad til dekning av utgifter til fysioterapi m.m. FOR-2021-06-24-2191. Available from: https://lovdata.no/dokument/LTI/forskrift/2021-06-24-2191
68. Winge A, Personal communication about data from NPR reported by the Central Norway Regional Health Authority. 05.08.2021.
69. Ly-Pen D, Andreu JL, Millan I, de Blas G, Sanchez-Olaso A. Long-term Outcome of Local Steroid Injections Versus Surgery in Carpal Tunnel Syndrome: Observational Extension of a Randomized Clinical Trial. Hand 2020:1558944720944263.
70. Carpal tunnel syndrome. BMJ Best Practice [database]. London: BMJ Publishing group [updated October 2019; cited 16.09.2020]. Available from: https://bestpractice.bmj.com/topics/en-gb/380
71. Graham B, Peljovich AE, Afra R, Cho MS, Gray R, Stephenson J, et al. The American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guideline on: Management of Carpal Tunnel Syndrome. J Bone Joint Surg Am 2016;98(20):1750-4.
72. Evidence-Based Interventions: Response to the public consultation and next steps. England, UK: NHS England; 2018. Available from: https://www.england.nhs.uk/publication/evidence-based-interventions-response-to-the-public-consultation-and-next-steps/
73. Page MJ, Massy-Westropp N, O'Connor D, Pitt V. Splinting for carpal tunnel syndrome. Cochrane Database Syst Rev 2012;2012(7):Cd010003.
74. Atroshi I, Flondell M, Hofer M, Ranstam J. Methylprednisolone injections for the carpal tunnel syndrome: a randomized, placebo-controlled trial. Ann Intern Med 2013;159(5):309-17.
75. Chesterton LS, Blagojevic-Bucknall M, Burton C, Dziedzic KS, Davenport G, Jowett SM, et al. The clinical and cost-effectiveness of corticosteroid injection versus night splints for carpal tunnel syndrome (INSTINCTS trial): an open-label, parallel group, randomised controlled trial. Lancet 2018;392(10156):1423-33.
76. Kronlage SC, Menendez ME. The benefit of carpal tunnel release in patients with electrophysiologically moderate and severe disease. J Hand Surg Am 2015;40(3):438-44.e1.

# Appendix 1: Conflicts of interest

**Reported conflicts of interest by project participants**

Gjermund Rø (clinical expert)

- Reports financial activities outside the submitted work through being employed and having received payments and grants from a private orthopaedic clinic

Ulf Sundin (external reviewer)

- Reports being employed as a physician at Diakonhjemmet Hospital, which is a private, non-commercial, and publicly financed hospital that offers medical treatment for carpal tunnel syndrome
- Reports being employed as postdoc in a research project (the NOR-CACTUS trial) that will investigate surgical versus medical (steroid injection) treatment for carpal tunnel syndrome. The project is financed by the Regional South-Eastern Norway Health Authority
- Reports being an orthopaedic surgeon and thus may have a personal preference for medical and surgical treatment over other treatment modalities for carpal tunnel syndrome

Other project participants

- None of the other project participants, including authors, clinical experts, patient representatives or reviewers reported conflicts of interests

# Appendix 2: Search strategy

## Search for systematic reviews

Publication period: 2015-2020
Search performed November 23, 2020

**Epistemonikos (Epistemonikos Foundation)**
Advanced search, Title/Abstract

(("carpal tunnel syndrome" OR ((carpal OR median) AND (neuropath* OR "compression neuropathy" OR "compression neuropathies" OR "entrapment neuropathy" OR "entrapment neuropathies" OR "nerve entrapment" OR "nerve entrapments" OR "nerve compression" OR "nerve compressions")) OR ("flexor retinaculum" OR "transverse carpal ligament")) AND (surgery OR surgical OR surgeries OR release* OR decompress* OR neurolysis OR endoscop* OR operative OR operation* OR procedure*))
**Results: 66 (1 broad synthesis, 65 systematic reviews)**

**Cochrane Library of Systematic Reviews (Wiley)**
Advanced search, Search manager

#1 MeSH descriptor: [Carpal Tunnel Syndrome] this term only 694
#2 ((carpal OR median) near/4 (compression NEXT neuropath* OR entrapment NEXT neuropath* OR neuropath* OR nerve NEXT entrapment* OR nerve NEXT compression*)):ti,ab,kw 116
#3 ("flexor retinaculum" OR "transverse carpal ligament"):ti,ab,kw 74
#4 ((carpal next tunnel next syndrome*) or (carpal next canal next syndrome*)):ti,ab,kw 1443
#5 (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*):ti,ab,kw 458291
#6 MeSH descriptor: [Surgical Procedures, Operative] explode all trees 118177
#7 [mh "Carpal Tunnel Syndrome"/su] 221
#8 #1 or #2 or #3 or #4 1500
#9 #8 and (#5 or #6) 872
#10 #9 or #7 with Cochrane Library publication date Between Jan 2015 and Nov 2020, in Cochrane **Reviews** 6

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 20, 2020
Advanced search
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | Carpal Tunnel Syndrome/ | 8692 |
| 2 | ((carpal or median*) adj4 (neuropath* or compression neuropath* or entrapment neuropath* or nerve entrapment* or nerve compression* or entrapment neuropath*)).ti,ab,kf. | 1452 |
| 3 | (carpal tunnel syndrome* or carpal canal syndrome*).ti,ab,kf. | 8757 |
| 4 | (flexor retinaculum or transverse carpal ligament).ti,ab,kf. | 927 |
| 5 | or/1-4 | 12019 |
| 6 | exp Surgical Procedures, Operative/ | 3179356 |
| 7 | (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*).ti,ab,kf. | 3847529 |
| 8 | or/6-7 | 5669544 |
| 9 | 5 and 8 | 5092 |
| 10 | Carpal Tunnel Syndrome/su [Surgery] | 3040 |
| 11 | or/9-10 | 5558 |
| 12 | limit 11 to yr="2015 -Current" | 1318 |
| 13 | limit 12 to "reviews (best balance of sensitivity and specificity)" | 191 |

Database(s): **Embase (Ovid)** 1974 to 2020 November 2020
Advanced search
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | carpal tunnel syndrome/ | 15280 |
| 2 | ((carpal or median*) adj4 (neuropath* or compression neuropath* or entrapment neuropath* or nerve entrapment* or nerve compression* or entrapment neuropath*)).ti,ab,kw. | 1996 |
| 3 | (carpal tunnel syndrome* or carpal canal syndrome*).ti,ab,kw. | 11142 |
| 4 | (flexor retinaculum or transverse carpal ligament).ti,ab,kw. | 1096 |
| 5 | or/1-4 | 17432 |
| 6 | exp surgical technique/ | 1680819 |

| | | |
|---|---|---|
| 7 | (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*).ti,ab,kw. | 4987166 |
| 8 | or/6-7 | 5703814 |
| 9 | 5 and 8 | 6721 |
| 10 | carpal tunnel syndrome/su [Surgery] | 3613 |
| 11 | or/9-10 | 7438 |
| 12 | limit 11 to yr="2015 -Current" | 2065 |
| 13 | limit 12 to "reviews (best balance of sensitivity and specificity)" | 268 |

November 23, 2020:
All databases (Cochrane, Epistemonikos, Medline and Embase) before removal of duplicates: 531.
*Total number of results exported to EndNote: 413.
Results in EndNote after removal of duplicates.: 359
Reults in Covidence after removal of duplicates: 356

*Duplicates were first removed in Ovid (Medline and Embase) before export to EndNote

**Web sites:**

**CADTH** (Canadian Agency for Drugs and Technologies in Health)
Keyword: carpal tunnel syndrome
Limitation to 2015-2020 and Product lines
-Health Technology Assessment
-Rapid Response
-Technology Review
-Therapeutic Review
-INESS (= Institut national d'excellence en santé et en services sociaux)
*7 results

*Since the search was performed, the web site has undergone major changes. This may affect the reproducibility of the search.

**NICE** (National Institute for Health and Care Excellence) – UK
NICE guidance
Keyword: carpal tunnel syndrome
0 results

**SBU** (Swedish Agency for Health Technology Assessment and Assessment of Social Services)
Keyword: karpaltunnelsyndrom
No relevant results in SBU Utvärderar, SBU bereder and Regional HTA

**INAHTA** (International HTA Database)
Carpal AND surg* in All fields
1 result

## Search for randomized controlled trials and ongoing studies

### Ongoing studies

NIH Clinical Trials
Condition or Disease: Carpal Tunnel Syndrome
AND
Other terms: Surgery OR surgical OR surgeries OR endoscopic OR procedure OR operative OR operation OR decompression OR neurolysis OR release
254 results

ICTRP - WHO International Clinical Trials Registry Platform
Simple Search carpal tunnel syndrome AND surg* OR carpal tunnel syndrome AND procedure* OR carpal tunnel syndrome AND operat* OR carpal tunnel syndrome AND endoscopic OR carpal tunnel syndrome AND decompression* OR carpal tunnel syndrome AND neurolys* OR carpal tunnel syndrome AND release
171 results

Total results after removal of duplicates in EndNote: 346

### Randomized controlled trials

Search date December 21, 2020

Database(s): **Ovid MEDLINE(R) ALL** 1946 to December 18, 2020
Advanced search
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | Carpal Tunnel Syndrome/ | 8714 |
| 2 | ((carpal or median*) adj4 (neuropath* or compression neuropath* or entrapment neuropath* or nerve entrapment* or nerve compression* or entrapment neuropath*)).ti,ab,kf. | 1455 |
| 3 | (carpal tunnel syndrome* or carpal canal syndrome*).ti,ab,kf. | 8788 |
| 4 | (flexor retinaculum or transverse carpal ligament).ti,ab,kf. | 930 |

| | | |
|---|---|---|
| 5 | or/1-4 | 12054 |
| 6 | exp Surgical Procedures, Operative/ | 3190129 |
| 7 | (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*).ti,ab,kf. | 3870122 |
| 8 | or/6-7 | 5697126 |
| 9 | 5 and 8 | 5111 |
| 10 | Carpal Tunnel Syndrome/su [Surgery] | 3046 |
| 11 | or/9-10 | 5577 |
| 12 | (randomized controlled trial or controlled clinical trial).pt. | 608339 |
| 13 | (randomized or placebo or randomly or trial or groups).ab. | 2931467 |
| 14 | 12 or 13 | 3074371 |
| 15 | exp animals/ not humans.sh. | 4767460 |
| 16 | 14 not 15 | 2624475 |
| 17 | 11 and 16 | 840 |
| 18 | limit 17 to yr="2016 -Current" | 259 |

We used Cochrane's sensitive filter for RCTs, adapted to Medline, but removed drug therapy.sh

