The epidemiology, prognosis and management of carpal tunnel syndrome in primary care

Claire Louise BURTON

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Declaration

The idea for this thesis arose from discussions between Dr Linda Chesterton, Professor Danielle Van der Windt, Dr Ying Chen and myself.

The systematic search and reviews were planned and carried out by me with advice from research information manager, Joanne Jordan. Dr Linda Chesterton assisted with the quality appraisal and data extraction as a second reviewer. The interpretation of the results is my own.

The design of the CPRD studies were my own. Advice regarding the writing of the ISAC protocol was sought from Professor Kelvin Jordan and the data was downloaded by Dr Dahai Yu. The further manipulation and analysis of the data was undertaken by me with advice from a biostatistician, Dr Ying Chen. The interpretation of the results is my own.

Two of the studies in this thesis were nested within the Injection versus night splints for carpal tunnel syndrome trial (INSTINCTS), which was supported by the Keele Clinical Trials Unit, Keele University. I was involved as a member of the Trial Management Group in the design, recruitment and reporting of the trial. The work presented in this thesis, which uses data from the trial, is my own. I received statistical advice from Dr Ying Chen and Dr Kym Snell.

The interpretation and discussion of the findings in this thesis are my own.

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Abstract

Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve. Patients may experience discomfort in the hand and wrist, altered sensation and functional deficit. The management of mild to moderate CTS involves local corticosteroid injection (CSI) and night splinting (NS). The aims of the studies presented in this thesis were to describe the epidemiology of CTS and to develop prognostic models to predict future likely outcomes in patients presenting with CTS in a primary care setting. Evidence for predictors of treatment effect (CSI or NS) were also explored.

The estimated crude prevalence of patients presenting with CTS in UK primary care (using data from the Clinical Practice Research Datalink - CPRD) increased from 26.03 per 10,000 person years in 1993 (95% CI 25.10 to 27.00) to 36.08 per 10,000 person years (95% CI 35.45 to 36.72) in 2013. The proportion of patients having carpal tunnel release surgery (CTR) changed over the study period increasing from 19.35% in 1993 to a peak in 2009 at 29.32% and then decreasing to 27.3% in 2013.

A systematic review of 16 cohort studies reporting on the course and prognosis of CTS showed that prolonged symptom duration, a positive Phalen's test, and thenar wasting were associated with poor outcome over a follow-up period of between six months and 12 years. However, not all associations were statistically significant and many studies were deemed to be at increased risk of bias (particularly relating to study attrition, confounding, and/or statistical analysis or reporting), hence the overall judgement regarding their predictive value remained inconclusive. A CPRD cohort of 91,412 patients with CTS was developed. 20.24% of the cohort had a recorded episode of CTR within 3 years of diagnosis. A prognostic model predicting time to surgical intervention was developed using Cox regression and included age, obesity, alcohol use, smoking and having multi-site pain, an inflammatory condition or a neck symptoms (adjusting for region and deprivation). The predictive capability of the model was limited, C statistic 0.59 (95% CI 0.58 to 0.59). Multivariable linear regression modelling using data from a randomised controlled trial (INSTINCTS) was used to develop a prognostic model predicting patient reported outcome at six months. The final model included the baseline Boston

Carpal Tunnel Questionnaire score, the symptom severity score, and the absence of any other neck or upper limb symptom. The optimism-adjusted model calibrated poorly, overestimating the severity of outcome in patients with less severe observed CTS, and underestimating the severity of outcome in patients with more severe observed CTS.

A second systematic review including four RCTs summarised evidence for predictors of treatment effect. The results from one trial indicated that the effect of CSI was larger in patients with more severe nerve conduction and baseline symptom scores. Exploratory analysis of a small set of a priori defined candidate predictors of treatment effect using INSTINCTS data suggested that at six months, CSI was less effective than NS in patients with unilateral symptoms compared to those with bilateral CTS. However, results need to be carefully interpreted given the lack of significant interaction, the possibility of a unit of analysis error and a very small sample size.

In summary, patients with CTS presented in primary care with increasing frequency between 1993 and 2013. However, since around 2008, the proportion of patients receiving surgical treatment was observed to decrease, despite being considered clinically effective for most patients. Lower rates of surgery may be associated with changes in access to the procedure. This highlights the need for optimal management to be provided in primary care. Assuming the CPRD population to be representative, at least 20% of patients presenting with CTS did not respond well to their initial management in primary care. There is likely to be clinical benefit in identifying this group early in the course of their symptoms, and explore any differential treatment response, in order to better target treatment to the individual and identify those who are likely to require surgery. However, the prognostic models developed in this thesis performed poorly. It seems that the prediction of CTS is complex and potentially includes prognostic factors not measurable in CPRD or trial data. Similarly, no confirmatory evidence was found that could be used to match treatment options to individuals. Therefore, patients with CTS can be initially managed in primary care using current guidance and should be routinely followed up and referred for surgery if they fail to experience initial satisfactory improvement.