Database(s): **Embase (Ovid)** 1974 to 2020 December 18
Advanced search
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | carpal tunnel syndrome/ | 15292 |
| 2 | ((carpal or median*) adj4 (neuropath* or compression neuropath* or entrapment neuropath* or nerve entrapment* or nerve compression* or entrapment neuropath*)).ti,ab,kw. | 1998 |
| 3 | (carpal tunnel syndrome* or carpal canal syndrome*).ti,ab,kw. | 11161 |
| 4 | (flexor retinaculum or transverse carpal ligament).ti,ab,kw. | 1098 |
| 5 | or/1-4 | 17461 |
| 6 | exp surgical technique/ | 1684873 |

| | | |
|---|---|---|
| 7 | (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*).ti,ab,kw. | 5002849 |
| 8 | or/6-7 | 5720550 |
| 9 | 5 and 8 | 6737 |
| 10 | carpal tunnel syndrome/su [Surgery] | 3608 |
| 11 | or/9-10 | 7453 |
| 12 | randomized controlled trial/ | 636178 |
| 13 | controlled clinical trial/ | 465573 |
| 14 | random*.ti,ab. | 1612934 |
| 15 | randomization/ | 89351 |
| 16 | intermethod comparison/ | 266876 |
| 17 | placebo.ti,ab. | 316852 |
| 18 | (compare or compared or comparison).ti. | 527403 |
| 19 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 2223336 |
| 20 | (open adj label).ti,ab. | 83777 |
| 21 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 239750 |
| 22 | double blind procedure/ | 179422 |
| 23 | parallel group*1.ti,ab. | 26668 |
| 24 | (crossover or cross over).ti,ab. | 108644 |
| 25 | ((assign* or match or matched or allocation) adj5 (alternate or group*1 or intervention*1 or patient*1 or subject*1 or participant*1)).ti,ab. | 344672 |
| 26 | (assigned or allocated).ti,ab. | 406014 |
| 27 | (controlled adj7 (study or design or trial)).ti,ab. | 366385 |
| 28 | (volunteer or volunteers).ti,ab. | 253425 |
| 29 | human experiment/ | 527508 |
| 30 | trial.ti. | 317442 |
| 31 | or/12-30 | 5240726 |

| | | |
|---|---|---|
| 32 | (random* adj sampl* adj7 (cross section* or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) | 8366 |
| 33 | Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.) | 255649 |
| 34 | (((case adj control*) and random*) not randomi?ed controlled).ti,ab. | 17956 |
| 35 | (Systematic review not (trial or study)).ti. | 161459 |
| 36 | (nonrandom$ not random$).ti,ab. | 16660 |
| 37 | random field*.ti,ab. | 2431 |
| 38 | (random cluster adj3 sampl*).ti,ab. | 1330 |
| 39 | (review.ab. and review.pt.) not trial.ti. | 852748 |
| 40 | we searched.ab. and (review.ti. or review.pt.) | 34544 |
| 41 | update review.ab. | 111 |
| 42 | (databases adj4 searched).ab. | 39648 |
| 43 | (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ | 1093715 |
| 44 | Animal experiment/ not (human experiment/ or human/) | 2300931 |
| 45 | or/32-44 | 3612509 |
| 46 | 31 not 45 | 4659862 |
| 47 | 11 and 46 | 1377 |
| 48 | conference abstract.pt. | 3942555 |
| 49 | 47 not 48 | 1228 |
| 50 | limit 49 to yr="2016 -Current" | 339 |

We used Cochrane's sensitive filter for RCTs adapted to Embase with some adjustments.

**Cochrane Central (Wiley)**
**Search date December 21, 2020**
**340 results**
Advanced search, Search manager

Search strategy:

#1 MeSH descriptor: [Carpal Tunnel Syndrome] this term only
#2 ((carpal OR median) near/4 (compression NEXT neuropath* OR entrapment NEXT neuropath* OR neuropath* OR nerve NEXT entrapment* OR nerve NEXT compression*)):ti,ab,kw
#3 ("flexor retinaculum" OR "transverse carpal ligament"):ti,ab,kw
#4 ((carpal next tunnel next syndrome*) or (carpal next canal next syndrome*)):ti,ab,kw
#5 (surgery or surgical or surgeries or release* or decompress* or neurolysis or endoscop* or operative or operation* or procedure*):ti,ab,kw
#6 MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#7 [mh "Carpal Tunnel Syndrome"/su]
#8 #1 or #2 or #3 or #4
#9 #8 and (#5 or #6) with Publication Year from 2016 to 2020, in **Trials**

Total number of records before removal of duplicates: 938.
*Total number of results exported to EndNote: 806.
Results in EndNote after removal of duplicates: 747
Results in Covidence after removal of duplicates: 678

*Duplicates were first removed in Ovid (Medline and Embase) before export to EndNote

# Appendix 3: Studies excluded after full text review

***Table 1**. Overview of publications from primary studies identified through the systematic reviews and search for primary literature that we excluded after full text review*

| Study | Reason for exclusion |
|---|---|
| Abedi, M., Mirkazemi, M., Jamebozorgi, K., Padidar, S., & Izanloo, A. (2019). Evaluating the Effectiveness of Surgical Treatment and Local Steroid Injection in Patients with Carpal Tunnel Syndrome. Razavi Int Med. 2018;6(3):e14338 | Wrong study design. The intervention groups were not randomized. |
| Awan AS, Khan A, Afridi SA, Khan IU, Bhatti SN, Ahmed E, Muhammad G, Khan RS, Sultan S, Lodhi FS. Early response of local steroid injection versus mini incision technique in treatment of carpal tunnel syndrome. J Ayub Med Coll Abbottabad. 2015 Jan-Mar;27(1):192-6. PMID: 26182774. | Follow-up <6 months |
| Berwin JT, Cooper C, Mason W. Injection versus decompression for carpal tunnel syndrome (INDICATE): feasibility trial. J Hand Surg Eur Vol. 2020 Nov;45(9):988-990. doi: 10.1177/1753193420929249. Epub 2020 Jun 5. PMID: 32501127. | Feasibility study |
| Fernández-de-Las-Peñas C, de-la-Llave-Rincón AI, Cescon C, Barbero M, Arias-Buría JL, Falla D. Influence of Clinical, Psychological, and Psychophysical Variables on Long-term Treatment Outcomes in Carpal Tunnel Syndrome: Evidence from a Randomized Clinical Trial. Pain Pract. 2019 Jul;19(6):644-655. doi: 10.1111/papr.12788. Epub 2019 May 23. PMID: 31046185. | Wrong outcomes. The study explores predictors of outcomes after carpal tunnel syndrome. |
| Gurcay AG, Karaahmet OZ, Gurcan O, Kazanci A, Karsli PB, Umay EK, Acer S, Unlu E, Cakci A. Comparison of Short-Term Clinical and Electrophysiological Out- | Wrong study design. The patients were not randomized. |

| | |
|---|---|
| comes of Local Steroid Injection and Surgical Decompression in the Treatment of Carpal Tunnel Syndrome. Turk Neurosurg. 2017;27(3):447-452. doi: 10.5137/1019-5149.JTN.15936-15.0. PMID: 27593766. | |
| Ismatullah. Local steroid injection or carpal tunnel release for carpal tunnel syndrome – which is more effective? J. Postgrad Med Inst 2013; 27(2):194-9 | Follow-up <6 months |
| Ly-Pen D, Andreu JL, Millán I, de Blas G, Sánchez-Olaso A. Long-term Outcome of Local Steroid Injections Versus Surgery in Carpal Tunnel Syndrome: Observational Extension of a Randomized Clinical Trial. Hand (N Y). 2020 Aug 6:1558944720944263. doi: 10.1177/1558944720944263. Epub ahead of print. PMID: 32757777. | Follow-up >5 years |
| Rojo-Manaute JM, Capa-Grasa A, Chana-Rodríguez F, Perez-Mañanes R, Rodriguez-Maruri G, Sanz-Ruiz P, Muñoz-Ledesma J, Aburto-Bernardo M, Esparragoza-Cabrera L, Cerro-Gutiérrez MD, Vaquero-Martín J. Ultra-Minimally Invasive Ultrasound-Guided Carpal Tunnel Release: A Randomized Clinical Trial. J Ultrasound Med. 2016 Jun;35(6):1149-57. doi: 10.7863/ultra.15.07001. Epub 2016 Apr 22. PMID: 27105949. | Wrong comparison: the study compares two surgical methods. |
| Siegmund-Schultze, N. Carpal tunnel syndrome: Manual therapy is over one year as effective as surgery. Deutsches Arzteblatt international 2017;114(19):A952 | Includes no primary data. The author summarizes the results from a study comparing surgery with manual therapy which is included in our health technology assessment. |
| Trull-Ahuir C, Sala D, Chismol-Abad J, Vila-Caballer M, Lisón JF. Efficacy of platelet-rich plasma as an adjuvant to surgical carpal ligament release: a prospective, randomized controlled clinical trial. Sci Rep. 2020 Feb 7;10(1):2085. doi: 10.1038/s41598-020-59113-0. PMID: 32034241; PMCID: PMC7005701. | Wrong comparison. All patients had surgery before randomization to receive one of two types of plasma. |

# Appendix 4: Included studies identified from the systematic reviews

**Table 1.** Overview of included primary studies identified from the systematic reviews

| | Huisstede 2018 (42) | Klokkari 2018 (43) | Shi 2020 (41) | D'Angelo 2015 (44) |
|---|---|---|---|---|
| Andreu 2014[a] | x | x | - | - |
| Fernández-de-las-Peñas 2015 | x | x | x | - |
| Garland1964 | x | - | - | - |
| Gerritsen 2002 | x | x | x | x |
| Hui 2005 | x | x | x | - |
| Jarvik 2009 | x | x | x | - |
| Ly-Pen 2005 | x | x | x | - |
| Ly-Pen 2012[a] | x | x | - | - |
| Ucan 2006 | x | x | x | - |

[a]Publications from the trial by Ly-Pen (2005)

# Appendix 5: Characteristics of included studies

***Table 1***. *Description of each included trial and risk of bias assessments*

| | **De Kleermaeker 2017 (47)** | |
|---|---|---|
| | *Title* | Treatment outcome in patients with clinically defined carpal tunnel syndrome but normal electrodiagnostic test results: a randomized controlled trial |
| | *First author* | De Kleermaeker FGCM |
| | *Year of publication* | 2017 |
| | *Setting* | Hospital |
| | *Country* | The Netherlands |
| | *Aim* | To compare the efficacy of surgery with conservative treatment (local steroid injection, splinting, or no intervention) for carpal tunnel syndrome in patients with normal electrodiagnostic tests |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | No information |
| | *Outcome assessments* | 6 months |
| | *Study registration* | No registration found |
| **Intervention** | *Intervention* | Surgery: Open procedure performed by well-experienced surgeons |
| | *Control* | Offered local steroid injection or nocturnal wrist splint |
| | *N total* | 57 patients |
| | *N intervention* | 39 patients |
| | *N control* | 18 patients |
| **Population** | *Age* | Intervention group: Mean (SD) 44 (12) years<br>Control group: Mean (SD) 41 (9) years |
| | *Sex* | 84% women (82% in the intervention group and 89% in the control group) |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS – moderate* | n/a |

| | | |
|---|---|---|
| | *Severity of CTS – severe* | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS based on a prespecified set of criteria and normal electrodiagnostic findings (no abnormal test results or one abnormal test result) |
| | *Exclusion criteria* | Age ≤18 years, significant language barrier, history of clinical signs of polyneuropathy or hereditary neuropathy with liability to pressure palsies, previous wrist trauma or surgery, rheumatoid arthritis, diabetes mellitus, thyroid disease, alcoholism, arthrosis of the wrist, pregnancy, severe thenar atrophy |
| | *Statistical analyses* | Independent samples T test for continuous variables and Chi square test for categorical variables |
| | *Power calculations* | Yes. Based on expected percent improvement in each group. Estimated sample size 26 patients in the intervention group and 13 patients in the control group. Notably, percent improvement was not an outcome measure in this trial. |
| | *Outcome measures* | Perceived treatment effect (Scale 1-6), BCTQ symptom and function scale. The outcome measures were not predefined as primary or secondary. |
| | *Minimal clinically important difference* | Not defined, but power calculations based on a 35% difference in symptom improvement between groups (tool not described) |
| | *Adverse event definition* | Not defined |
| **Results**[b] | *N at follow-up intervention* | 27/39 (69%) patients |
| | *N at follow-up control* | 16/18 (89%) patients |
| | *Function outcome* | Greater improvement in the intervention group compared to the control group |
| | *Symptom outcome* | Greater improvement in the intervention group compared to the control group |
| | *HRQoL* | n/a |
| | *Adverse events* | Report complex regional pain syndrome in one surgically treated patient, but it is unclear whether they have retrieved information on adverse events systematically |
| | *Nerve conduction studies* | n/a |
| | *Work status* | n/a |
| | | |
| | *Results based on pretreatment severity of CTS* | n/a |

| | | |
|---|---|---|
| | *Crossovers (from non-surgical treatment to surgery)* | n/a |
| | *Co-interventions* | n/a |
| **Risk of bias** | **Judgement**[b] | **Description** |
| *Random sequence generation (selection bias)* | *High risk* | The process of random sequence generation is not described. See "other bias" |
| *Allocation concealment (selection bias)* | *Unclear risk* | Quote: "Patients were assigned by chance using opaque sealed envelopes to surgical decompression or non-surgical treatment, in a ratio of 2:1." See "other bias" |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | No blinding |
| *Incomplete outcome data (attrition bias)* | *High risk* | High attrition rates, attrition unevenly distributed across groups (higher attrition in the intervention group). No ITT analyses performed |
| *Selective reporting (reporting bias)* | *High risk* | No published protocol was identified and therefore it was unclear whether all predefined outcomes were reported |
| *Other bias* | *High risk* | No information about the recruitment process and recruitment period is provided. No patients were excluded due to abnormal findings on electrodiagnostic testing. The trial was not registered in a trial register despite published as late as in 2017. Altogether, this rise the question whether the trial is randomized. |
| **Comment** | | |

*Abbreviations: CTS, carpal tunnel syndrome; BCTQ, Boston Carpal Tunnel Questionnaire; GSS, Global Symptom Score*

[a]*A brief summary of results relevant for this review is reported in this table*

[b]*Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

***Table 2****. Description of each included trial and risk of bias assessments*

| | **Fernández-de-las-Peñas 2017 (pain) (49)** | |
|---|---|---|
| | *Title* | Effectiveness of manual therapy versus surgery in pain processing due to carpal tunnel syndrome: A randomized clinical trial |
| | *First author* | Fernández-de-las-Peñas, C |
| | *Year of publication* | 2017 |

| | | |
|---|---|---|
| | *Setting* | Local hospital in Madrid |
| | *Country* | Spain |
| | *Aim* | To compare the efficacy of manual therapy and surgery for improvement of pain and pain processing in carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | August 2014 – February 2015 |
| | *Outcome assessments* | 3, 6, 9 and 12 months |
| | *Study registration* | Clinicaltrials.gov NCT02219919 (registered August 2014) |
| **Intervention** | *Intervention* | Manual therapy: Desensitization maneuvres with soft tissue mobilization and nerve/tendon gliding exercises, 30 min. per per week for 3 weeks, and home exercises twice per day for 1 month. |
| | *Control* | Surgery: Open or endoscopic by the surgeons' preference. Highly experienced surgeons. Additionally, the same home tendon/nerve gliding exercises as the intervention group. |
| | *N total* | 100 |
| | *N intervention* | 50 |
| | *N control* | 50 |
| **Population** | *Age* | Intervention: Mean (SD) 47 (10) years<br>Control: Mean (SD) 48 (9) years |
| | *Sex* | 100% female |
| | *Severity of CTS – mild*[a] | Manual therapy 18 (36%) and surgery 15 (30%) |
| | *Severity of CTS -moderate*[a] | Manual therapy 16 (32%) and surgery 17 (34%) |
| | *Severity of CTS -severe*[a] | Manual therapy 16 (32%) and surgery 18 (36%) |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, positive Tinel sign, positive Phalen sign, symptom duration at least 6 months, pathological findings on neurography |
| | *Exclusion criteria* | Age >65 years, men, systemic disease (diabetes, thyroid disease, rheumatic disease, other musculoskeletal disease etc.), other upper extremity disease or condition, pregnancy, previous treatment with surgery or steroid injection |
| | *Statistical analyses* | Report performing ITT-analyses. Multiple imputation used for missing data. Outcomes presented as mean (95%) CI, difference between groups analysed with ANCOVA |
| | *Power calculations* | Yes. Calculated based on difference in the primary endpoint (time point not provided). Estimated sample size 40 patients in each group, 50 including expected dropouts |

| | | |
|---|---|---|
| | *Outcome measures* | Primary endpoint: Pressure pain sensitivity (time point not provided)<br>Secondary endpoints: a) Pain (current and highest/lowest in the preceding week); NPRS b) Thermal pain thresholds |
| | *Minimal clinically important difference* | n/a |
| | *Adverse event definition* | Sequelae of medium-term duration perceived distressing by the patient and requiring further treatment |
| **Results**[b] | *N at follow-up intervention* | 48 (96%) at 6 months, 47 (94%) at 12 months |
| | *N at follow-up control* | 50 (100%) at 6 months, 48 (96%) at 12 months |
| | *Function outcome* | n/a |
| | *Symptom outcome* | Pain: No difference between groups at 6 and 12 months. Results are presented graphically, not with exact numbers. Exact numbers were retrieved from personal communication with the author. |
| | *HRQoL* | n/a |
| | *Adverse events* | No adverse events reported |
| | *Nerve conduction studies* | n/a |
| | *Work status* | n/a |
| | *Results based on pretreatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | None |
| | *Co-interventions* | 2 patients in the manual therapy group received steroid injections at 12 months, 2 patients in the surgery group had a new surgical procedure at 12 months |
| **Risk of bias** | **Judgement**[c] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated by an external researcher not involved in recruitment |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed envelopes by a researcher not involved in recruitment |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | Follow-up personnel were attempted blinded to group assignment. However, outcomes are patient-reported and are therefore considered to confer a high risk of bias. |

| | | |
|---|---|---|
| *Incomplete outcome data (attrition bias)* | *Low risk* | Low attrition rates. The authors report doing ITT analyses, but patients receiving co-intervention seem to be excluded from the analyses. However, the numbers were small and do probably not have a serious effect on the results. |
| *Selective reporting (reporting bias)* | *Low risk* | All predefined outcomes are reported. Trial registered on clinicaltrials.gov prior to study start. |
| *Other bias* | *Unclear risk* | All patients who were eligible for study inclusion accepted to participate. This seems unlikely in a clinical setting, where patients often have a treatment preference. This rises question about the recruitment process. |
| **Comment** | | |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat, ANCOVA, analysis of covariance; NPRS, Numerical Pain Rating Scale; HRQoL, health-related quality of life*

*[a]Carpal tunnel syndrome severity classification according to findings on electrophysiological testing*

*[b]A brief summary of results relevant for this review is reported in this table*

*[c]Risk of bias stratification: **Low risk**, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results; **Unclear risk**, there is an unclear risk of bias, which may influence the results; **High risk**, the detected risk of bias may have a serious effect on the results*

***Table 3**. Description of each included trial and risk of bias assessments*

| | **Fernández-de-las-Peñas 2015 and 2020 (48;57)** | |
|---|---|---|
| | *Title* | I) Manual physical therapy versus surgery for carpal tunnel syndrome: A randomized parallel-group trial<br>II) Manual therapy versus surgery for carpal tunnel syndrome: 4 year follow-up from a randomized controlled trial |
| | *First author* | Fernández-de-las-Peñas, C |
| | *Year of publication* | I: 2015<br>II: 2020 |
| | *Setting* | Public hospital and 2 physical therapy practices in Madrid |
| | *Country* | Spain |
| | *Aim* | To compare the efficacy of manual physical therapy including desensitization maneuvers of the central nervous system with surgery in patients with carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | February 2013 – January 2014 |
| | *Outcome assessments* | I: 1, 3, 6 and 12 months<br>II: 4 years |
| | *Study registration* | www.clinicaltrials.gov NCT01789645 (February 2013) |
| **Intervention** | *Intervention* | Manual therapy: Treatment sessions of 30 min, once per week for 3 weeks. The treatment included desensitization maneuvers with soft tissue mobilization and nerve/tendon gliding exercises directed at anatomical sites of potential entrapment |

| | | |
|---|---|---|
| | | of the median nerve. Additionally, educational tendon and nerve gliding exercises at home. Experienced physical therapists. |
| | *Control* | Surgery: Open or endoscopic by the surgeons' preference. Highly experienced surgeons. Additionally, the same home exercises as the intervention group. |
| | *N total* | 120 |
| | *N intervention* | 60 |
| | *N control* | 60 |
| **Population** | *Age* | Intervention group: Mean (SD) 47 (10) years<br>Control group: Mean (SD) 46 (9) years |
| | *Sex* | 100% female |
| | *Severity of CTS – mild*[a] | Manual therapy 16 (26%) and surgery 17 (28%) |
| | *Severity of CTS -moderate*[a] | Manual therapy 23 (39%) and surgery 20 (34%) |
| | *Severity of CTS -severe*[a] | Manual therapy 21 (35%) and surgery 23 (38%) |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, positive Tinel sign, positive Phalen sign, symptom duration at least 12 months, pathological findings on neurography, women |
| | *Exclusion criteria* | Age >65 years, men, systemic disease (diabetes, thyroid disease, rheumatic disease, other musculoskeletal disease etc.), pregnancy, depression, other upper extremity disease or condition including trauma, previous treatment with surgery or steroid injection |
| | *Statistical analyses* | I: Report performing ITT-analyses. Last information carried forward used for missing data. Continuous outcomes presented as mean (95% CI), difference between groups analysed with ANCOVA. Self-perceived improvement and success rates analysed with Chi-square test.<br>II: ITT and per protocol analyses. Multiple imputation for missing data. Mixed model analyses used for continuous outcomes and presented as mean (95% CI). |
| | *Power calculations* | Yes. Calculated based on pilot data on difference in the primary endpoint. Estimated sample size 50 patients in each group, 60 including expected dropouts |
| | *Outcome measures* | Primary endpoint: Hand pain – current and worst in the preceding week: NPRS at 12 months<br>Secondary endpoints: a) Hand pain: NPRS at other time points b) Function: BCTQ c) Symptoms: BCTQ d) Self-perceived improvement: GROC |
| | *Minimal clinically important difference* | NPRS: 30% decrease in pain intensity. BCTQ function: 0.74 points. BCTQ symptoms: 1.14 points. GROC: +4 and +5 points |