Abbreviations

AAPMR	American Academy of Physical Medicine and Rehabilitation
AAN	American Academy of Neurology
AANEM	American Association of Neuromuscular & Electrodiagnostic Medicine
AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
AMED	Allied and Complementary Medicine Database
APC	Annual percentage change
BCTQ	Boston Carpal Tunnel Questionnaire
BMI	Body mass index
BSO	British Society of Orthopaedics
BSSH	The British Society for Surgery of the Hand
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CiPCA	Consultations in Primary Care Archive
CPCI-S	Conference Proceedings Citation Index – Science
CPRD	Clinical Practice Research Datalink
CSI	Corticosteroid injection (to the carpal tunnel)
CTR	Carpal tunnel release (surgery)
CTS	Carpal tunnel syndrome
CTV	Clinical terms version
(quick) DASH	The Disabilities of the Arm, Shoulder and Hand Score
DOH	Department of Health
EMBASE	Excerpta Medical Database
EHR	Electronic health record
EMG	Electromyography
EMIS	Egton Medical Information Systems
FDP	Flexor digitorum profundus
FDS	Flexor digitorum superficialis
FPL	Flexor pollicis longus
FSS	Function status scale
GMS	General Medical Services
GP	General Practitioner
HES	Hospital Episode Statistics
Hi-Ob	Historic and Objective Scale
HMIC	Health Management Information Consortium
INSTINCTS	Injection versus night splints for carpal tunnel syndrome
LA	Local anaesthetic
LP	Linear predictor
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Regulatory Agency
MI	Multiple imputation
MIC	Musculoskeletal interface clinic
NCS	Nerve conduction studies

NCV	Nerve conduction velocity
NHS	National Health Service
NIHR	Nation Institute for Health Research
NLM	National Library of Medicine
NS	Night splinting (of the wrist)
NSAID	Nonsteroidal anti-inflammatory
OXMIS	Oxford Medical Information System
PBC	Practice based commissioning
PCRMM	Primary Care Rheumatology and Musculoskeletal Medicine Society
PCT	Primary Care Trust
PPV	Positive predictive value
PRCTS	Pregnancy related carpal tunnel syndrome
PROGRESS	PROGnosis RESearch Strategy
QOF	Quality and Outcomes Framework
QUIPS	Quality in prognosis studies
RCS	Royal College of Surgeons
RCT	Randomised controlled trial
SCI-EXPANDED	Science Citation Index Expanded
SNOMED	Systemised Nomenclature of Medicine
SSS	Symptom severity scale
TCL	Transverse carpal ligament
THIN	The Health Improvement Network
TRIPOD	Transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

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Publications and presentations associated with the work presented in this thesis

Peer-reviewed publications

Burton C, Chesterton LS, Davenport G. Diagnosing and managing carpal tunnel syndrome in primary care. *BJGP*. May 2014.64 (622)2 262-263

Burton C, Chen Y, Chesterton LS, Van der Windt D. Describing the clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: A systematic review. *Archives of Physical Medicine and Rehabilitation*. October 2015 97(5): 836-852

Burton C, Chesterton LS, Davenport G. The painful tingling hand: 10 minute consultation. *BMJ* 2016. 355:i6386

Burton C, Chen Y, Chesterton LS, Van der Windt D Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records *BMJ Open* 2018;8:e020166

Burton C, Chesterton LS, Chen Y, Van der Windt DA. Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care. *Clinical Epidemiology*. 2018;10:739-748.

Oral presentations

Burton C, Chesterton LS, Chen Y, Van der Windt D. Carpal Tunnel Syndrome: a plan of study. Postgraduate Symposium 2014, Primary Care Sciences, Keele University

Burton C, Chesterton LS, Chen Y, Van der Windt D. Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care. SAPC 2017

Burton C, Chesterton LS, Chen Y, Van der Windt D. The epidemiology and prognosis of carpal tunnel syndrome in primary care. SPCR Trainee Event 2017

Burton C, Chen Y, Van der Windt D. Predicting outcome in patients with carpal tunnel syndrome receiving conservative management, as part of a randomised controlled trial (Injection versus Night Splints in Carpal Tunnel Syndrome). RCGP Midlands Research Symposium 2019 & SPCR Research Showcase

Poster presentations

Burton C, Chesterton LS, Chen Y, Van der Windt D. Using primary care records to describe patterns in the annual prevalence, incidence and surgical management of carpal tunnel syndrome between 2000 and 2010. SAPC North 2014

Burton C, Chesterton LS, Chen Y, Van der Windt D. Matching patients to treatments in carpal tunnel syndrome: what we already know. NIHR Trainee Meeting 2016

Burton C, Chesterton L.S., Chen Y, Van der Windt. Patterns in the annual prevalence, incidence and management of carpal tunnel syndrome. BSR 2017

1 Background and introduction

Summary

Carpal tunnel syndrome (CTS) is a common focal compressive neuropathy caused by entrapment of the median nerve at the level of the wrist. CTS can be classified into three clinical categories of mild, moderate and severe, according to symptom severity. Most research to date has been conducted in the moderate to severe categories and within a secondary care setting. However, most patients will initially present in primary care, a setting where little research into CTS has been conducted. The rationale of this thesis is therefore to investigate the epidemiology, prognosis and primary care management of carpal tunnel syndrome, with a view to exploring ways in which the treatment of patients presenting in primary care can be improved and streamlined.