| | | |
|---|---|---|
| | *Adverse event definition* | Sequela of medium-term duration with any symptom perceived as distressing and unacceptable to the patient and requiring further treatment. Information retrieved at each follow-up visit |
| **Results**[b] | *N at follow-up intervention* | I: 58 (97%) at 6 months, 55 (92%) at 12 months<br>II: 48 (80%) |
| | *N at follow-up control* | I: 60 (100%) at 6 months, 56 (93%) at 12 months<br>II: 49 (82%) |
| | *Function outcome* | I: No difference between groups at 6 and 12 months<br>II: No difference between groups at 4 years |
| | *Symptom outcome* | I: No difference between groups at 6 and 12 months.<br>II: No difference between groups at 4 years |
| | *HRQoL* | n/a |
| | *Adverse events* | I: No adverse events reported |
| | *Nerve conduction studies* | n/a |
| | *Work status* | n/a |
| | *Results based on pr-treatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | I: 3 patients at 12 months<br>II: 9 patients at 4 years |
| | *Co-interventions* | I: 3 patients in the surgery group had surgery in the other hand at 12 months<br>II: 8 patients in the surgery group had a new surgical procedure at 4 years. 12 patients in the manual therapy group and 16 patients in the surgery group had other treatments, for example physical therapy |
| **Risk of bias** | **Judgement**[c] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated randomization table created by statistician not involved in the trial |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed envelopes by a researcher not involved in recruitment |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | Follow-up personnel were blinded to group assignment. However, outcomes were patient-reported and were therefore considered to confer a high risk of bias |
| *Incomplete outcome data (attrition bias)* | *Low risk* | Low attrition rates at 12 months. The authors report doing ITT analyses, but patients in the manual therapy group who re- |

| | | |
|---|---|---|
| | | ceived surgery and patients in the surgery group who had repeat surgery or surgery on the other hand seem to be excluded from the analyses. However, the numbers were small and do probably not have a serious effect on the results. |
| *Selective reporting (reporting bias)* | *Low risk* | All predefined outcomes are reported |
| *Other bias* | *Unclear risk* | All patients who were eligible for inclusion accepted to participate. This seems unlikely in a clinical setting, where patients often have a treatment preference. This rises question about the recruitment process. |
| **Comment** | | Risk of bias judgement is based on the main publication. In the 4-year follow-up attrition rates were higher, there were more crossovers and co-intervention which could have a serious effect on the results. |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat; ANCOVA, analysis of covariance, BCTQ, Boston Carpal Tunnel Questionnaire; BCTQ; NPRS, Numerical Pain Rating Scale; GROC, Global Rating of Change, HRQoL, health-related quality of life*

*[a]Carpal tunnel syndrome severity classification according to findings on electrophysiological testing*

*[b]A brief summary of results relevant for this review is reported in this table*

*[c] Risk of bias stratification: **Low risk**, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results; **Unclear risk**, there is an unclear risk of bias, which may influence the results; **High risk**, the detected risk of bias may have a serious effect on the results*

***Table 4**. Description of each included trial and risk of bias assessments*

| | **Fernández-de-las-Peñas 2017 (function) (50)** | |
|---|---|---|
| | *Title* | The effectiveness of manual therapy versus surgery on self-reported function, cervical range of motion, and pinch grip force in carpal tunnel syndrome: A randomized clinical trial |
| | *First author* | Fernández-de-las-Peñas, C |
| | *Year of publication* | 2017 |
| | *Setting* | Local hospital in Madrid |
| | *Country* | Spain |
| | *Aim* | To compare the efficacy of manual therapy and surgery for improvement of function, cervical range of motion and pinch-tip grip force in women with carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | September 2014 – February 2015 |
| | *Outcome assessments* | 1, 3, 6 and 12 months |
| | *Study registration* | Clinicaltrials.gov NCT02233660 (September 2014) |

| | | |
|---|---|---|
| **Intervention** | *Intervention* | Manual therapy: Maneuvers targeted to the cervical spine and areas anatomically related to potential entrapment of the median nerve, 30 min. per week for 3 weeks. Additionally, home exercises were given. |
| | *Control* | Surgery: Open or endoscopic by the surgeons' preference. Highly experienced surgeons. Additionally, the same home exercises as the intervention group. |
| | *N total* | 100 |
| | *N intervention* | 50 |
| | *N control* | 50 |
| **Population** | *Age* | Intervention group: Mean (SD) 46 (9) years<br>Control group: Mean (SD) 47 (8) years |
| | *Sex* | 100% female |
| | *Severity of CTS – mild*[a] | Manual therapy 12 (24%) and surgery 10 (20%) |
| | *Severity of CTS -moderate*[a] | Manual therapy 19 (38%) and surgery 23 (46%) |
| | *Severity of CTS -severe*[a] | Manual therapy 19 (38%) and surgery 16 (32%) |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, positive Tinel sign, positive Phalen sign, symptom duration at least 12 months, pathological findings on neurography |
| | *Exclusion criteria* | Age >65 years, men, systemic disease (diabetes, thyroid, rheumatic, or other musculoskeletal disease), other upper extremity disease or condition, pregnancy, previous treatment with surgery or steroid injection |
| | *Statistical analyses* | Report performing ITT-analyses. Multiple imputation used for missing data. Outcomes presented as mean (95% CI), differences between groups analysed with ANCOVA. Success rates analysed with Chi-square test. |
| | *Power calculations* | Yes. Calculated based on difference in the primary endpoint (12 months). Estimated sample size 39 patients in each group, 50 including expected dropouts. |
| | *Outcome measures* | Primary endpoint: Function: BCTQ at 12 months<br>Secondary endpoints: a) Function: BCTQ at other time points, b) Symptoms: BCTQ, c) BCTQ severity subscales, d) Cervical range of motion, e) Pinch grip force |
| | *Minimal clinically important difference* | n/a |
| | *Adverse event definition* | No information provided |
| **Results**[b] | *N at follow-up intervention* | 49 (98%) at 6 months, 47 (94%) at 12 months |
| | *N at follow-up control* | 50 (100%) at 6 months, 47 (94%) at 12 months |

| | | |
|---|---|---|
| | *Function outcome* | No difference between groups at 6 and 12 months |
| | *Symptom outcome* | No difference between groups at 6 and 12 months |
| | *HRQoL* | n/a |
| | *Adverse events* | No clinically important adverse events |
| | *Nerve conduction studies* | n/a |
| | *Work status* | n/a |
| | *Results based on pre-treatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | 3 patients at 12 months |
| | *Co-interventions* | 3 patients in the surgery group were treated with steroid injection at 12 months |
| **Risk of bias** | **Judgement**[c] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated by an external researcher not involved in recruitment |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed envelopes by a researcher not involved in recruitment |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | Follow-up personnel were attempted blinded to group assignment. However, outcomes are patient-reported and are therefore considered to confer a high risk of bias. |
| *Incomplete outcome data (attrition bias)* | *Low risk* | Low attrition rates. The authors reported doing ITT analyses, but crossovers[d] and patients receiving co-intervention seemed to be excluded from the analyses. However, the numbers were small and do probably not have a serious effect on the results. |
| *Selective reporting (reporting bias)* | *Low risk* | All predefined outcomes were reported. Trial registered on clinicaltrials.gov prior to study start. |
| *Other bias* | *Unclear risk* | All patients who were eligible for inclusion accepted to participate. This seems unlikely in a clinical setting, where patients often have a treatment preference. This rises question about the recruitment process. |
| **Comment** | | |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat, ANCOVA, analysis of covariance, BCTQ, Boston Carpal Tunnel Questionnaire; HRQoL, health-related quality of life*

[a]*Carpal tunnel syndrome severity classification according to findings on electrophysiological testing*

[b]*A brief summary of results relevant for this review is reported in this table*

[c] *Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

[d]*Crossovers refers to patient allocated to non-surgical treatment who had surgery during follow-up*

***Table 5****. Description of each included trial and risk of bias assessments*

| | **Garland 1964 (46)** | |
|---|---|---|
| | *Title* | Surgical treatment for the carpal tunnel syndrome |
| | *First author* | Garland H |
| | *Year of publication* | 1964 |
| | *Setting* | Hospital in Leeds |
| | *Country* | England |
| | *Aim* | To compare the efficacy of surgery with splinting for carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | Not specified |
| | *Outcome assessments* | 6 months |
| | *Study registration* | No registration |
| **Intervention** | *Intervention* | Surgery: Open procedure |
| | *Control* | Splinting for 1 months |
| | *N total* | 22 patients |
| | *N intervention* | Unclear |
| | *N control* | Unclear |
| **Population** | *Age* | Mean 47 (range 35 to 63) years |
| | *Sex* | 100% women |
| | *Severity of CTS – mild*[a] | n/a |
| | *Severity of CTS -moderate*[a] | n/a |
| | *Severity of CTS -severe*[a] | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS combined with predefined findings on nerve conduction studies. If both wrists were affected, the worst side was selected for the trial |
| | *Exclusion criteria* | Not specified |

| | | |
|---|---|---|
| | *Statistical analyses* | Not specified |
| | *Power calculations* | No |
| | *Outcome measures* | Not prespecified. Results were reported as number of patients with treatment success, probably as judged by the surgeon |
| | *Minimal clinically important difference* | Not defined |
| | *Adverse event definition* | Not defined |
| **Results**[b] | *N at follow-up intervention* | All surgically treated patients (the exact number is unclear) |
| | *N at follow-up control* | All conservatively treated patients (the exact number is unclear) |
| | *Function outcome* | n/a |
| | *Symptom outcome* | n/a |
| | *HRQoL* | n/a |
| | *Adverse events* | Quote: "No surgical failures" |
| | *Nerve conduction studies* | No results presented except "Nerve conduction tests were normalized in all surgical cases". No results from the control group are reported |
| | *Work status* | n/a |
| | *Results based on pre-treatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | 8 patients in the control group |
| | *Co-interventions* | Not reported |
| **Risk of bias** | **Judgement**[b] | **Description** |
| *Random sequence generation (selection bias)* | *High risk* | The process of random sequence generation is not described |
| *Allocation concealment (selection bias)* | *High risk* | A secretary allocated patients in accordance with a randomization list |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | No blinding |

| | | |
|---|---|---|
| *Incomplete outcome data (attrition bias)* | *High risk* | The attrition is poorly described, but it seems that all patients have been evaluated after the intervention. However, it is unclear how many who attended the study. There is no time frame for follow-up reported |
| *Selective reporting (reporting bias)* | *High risk* | No published protocol or study registration (not expected in 1964). Outcome measures not predefined even in the methods section. The only results reported are success as judged by the surgeon. No objective measures or patient-reported outcomes were systematically retrieved. |
| *Other bias* | *Low risk* | |
| **Comment** | | Most of the results from this study were judgements from the author/surgeon and could not be presented in meta-analyses or summary of findings-tables |

*Abbreviations: CTS, carpal tunnel syndrome*

*[a] A brief summary of results relevant for this review is reported in this table*

*[b] Risk of bias stratification: **Low risk**, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results; **Unclear risk**, there is an unclear risk of bias, which may influence the results; **High risk**, the detected risk of bias may have a serious effect on the results*

***Table 6**. Description of each included trial and risk of bias assessments*

| | **Gerritsen 2002 (54)** | |
|---|---|---|
| | *Title* | Splinting vs surgery in the treatment of carpal tunnel syndrome: A randomized controlled trial |
| | *First author* | Gerritsen, AA |
| | *Year of publication* | 2002 |
| | *Setting* | Multicenter trial from 13 hospitals (neurological outpatient clinics) |
| | *Country* | The Netherlands |
| | *Aim* | To compare the efficacy of splinting and surgery for relieving symptoms of carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | October 1998 – April 2020 |
| | *Outcome assessments* | 3, 6, 12 and 18 months |
| | *Study registration* | Protocol published in 2001 (58) |
| **Intervention** | *Intervention* | Splinting: Prefabricated or custom made splint at night for 6 weeks, and voluntarily during the day. From 6 weeks, further treatment was considered, including further splinting, other conservative treatment, or surgery |
| | *Control* | Surgery: Open surgery, standard carpal tunnel release with no concomitant procedures. Patients instructed in postoperative exercises. Surgery performed by a general surgeon, orthopaedic surgeon, plastic surgeon, or neurosurgeon, depending on the usual hospital procedures |

| | | |
|---|---|---|
| | *N total* | 176 |
| | *N intervention* | 87 |
| | *N control* | 89 |
| **Population** | *Age* | Intervention group: Mean (SD) 49 (11) years<br>Control group: Mean (SD) 49 (12) years |
| | *Sex* | 81% women (76% in the surgery group and 87% in the splinting group) |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS -moderate*[a] | n/a |
| | *Severity of CTS -severe*[a] | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, electrophysiological confirmation of the diagnosis, ≥18 years |
| | *Exclusion criteria* | Previous treatment with splinting or surgery, a history of wrist trauma or surgery, metabolic disease such as diabetes mellitus, pregnancy, other possible conditions, or diagnosis in the hand, severe thenar muscle atrophy |
| | *Statistical analyses* | Report performing ITT-analyses. Continuous outcomes analysed as change scores from baseline with T-tests or linear regression. Categorical outcomes analysed with Chi-square test or logistic regression |
| | *Power calculations* | Yes. Calculated based on a clinically important difference in success rates of at least 20% after 3 months. Estimated sample size 190 patients |
| | *Outcome measures* | Primary endpoint: General improvement (6-point scale) and success rate dichotomized, night awakenings, most severe symptoms (11-point scale)<br>Secondary endpoints: a) Symptom Severity Scale, b) Functional status scale, c) Overall severity judged by physiotherapist, d) Results from electrodiagnostic tests |
| | *Minimal clinically important difference* | Difference in success rate of at least 20% after 3 months (from power calculations) |
| | *Adverse event definition* | All adverse events recorded regardless of severity |
| **Results**[a] | *N at follow-up intervention* | 77 (86%) at 6 months, 73 (84%) at 12 months, 68 (87%) at 18 months |
| | *N at follow-up control* | 86 (94%) at 6 months, 83 (93%) at 12 months, 79 (89%) at 18 months |
| | *Function outcome* | Greater improvement in the surgery group compared to the splinting group at 6 and 12 months, no difference at 18 months |
| | *Symptom outcome* | Greater improvement in the surgery group at all time points |

| | | |
|---|---|---|
| | *HRQoL* | n/a |
| | *Adverse events* | Adverse events were presented, but no statistics done. The number of adverse events were higher in the surgery group. Painful or hypertrophic scar was most frequently reported. One patient had complex regional pain syndrome after surgery |
| | *Nerve conduction studies* | n/a |
| | *Work status* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | 31% patients at 6 months, 39% at 12 months, 41% at 18 months |
| | *Co-interventions* | Specified only at 6 weeks |
| **Risk of bias** | **Judgement**[b] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Randomization stratified by study center. Permuted blocks of 4 patients were generated using random number tables |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed opaque envelopes by the principal investigator, who was not involved in recruitment |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | Follow-up personnel (physiotherapists) were attempted to be blinded to group assignment. The number of physiotherapists wo guessed the received treatment are reported and confirms that blinding in this type of study is difficult. Additionally, most outcomes are patient-reported and are therefore considered to confer a high risk of bias. |
| *Incomplete outcome data (attrition bias)* | *Low risk* | Data analysed with ITT-principle. Increasing attrition rates with time, evenly distributed across groups |
| *Selective reporting (reporting bias)* | *Low risk* | All predefined outcomes were reported except from patient satisfaction, which was specified in the study protocol. Scores on pain and hypoesthesia were not presented with numbers. The risk of bias was still considered as low. |
| *Other bias* | *Low risk* | |
| **Comment** | | Crossovers from the splinting group to surgery probably underestimates the effect of surgical treatment. We have not judged this as a risk of bias |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat, HRQoL, health-related quality of life*

[a]*A brief summary of results relevant for this review is reported in this table*

[b]*Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which*

*may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

***Table 7****. Description of each included trial and risk of bias assessments*

| | **Hui 2005 (52)** | |
|---|---|---|
| | *Title* | A randomized controlled trial of surgery vs steroid injection for carpal tunnel syndrome |
| | *First author* | Hui ACF |
| | *Year of publication* | 2005 |
| | *Setting* | Hospital in Hong Kong |
| | *Country* | China |
| | *Aim* | To compare the effect of surgery with local steroid injection for carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | January 2002 to March 2003 |
| | *Outcome assessments* | (6 and) 20 weeks |
| | *Study registration* | No registration |
| **Intervention** | *Intervention* | Surgery: Open procedure with 2,5–3 cm long incision |
| | *Control* | Local steroid injection: 15 mg methylprednisolone acetate injected median to the palmaris longus tendon. Not ultrasound-guided |
| | *N total* | 50 patients |
| | *N intervention* | 25 patients |
| | *N control* | 25 patients |
| **Population** | *Age* | Intervention group: Mean (SD) 51 (12) years<br>Control group: Mean (SD) 48 (7) years |
| | *Sex* | 96% women |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS -moderate* | n/a |
| | *Severity of CTS -severe* | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS supplied with nerve conduction studies |
| | *Exclusion criteria* | Severe carpal tunnel syndrome (including thenar muscle atrophy and findings on nerve conduction studies), other neuropathies in the upper extremities, coexisting disorders that may mimic CTS, contraindication to steroid use such as active affective disorder and recent peptic ulcer, underlying disorders (including diabetes mellitus, thyroid disease, rheumatoid arthritis, acromegaly), wrist trauma, pregnancy |

| | | |
|---|---|---|
| | *Statistical analyses* | Between-group changes analysed with ANOVA, within-group changes with paired Student t test |
| | *Power calculations* | Yes. Based on assumptions of 90% response in the intervention group and 50% in the control group, i.e. 40% between-group difference for the primary end point. Estimated sample size 50 patients |
| | *Outcome measures* | Primary endpoint: GSS at 20 weeks. Secondary endpoints: Electrodiagnostic tests (median nerve distal motor latency and sensory nerve conduction velocity). Grip strength measurements (hydraulic hand dynamometer) |
| | *Minimal clinically important difference* | Not defined, but power calculations based on a 40% difference between groups in the GSS score |
| | *Adverse event definition* | Not defined |
| **Results**[a] | *N at follow-up intervention* | 25 patients |
| | *N at follow-up control* | 25 patients |
| | *Function outcome* | Greater improvement in grip strength in the control group (20 weeks) |
| | *Symptom outcome* | Greater improvement in GSS score in the intervention group at 20 weeks |
| | *HRQoL* | n/a |
| | *Adverse events* | Adverse events presented, but no statistics done. All complications considered as minor, no major complications |
| | *Nerve conduction studies* | Greater improvement in distal motor latency and sensory nerve conduction velocity in the surgery group |
| | *Work status* | n/a |
| | *Results based on pre-treatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | Not reported |
| | *Co-interventions* | Not reported |
| **Risk of bias** | **Judgement**[b] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated code. A research assistant not involved in the patient follow-up prepared the coded envelopes containing the treatment allocation. |
| *Allocation concealment (selection bias)* | *Unclear risk* | Coded envelopes were used, no other information regarding the allocation process was provided |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |

| | | |
|---|---|---|
| *Blinding of outcome assessment (detection bias)* | *High risk* | Blinding of follow-up personnel was attempted. However, there are several factors that may have unmasked allocation: Assessors obtained information on adverse effects, patients had follow-up at different departments (patients with surgery attended the neurosurgical clinic and patients with steroid injection attended the neurosurgery clinic). |
| *Incomplete outcome data (attrition bias)* | *Low risk* | They report 100% follow-up. Information on number of patients for each outcome measurement was not provided. |
| *Selective reporting (reporting bias)* | *Unclear risk* | No study registration identified, consequently it was unclear whether all predefined outcomes were reported |
| *Other bias* | *Low risk* | |
| **Comment** | | |

*Abbreviations: CTS, carpal tunnel syndrome; ANOVA, Analysis of variance; GSS, Global Symptome Score, BCTQ, Boston Carpal Tunnel Questionnaire*

*[a]A brief summary of results relevant for this review is reported in this table*

*[b]Risk of bias stratification: **Low risk**, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results; **Unclear risk**, there is an unclear risk of bias, which may influence the results; **High risk**, the detected risk of bias may have a serious effect on the results*

***Table 8**. Description of each included trial and risk of bias assessments*

| | **Jarvik 2009 (45)** | |
|---|---|---|
| | *Title* | Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomized parallel-group trial |
| | *First author* | Jarvik, JG |
| | *Year of publication* | 2009 |
| | *Setting* | Multicenter trial from four academic and three private practice centres in Washington state and New Hampshire |
| | *Country* | United States of America |
| | *Aim* | To compare surgery versus multi-modal, non-surgical treatment for carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | October 1998 – April 2020 |
| | *Outcome assessments* | 3, 6, 9 and 12 months |
| | *Study registration* | www.clinicaltrials.gov NCT00032227 |
| **Intervention** | *Intervention* | Surgery: Open or endoscopic procedure, depending on the surgeon's preference. Highly experienced surgeons. Patients referred to hand therapy after surgery as usual care |
| | *Control* | Multi-modal treatment: Non-steroidal anti-inflammatory drugs (ibuprofen 200 mg x 3 daily), hand therapy (one visit per week for 6 weeks) with focus on ligament stretching, tendon gliding, and splint use, splinting recommended at night and during day |

| | | |
|---|---|---|
| | | as tolerated. At 6 weeks; new evaluation. If necessary therapeutic ultrasound (up to 12 sessions in a period of 6 weeks). At 3 months: new evaluation. Referred to surgery if lack of improvement and the patient wanted surgery |
| | *N total* | 116 |
| | *N intervention* | 57 |
| | *N control* | 59 |
| **Population** | *Age* | Intervention group: Mean (SD) 50 (10) years<br>Control group: Mean (SD) 51 (9) years |
| | *Sex* | 53% women (49% in the intervention group and 58% in the control group) |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS -moderate* | n/a |
| | *Severity of CTS -severe* | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, certain electrophysiological criteria, symptom duration at least 2 weeks, non-surgical treatment including splinting for at least 2 weeks, age ≥18 years |
| | *Exclusion criteria* | Severe carpal tunnel syndrome (including thenar muscle atrophy and electrodiagnostic evidence of denervation), history of trauma or hand surgery, arthritis, tumor or deformity of the hand or wrist, pregnancy or lactation, diffuse peripheral neuropathy or cervical radiculopathy |
| | *Statistical analyses* | ITT-analyses. Between-group differences analysed with ANCOVA, success rates analysed with Chi-square test, sensitivity ("as-treated") analyses with mixed models |
| | *Power calculations* | Yes. Calculated based on a treatment effect size of 0.5 points on the CTSAQ function scale at 1 year. Estimated sample size including dropouts 113 patients |
| | *Outcome measures* | Primary endpoint: Function; CTSAQ<br>Secondary endpoints: a) Symptoms: CTSAQ, b) Measures of hand and wrist pain intensity, c) Effect on work and other activities, d) Health-related quality of life: SF-36, e) Additional treatments, f) Successful outcome (prespecified specific criteria) |
| | *Minimal clinically important difference* | Difference between groups of 0.5 points (from power calculations) |
| | *Adverse event definition* | na |
| **Results**[b] | *N at follow-up intervention* | 50/57 (88%) at 6 months, 49/57 (86%) at 12 months |
| | *N at follow-up control* | 54/59 (92%) at 6 months, 52/59 (88%) at 12 months |

| | | |
|---|---|---|
| | *Function outcome* | Greater improvement after surgery compared to the control group at 6 and 12 months, but effect size was slightly less than what was considered clinically important |
| | *Symptom outcome* | Greater improvement in the surgery compared to the control group at 6 and 12 months, but effect size was slightly less than what was considered clinically important. For pain, there were no difference between groups. |
| | *HRQoL* | No difference between groups |
| | *Adverse events* | There were no clinically important complications or adverse events in either group |
| | *Nerve conduction studies* | n/a |
| | *Work status* | No difference between groups |
| | *Crossovers (from non-surgical treatment to surgery)* | 7 (13%) patients at 6 months, 23 (44%) patients at 12 months |
| | *Co-interventions* | One (2%) patient in the surgery group and 15 (26%) patients in the control group had at least one therapeutic ultrasound treatment during the first 6 months (specified in the protocol). |
| **Risk of bias** | **Judgement**[c] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated randomization stratified by site, randomized block sizes of 4-12, performed by personnel not involved in recruitment |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed opaque envelopes by personnel not involved in recruitment |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | Follow-up personnel were attempted to be blinded to group assignment. However, outcomes were patient-reported and are therefore considered to confer a high risk of bias. |
| *Incomplete outcome data (attrition bias)* | *Low risk* | Low attrition rates. Primary analyses done according to ITT principle, secondary analyses with as treated analyses. |
| *Selective reporting (reporting bias)* | *Low risk* | According to the registration on clinicaltrials.gov, end points were predefined at 3 and 12 months, not 6 and 12 months as reported. Additionally, the trial was supposed to evaluate the role of magnetic resonance (MR) for predicting who would likely benefit from surgical treatment, but this was not reported. Risk of bias was still considered low. |
| *Other bias* | *Low risk* | |
| **Comment** | | "As treated" analyses showed greater benefits of surgery compared to controls for some outcomes. |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat; CTSAQ, Carpal Tunnel Assessment Questionnaire; ANCOVA, analysis of covariance; HRQoL, health-related quality of life*

[a]*A brief summary of results relevant for this review is reported in this table*

[b]*Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

***Table 9****. Description of each included study and risk of bias assessments*

| | **Ly-Pen 2005 (51;55;56)** | |
|---|---|---|
| | *Title* | I: Surgical decompression versus local steroid injection in carpal tunnel syndrome: a one-year, prospective, randomized, open, controlled clinical trial<br>II: Comparison of surgical decompression and local steroid injection in the treatment of carpal tunnel syndrome: 2-year clinical results from a randomized trial<br>III: Local injection versus surgery in carpal tunnel syndrome: Neurophsiologic outcomes of a randomized clinical trial |
| | *First author* | I and II: Lyp-Pen D III: Andreu JL |
| | *Year of publication* | I: 2005, II: 2012, III: 2014 |
| | *Setting* | Primary care setting and public general university hospital |
| | *Country* | Spain |
| | *Aim* | To compare local steroid injection with surgical decompression for carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | October 1998 – May 2001 |
| | *Outcome assessments* | I: 3, 6,12 months<br>II: 2 years<br>III: 12 months |
| | *Study registration* | ISRCTN registry, ID26264638 (registered retrospectively) |
| **Intervention** | *Intervention* | Surgery: Open procedure (limited palmar incision technique). |
| | *Control* | Local steroid injection: 1 ml/20 mg paramethasone acetonide injected beneath the transverse carpal ligament from the ulnar side of the wrist. New evaluation after 2 weeks, second injection if nocturnal paresthesia had not disappeared completely. Injections were not ultrasound-guided |
| | *N total* | 163 wrists,101 patients |
| | *N intervention* | 80 |
| | *N control* | 83 |
| **Population** | *Age* | Intervention group: Mean (SD) 51 (11) years<br>Control group: Mean (SD) 53 (14) years |
| | *Sex* | 92% women |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS -moderate* | n/a |

| | | |
|---|---|---|
| | *Severity of CTS -severe* | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS, symptom duration at least 3 months, conservative treatment (non-steroidal anti-inflammatory drugs or splinting) for at least 2 weeks, age ≥18 years. Electrodiagnostic testing used to confirm diagnosis |
| | *Exclusion criteria* | Thenar muscle atrophy, previous treatment with surgery or local steroid injection, pregnancy, diabetes mellitus, hypothyroidism, inflammatory arthropathy, polyneuropathy |
| | *Statistical analyses* | Report performing ITT-analyses but did not retrieve follow-up data from patients who did not receive the allocated treatment or patients who were considered as treatment failures. Categorical variables analysed with Chi-square tests. Hierarchical generalized linear model was used to explore the effect of dependence since wrists, and not patients, were included. Additionally, per protocol analyses were done. |
| | *Power calculations* | Yes. Calculated based on a treatment effect of 20 units between groups in VAS score for nocturnal paraesthesia. Estimated sample size including dropouts was 72 wrists in each group. |
| | *Outcome measures* | Primary endpoint: Percentage of wrists reaching at least 20% improvement in the VAS score for nocturnal paraesthesia at 3 months<br>Secondary endpoints: a) Percentage of wrists reaching at least 20% improvement in the VAS score for nocturnal paraesthesia at 6 and 12 months, b) Percentage of wrists reaching at least 20% improvement in the VAS score for pain and functional impairment at 3, 6 and 12 months, c) Percentage of wrists reaching at least 50% and 70% improvement in the VAS score for nocturnal paraesthesia, pain, and functional impairment at 3, 6 and 12 months |
| | *Minimal clinically important difference* | 20% reduction in VAS scale for all outcomes |
| | *Adverse event definition* | n/a |
| **Results**[a] | *N at follow-up intervention* | I: 63/80 (79%) at 6 months, 57/80 (71%) at 12 months<br>II: 55/80 (69%) at 2 years<br>III: 45/80 (56%) at 12 months |
| | *N at follow-up control* | I: 77/83 (93%) at 6 months, 66/83 (80%) at 12 months<br>II: 48/83 (58%) at 2 years<br>III: 50/83 (60%) at 12 months |
| | *Function outcome* | I: The proportion of patients with 70% improvement in VAS was slightly greater in the surgery group at 12 months. For all other outcomes there were no differences between groups<br>II: The proportion of patients with 70% improvement in VAS was greater in the surgery group at 2 years |
| | *Symptom outcome* | I: No differences between groups in nocturnal paraesthesia or pain |

| | | |
|---|---|---|
| | | II: The proportion of patients with 70% improvement in VAS for nightly paraesthesia was greater in the surgery group at 2 years. No differences between groups in pain |
| | *HRQoL* | n/a |
| | *Adverse events* | I: Adverse events reported, no statistics done. The authors considered the events as clinically irrelevant, or not related to the initial treatment<br>II: n/a |
| | *Nerve conduction studies* | III: Improvement in 3 out of 4 outcome measures within the intervention group, no changes in outcomes within the control group. No between-group analyses were presented. |
| | *Work status* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | I: Not reported<br>II: 10/66 (15,1%) at 2 years |
| | *Co-interventions* | 69/83 (83%) patients in the control group received a second steroid injection according to protocol. Treatment failures were offered alternative treatment as follows: wide-incision surgical decompression for patients who had surgery and limited palmar incision surgery in patients who had received steroid injection. At 2 years, 9 wrists in the surgery group and 26 wrists in the steroid injection group were considered as treatment failures. The number of wrists who received alternative treatment was not reported |
| **Risk of bias** | **Judgement**[b] | **Description** |
| *Random sequence generation (selection bias)* | *Low risk* | Computer-generated randomization in blocks of 6 cases was performed by personnel not involved in recruitment. |
| *Allocation concealment (selection bias)* | *Low risk* | Treatment assignment prepared in sealed opaque envelopes by personnel not involved in recruitment. Envelope with treatment assignment was opened immediately after enrolment. |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | No blinding |
| *Incomplete outcome data (attrition bias)* | *High risk* | Primary analyses were reported done according to ITT principle, but wrists who did not receive the allocated treatment (n=11 in the intervention group and n=1 in the control group), wrists considered as treatment failures, and wrists lost to follow-up were excluded from the analyses. Follow-up data was different across groups. |
| *Selective reporting (reporting bias)* | *Unclear risk* | The trial was registered retrospectively. In the “as treated” analyses, total VAS score for all outcomes were reported instead of proportion of wrists with specific improvements as described in the predefined endpoints. |

| | | |
|---|---|---|
| *Other bias* | *Low risk* | |
| **Comment** | | A substantial proportion of patients had bilateral carpal tunnel syndrome. Since wrists, and not patients, were randomized, the statistical analyses may introduce bias as the patients were not handled as clusters in the statistical analyses. |

*Abbreviations: CTS, carpal tunnel syndrome; ITT, intention to treat; VAS, Visual Analogue Scale*
*[a]A brief summary of results relevant for this review is reported in this table*
*[b] Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

***Table 10****. Description of each included trial and risk of bias assessments*

| | **Ucan 2006 (53)** | |
|---|---|---|
| | *Title* | Comparison of splinting, splinting plus local steroid injection and open carpal tunnel release outcomes in idiopathic carpal tunnel syndrome |
| | *First author* | Ucan, H |
| | *Year of publication* | 2006 |
| | *Setting* | Hospital in Ankara |
| | *Country* | Turkey |
| | *Aim* | Three-armed trial to compare the efficacy of surgery with splinting and splinting combined with local steroid injection for carpal tunnel syndrome |
| | *Study design* | Randomized controlled trial |
| | *Inclusion period* | n/a |
| | *Outcome assessments* | (3 and) 6 months |
| | *Study registration* | No registration |
| **Intervention** | *Intervention* | Surgery: Open procedure. The flexor retinaculum was sectioned completely with a short incision. Early mobilization of fingers was recommended |
| | *Control* | i) Splinting: Hand in neutral position, recommended used every night and at daytime when possible for 3 months.<br>ii) Local steroid injection: A mix of 20 mg triamsinolone acetonid and 20 mg lidocaine was injected ulnar to the palmaris longus tendon. Not ultrasound-guidance. Splinting with hand in neutral position, recommended used every night and at daytime when possible for 3 months |
| | *N total* | 57 wrists |
| | *N intervention* | 11 wrists |
| | *N control* | 46 wrists (23 in the splinting group and 23 in the splinting + steroid injection group) |

| | | |
|---|---|---|
| **Population** | *Age* | Intervention group: Mean (SD) 45 (13) years<br>Control groups: i) Mean (SD) 45 (7) years, ii) Mean (SD) 44 (9) years |
| | *Sex* | 93% women |
| | *Severity of CTS – mild* | n/a |
| | *Severity of CTS -moderate* | n/a |
| | *Severity of CTS -severe* | n/a |
| **Methods** | *Inclusion criteria* | Clinical diagnosis of CTS supplied with electrodiagnostic tests. No age or symptom duration criteria |
| | *Exclusion criteria* | Severe carpal tunnel syndrome (including thenar muscle atrophy and findings on nerve conduction studies), metabolic disease (including diabetes mellitus, thyroid disease, kidney disease, connective tissue disorders), malignancy, previous distal radius fracture, pregnancy, and other conditions such as cervical disc symptoms and fibromyalgia |
| | *Statistical analyses* | As treated analyses. General linear models for changes within groups. No information provided on other analyses including statistical analyses used for between-group differences |
| | *Power calculations* | No power analyses done |
| | *Outcome measures* | BCTQ function and symptom score. Patient satisfaction (1-5 point scale). Electrodiagnostic testing. |
| | *Minimal clinically important difference* | n/a |
| | *Adverse event definition* | Not defined |
| **Results**[a] | *N at follow-up intervention* | 11 wrists at 6 months (number of included patients not provided) |
| | *N at follow-up control* | 23 wrists in each control group (number of included patients not provided) |
| | *Function outcome* | Greater improvement in the BCTQ function score in the surgical group compared to the non-surgical groups at 6 months (but statistical method used is unclear) |
| | *Symptom outcome* | Greater improvement in the BCTQ symptom score in the surgical group compared to the non-surgical groups at 6 months (but statistical method used is unclear) |
| | *HRQoL* | n/a |
| | *Adverse events* | Adverse events presented, but no statistics done |
| | *Nerve conduction studies* | Results of electrodiagnostic tests presented in table |
| | *Work status* | n/a |

| | | |
|---|---|---|
| | *Results based on pre-treatment severity of CTS* | n/a |
| | *Crossovers (from non-surgical treatment to surgery)* | Not reported |
| | *Co-interventions* | Not reported |
| **Risk of bias** | **Judgement**[b] | **Support for judgement** |
| *Random sequence generation (selection bias)* | *High risk* | No information about the randomization process. An uneven number of wrists in each group and baseline differences between groups for several characteristics may indicate bias in the randomization process. Baseline differences between groups suggests that the randomization and/or allocation was not satisfactorily performed. |
| *Allocation concealment (selection bias)* | *High risk* | Prepared, randomly enumerated closed envelopes were given consecutively to each patient. No other information was provided. Wrists, and not patients, were included. There was no information about how bilateral CTS was handled, whether both wrists were included etc. Baseline differences between groups suggests that the randomization and/or allocation was not satisfactorily performed. |
| *Blinding of participants and personnel (performance bias)* | *High risk* | No blinding |
| *Blinding of outcome assessment (detection bias)* | *High risk* | No blinding |
| *Incomplete outcome data (attrition bias)* | *High risk* | The recruitment process poorly described. Only patients with follow-up data were included in the trial. 10/67 (15%) were excluded after randomization for different reasons |
| *Selective reporting (reporting bias)* | *High risk* | We could not identify a published protocol. Therefore, it was unclear whether all predefined outcomes were reported. The statistical analyses used to compare the groups were not described, and no confidence intervals were presented. |
| *Other bias* | *Low risk* | |
| **Comment** | | Wrists, and not patients, were randomized. It is unclear whether both wrists could be included in patients with bilateral CTS. If this was done, statistical analyses may have introduced bias if the patients were not handled as clusters. There was no information about statistical analyses. |

*Abbreviations: CTS, carpal tunnel syndrome; BCTQ Boston Carpal Tunnel Questionnaire*

[a] *A brief summary of results relevant for this review is reported in this table*

[b] *Risk of bias stratification:* ***Low risk****, there was no risk of bias or the detected risk of bias is not considered to have serious effect on the results;* ***Unclear risk****, there is an unclear risk of bias, which may influence the results;* ***High risk****, the detected risk of bias may have a serious effect on the results*

# Appendix 6: Ongoing studies

***Table 1**. Identified ongoing randomized controlled trials comparing surgery with non-surgical treatments*

| Study ID/ name | Country | Study registration/status | Comparator | Number of participants | Main outcome |
|---|---|---|---|---|---|
| CTRI/2019/01/016881: A Comparison of Ultrasound guided steroid injection and Endoscopic carpal tunnel release for the treatment of carpal tunnel syndrome | India | 2021/not yet recruiting | Ultrasound guided corticosteroid injection | 64 | Return to work 1-month post intervention |
| ISRCTN13164336: The Dutch injection versus operation trial in carpal tunnel syndrome patients | The Netherlands | 2021/recruiting | Steroid injection | 940 | Patients recovered, defined according to the 6-item carpal tunnel symptom scale at 18 months |
| IRCT20200629047948N1: Ultrasound guided corticosteroid injection: Comparison of the effectiveness of open surgery versus ultrasound guided median nerve dissection with injection of methyl prednisolone acetate in treatment of carpal tunnel syndrome | Iran | 2020/recruiting | Ultrasound guided corticosteroid injection | 40 | Numbness, pain, paresthesia, weakness up to 3 months after surgery |
| ISRCTN59894749: Steroid injection versus surgical decompression for carpal tunnel syndrome[a] | United Kingdom | 2016/completed | Steroid injection | 40 | Eligibility rate, recruitment |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | rate, adherence rate |
| EUCTR2013-000873-56-ES: Randomized, two parallel groups, open clinical trial stratified by severity to estimate the cost-effectivity of surgical vs corticosteroid injection treatment on carpal tunnel syndrome | Spain | 2013/unknown | Steroid injection | 70 | Health economy Secondary outcome: complication at 12 months |

[a]Feasibility study

# Appendix 7: Assessment of certainty of evidence with GRADE

## Surgery versus splinting

***Table 1***. *Certainty of evidence assessed with GRADE comparing surgery with splinting*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | splinting | Relative (95% CI) | Absolute (95% CI) | | |
| **Symptom severity (follow-up: 1 year; Scale from: 1 to 5)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 73 | 83 | - | SMD **0.47 SD lower** (0.78 lower to 0.15 lower) | ⨁⨁◯◯ Low | |
| **Paraesthesia during day (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 73 | 83 | - | MD **1.5 SD lower** (2.43 lower to 0.57 lower) | ⨁⨁◯◯ Low | |
| **Paraesthesia during night (follow-up: 1 year)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | splinting | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 73 | 83 | - | MD **0.7 SD lower** (1.73 lower to 0.33 lower) | ⨁⨁◯◯ Low | |
| **Function (follow-up: 1year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 73 | 83 | - | SMD **0.35 SD lower** (0.67 lower to 0.03 lower) | ⨁⨁◯◯ Low | |

***Abbreviatons:*** *GRADE, Grading of Recommendations Assessment, Development and Evaluation; CI, confidence interval; MD, mean difference*

[a]*Downgraded one level due to lack of blinding*

[b]*Downgraded one level due to few participants and 95% confidence interval being close to no effect*

***Table 2**. Certainty of evidence assessed with GRADE comparing surgery with combinations of non-surgical treatments*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | multimodal treatment | Relative (95% CI) | Absolute (95% CI) | | |
| **Symptom severity (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 49 | 52 | - | MD **0.33 lower** (0.65 lower to 0.01 lower) | ⨁⨁◯◯ Low | |
| **Pain (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 49 | 52 | - | MD **0.8 lower** (2.03 lower to 0.43 higher) | ⨁⨁◯◯ Low | |
| **Function (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 49 | 52 | - | MD **0.43 lower** (0.77 lower to 0.09 lower) | ⨁⨁◯◯ Low | |
| **Healt-related quality of life - physical summary score (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 49 | 52 | - | MD **2 higher** (3.1 lower to 7.1 higher) | ⨁⨁◯◯ Low | |
| **Healt-related quality of life - mental summary score (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 45 | 47 | - | MD **2 lower** (7.85 lower to 3.85 higher) | ⨁⨁◯◯ Low | |

***Abbreviatons:** GRADE, Grading of Recommendations Assessment, Development and Evaluation; CI, confidence interval; MD, mean difference*

[a]*Downgraded one level due to lack of blinding*

[b]*Downgraded one level due to few participants and 95% confidence interval including no effect or being close to no effect*

## Surgery versus steroid injection

***Table 3**. Certainty of evidence assessed with GRADE comparing surgery with steroid injection*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | local steroid injection | Relative (95% CI) | Absolute (95% CI) | | |
| **Paraesthesia (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 60/80 (75.0%) | 58/83 (69.9%) | **RR 0.93** (0.77 to 1.13) | **49 fewer per 1 000** (from 161 fewer to 91 more) | ⨁◯◯◯ Very low | |
| **Pain (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 58/80 (72.5%) | 56/83 (67.5%) | **RR 0.93** (0.76 to 1.14) | **47 fewer per 1 000** (from 162 fewer to 94 more) | ⨁◯◯◯ Very low | |
| **Function (follow-up: 1 year)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 58/80 (72.5%) | 58/83 (69.9%) | **RR 1.00** (0.83 to 1.21) | **0 fewer per 1 000** (from 119 fewer to 147 more) | ⨁◯◯◯ Very low | |

***Abbreviatons:** GRADE, Grading of Recommendations Assessment, Development and Evaluation; CI, confidence interval; RR, relative risk*
*[a]Downgraded two levels due to lack of blinding, incomplete outcome data and possible selective reporting*
*[b]Downgraded one level due to few participants and 95% confidence interval including no effect or being close to no effect*

## Surgery versus physical therapy

***Table 4**. Certainty of evidence assessed with GRADE comparing surgery with manual therapy*

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | physical therapy | Relative (95% CI) | Absolute (95% CI) | | |
| **Symptom severity 1 year** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 106 | 104 | - | MD **0.09 SD lower** (0.29 lower to 0 ) | ⨁◯◯◯ Very low | |
| **Pain 1 year** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 104 | 102 | - | MD **0.05 SD higher** (0.45 lower to 0.55 higher) | ⨁◯◯◯ Very low | |
| **Function 1 year** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[a] | not serious | not serious | serious[b] | none | 103 | 102 | - | MD **0.04 higher** (0.2 lower to 0.11 higher) | ⨁◯◯◯ Very low | |

***Abbreviatons:** GRADE, Grading of Recommendations Assessment, Development and Evaluation; CI, confidence interval; MD, mean difference*

*[a]Downgraded two levels; one for lack of blinding and one for other bias*

*[b]Downgraded one level due to few participants and 95% confidence interval including no effect or bein close to no effect*

# Appendix 8: Budget impact analysis

For estimating population size in the future years, we used numbers from 2019 received from the Central RHA as a starting point since numbers from 2020 may be influenced by the Covid-19 pandemic. The analysis is for a five-year period and the suggested reduction is for patients with mild to moderate carpal tunnel syndrome.

In scenario 1, we show a situation where the number of surgeries has stabilised in 2019 and remains the same until 2026.

In scenario 2, we show a potential situation with yearly decrease of surgeries in the RHAs to reach a target rate corresponding to the RHA with the lowest rate in 2019. This was Western RHA with 124 surgeries per 100,000 inhabitants. For the Western RHA, we used a target rate of 110 surgeries per 100,000 inhabitants which corresponds to the hospital trust within the Western RHA, Haukeland, with the lowest rate in 2019.

In the scenarios, we have assumed that the patients who do not get surgery will have conservative treatment instead. We have used NOK 3,100 for the cost of conservative treatment (Table 12).

The assumed number of surgeries and conservative treatments for each RHA is presented in Table 1–4. Population growth in each RHA was included in the estimation of rate per 100,00 inhabitants in year 2026.

***Table 1.*** *Central RHA: assumed number of surgeries and conservative treatments in parenthesis*

| | **2022** | **2023** | **2024** | **2025** | **2026** | **Rate in 2026** | **Average yearly decrease** |
|---|---|---|---|---|---|---|---|
| Scenario 1: stabilisation | 1,244 | 1,244 | 1,244 | 1,244 | 1,244 | **161** | - |
| Scenario 2 | 1,181 (63) | 1,120 (124) | 1,063 (181) | 1,009 (235) | 958 (286) | **124** | 5.1% |

***Table 2.*** *Northern RHA: assumed number of surgeries and conservative treatments in parenthesis*

| | 2022 | 2023 | 2024 | 2025 | 2026 | Rate in 2026 | Average yearly decrease |
|---|---|---|---|---|---|---|---|
| Scenario 1: stabilisation | 734 | 734 | 734 | 734 | 734 | **151** | - |
| Scenario 2 | 706 (28) | 679 (55) | 653 (81) | 629 (105) | 605 (129) | **124** | 3.8% |

***Table 3.*** *South-Eastern RHA: assumed number of surgeries and conservative treatments in parenthesis*

| | 2022 | 2023 | 2024 | 2025 | 2026 | Rate in 2026 | Average yearly decrease |
|---|---|---|---|---|---|---|---|
| Scenario 1: stabilisation | 4,066 | 4,066 | 4,066 | 4,066 | 4,066 | **127** | - |
| Scenario 2 | 4,051 (15) | 4,035 (31) | 4,020 (46) | 4,005 (61) | 3,989 (77) | **124** | 0.4% |
| Scenario 3: Yearly reduction based on the trend for 2017–2019 | 3,937 (129) | 3,813 (253) | 3,693 (373) | 3,576 (490) | 3,463 (603) | **108** | 3.2% |

In the South-Eastern RHA there was a trend of 3.2% yearly average reduction in the period 2017–2019. This reduction leads to a lower rate per 100,000 than for the target rate of 124. Therefore, we present scenario 3 for this RHA, where the yearly reduction (3.2%) continues to 2026. With this reduction the South-Eastern RHA would be at about the same level as Haukeland (110) with the lowest rate per 100,00 inhabitants in the Western RHA in 2019. This level is also used as a target level for Western RHA.

***Table 4.*** *Western RHA: assumed number of surgeries and conservative treatments in parenthesis*

| | 2022 | 2023 | 2024 | 2025 | 2026 | Rate in 2026 | Average yearly decrease |
|---|---|---|---|---|---|---|---|
| Scenario 1: stabilisation | 1372 | 1372 | 1372 | 1372 | 1372 | **118** | - |
| Scenario 2 | 1353 (19) | 1334 (38) | 1315 (57) | 1297 (75) | 1279 (93) | **110** | 1.4% |

**Results of the budget impact analysis**

To estimate potential cost savings for each RHA, we calculated the difference in total costs (all five years) between scenario 1 and 2. For the South-Eastern RHA we also calculated the difference between scenario 1 and 3, so for this RHA the potential cost savings is shown as a range.

Potential cost savings per RHA depends on the reduction in number of procedures. The potential savings for each RHA are presented in Tables 5.5–5.8.

Central RHA

Based on our analysis, the Central RHA could potentially save NOK 7,162,000 over five years (Table 5).

***Table 5.*** *Suggested budget impact for Central RHA*

| | | 2022 | 2023 | 2024 | 2025 | 2026 |
|---|---|---|---|---|---|---|
| **Scenario 1 (stabilisation)** | Surgery cost | 13 873 000 | 13 873 000 | 13 873 000 | 13 873 000 | 13 873 000 |
| **Scenario 2 (5.1% yearly reduction)** | Surgery cost | 13 165 000 | 12 494 000 | 11 857 000 | 11 252 000 | 10 678 000 |
| | Cost conservative treatment | 197 000 | 383 000 | 560 000 | 729 000 | 888 000 |
| | Sum | 13 362 000 | 12 877 000 | 12 417 000 | 11 981 000 | 11 566 000 |
| | **Potential cost savings (scenario 1 minus scenario 2)** | 511 000 | 996 000 | 1 456 000 | 1 892 000 | 2 307 000 |

Northern RHA

Based on our analysis, the Northern RHA could potentially save NOK 3,200,000 over five years (Table 6).

***Table 6.*** *Suggested budget impact for Northern RHA*

| | | 2022 | 2023 | 2024 | 2025 | 2026 |
|---|---|---|---|---|---|---|
| **Scenario 1 (stabilisation)** | Surgery cost | 8 185 000 | 8 185 000 | 8 185 000 | 8 185 000 | 8 185 000 |
| **Scenario 2 (3.8% yearly reduction)** | Surgery cost | 7 874 000 | 7 575 000 | 7 287 000 | 7 010 000 | 6 744 000 |
| | Cost conservative treatment | 86 000 | 170 000 | 250 000 | 327 000 | 401 000 |
| | Sum | 7 961 000 | 7 745 000 | 7 537 000 | 7 337 000 | 7 145 000 |
| | **Potential cost savings (scenario 1 minus scenario 2)** | 224 000 | 440 000 | 648 000 | 848 000 | 1 040 000 |

South-Eastern RHA

Based on our analysis, the South-Eastern RHA could potentially save between NOK 1,856,000 and 14,883,000 over five years (Table 7).

***Table 7.*** *Suggested budget impact for South-Eastern RHA*

| | | 2022 | 2023 | 2024 | 2025 | 2026 |
|---|---|---|---|---|---|---|
| **Scenario 1 (stabilisation)** | Surgery cost | 45 343 000 | 45 343 000 | 45 343 000 | 45 343 000 | 45 343 000 |
| **Scenario 2 (0.4% yearly reduction)** | Surgery cost | 45 171 000 | 44 999 000 | 44 828 000 | 44 658 000 | 44 488 000 |
| | Cost conservative treatment | 48 000 | 96 000 | 143 000 | 191 000 | 238 000 |
| | Sum | 45 219 000 | 45 095 000 | 44 971 000 | 44 848 000 | 44 726 000 |
| | **Potential cost savings (scenario 1 minus scenario 2)** | 124 000 | 248 000 | 372 000 | 495 000 | 617 000 |
| **Scenario 3 (trend: 3.2% yearly reduction)** | Surgery cost | 43 910 000 | 42 522 000 | 41 178 000 | 39 877 000 | 38 617 000 |
| | Cost conservative treatment | 398 000 | 784 000 | 1 158 000 | 1 520 000 | 1 870 000 |
| | Sum | 44 308 000 | 43 306 000 | 42 336 000 | 41 396 000 | 40 486 000 |
| | **Potential cost savings (scenario 1 minus scenario 3)** | 1 035 000 | 2 037 000 | 3 007 000 | 3 947 000 | 4 857 000 |

Western RHA

Based on our analysis, the Western RHA could potentially save NOK 2,276,000 over five years (Table 8).

***Table 8.*** *Suggested budget impact for Western RHA*

| | | 2022 | 2023 | 2024 | 2025 | 2026 |
|---|---|---|---|---|---|---|
| **Scenario 1 (stabilisation)** | Surgery cost | 15 300 000 | 15 300 000 | 15 300 000 | 15 300 000 | 15 300 000 |
| **Scenario 2 (1.4% yearly reduction)** | Surgery cost | 15 086 000 | 14 875 000 | 14 667 000 | 14 461 000 | 14 259 000 |
| | Cost conservative treatment | 60 000 | 118 000 | 176 000 | 233 000 | 290 000 |
| | Sum | 15 146 000 | 14 993 000 | 14 843 000 | 14 694 000 | 14 548 000 |
| | **Potential cost savings (scenario 1 minus scenario 2)** | 154 000 | 307 000 | 457 000 | 606 000 | 752 000 |

On the national level, the potential cost savings could be between NOK 14,494,000 and NOK 27,521,000.

Published by the Norwegian Institute of Public Health
November 2021
P.O.B 4404 Nydalen
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The report can be downloaded as pdf
at www.fhi.no/en/publ/