This chapter will discuss: the clinical presentation and pathophysiology of CTS; available evidence with regards to its epidemiology across all healthcare settings; an approach to the diagnosis of CTS; treatment options commonly utilised in primary care and the cost implications of CTS. The PROGRESS framework, which underpins the structure of this thesis will also be introduced and associated terminology defined.

1.1 Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) can be defined as,

> "*a symptomatic compression neuropathy of the median nerve at the level of the wrist.*"[1] *pg 389*

Clinical symptoms include but are not limited to: pain and/or discomfort in the hand, wrist and forearm; paraesthesia and loss of sensation in the median nerve distribution of the hand, a weakened grip strength and associated functional loss.[2] Whilst there may be no objective examination findings,

a positive response to provocation tests (such as Phalen's or Tinnel's test) may be elicited and in severe cases, thenar wasting may be observed.

1.1.1 The history of carpal tunnel syndrome

CTS was first described by Paget in 1854, whereby two cases of compression of the median nerve, one post-traumatic and one idiopathic, and their successful treatment using splinting, were described. [3]

Putnam then published a case series describing 37 patients presenting with certain common features,

> *"…these cases agree in presenting as a common symptom a disturbance of the subjective sensibility of the skin, giving rise to what is known popularly as numbness, recurring periodically, coming on especially at night or very early in the morning."*[4] *pg 147*

Putnam, influenced by the thinking of Raynaud, hypothesised that the condition was caused by acroparaesthesia; an alteration in blood supply to the nerves supplying the affected district. Recommended treatments included galvanic current, phosphorus, strychnine, potassium bromide and cannabis.[4]

In the early 20th century Hunt, Marie and Fox provided an alternative hypothesis for the cause of atrophy of the thenar eminence, which at the time was understood to be due to an entirely different pathological process to that of the paraesthesia. They described the compression of the motor branch of the median nerve as the cause of muscle atrophy. Hunt, Marie and Fox concluded that transection of the annular ligament could stop the development of the condition. This conclusion was disregarded for the next 30 years, due to the existence of other possible explanations.[5] Clinicians had observed that motor alternations were often accompanied by sensory changes and hypothesised that this must be caused by compression of the brachial plexus at the thoracic outlet. The use of X-rays had recently been developed (1895), prompting cervical ribs to be targeted as the cause of compression, as they represented a visible anatomical anomaly in some patients with CTS. As a result, removal of the cervical rib became the most common treatment of CTS in the first 40 years of the 20th century.[5]

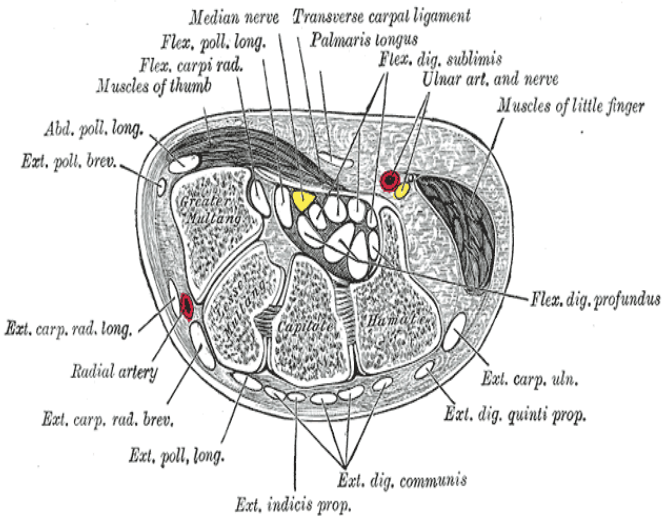
Learmonth published the first description of carpal tunnel release (CTR) surgery in cases of post-traumatic compression.[6] The open surgical technique remains a successfully used approach, as does endoscopic surgery, first described by Chow in 1989.[7]

Brain et al. and later Phalen et al. were the first to describe idiopathic CTS from clinical and anatomo-pathological perspectives. Brain et al described the idiopathic compression of the median nerve being frequent in the general population and hypothesised it was due to age-related vascular degeneration causing ischaemia and reactive oedema. He further hypothesised that this cycle of ischaemia, oedema and compression required CTR to interrupt it.[5] Phalen's series of publications included: a clear description of the clinical presentation and diagnostic tests (to include the Phalen's test); the epidemiology of CTS, based on his clinical observations, and a further recommendation of CTR as the correct approach to treatment.[5]

Simpson published the first paper describing the use of electromyography (EMG) to support the diagnosis of CTS in 1956.[8] Following the introduction of this investigative technique to quantify the level of disruption to neural function, little has changed in the approach to diagnosing, investigating and treating CTS: Phalen's test is still commonly used in diagnosis; EMG in its investigation and surgical intervention as an approach to treatment.[5]

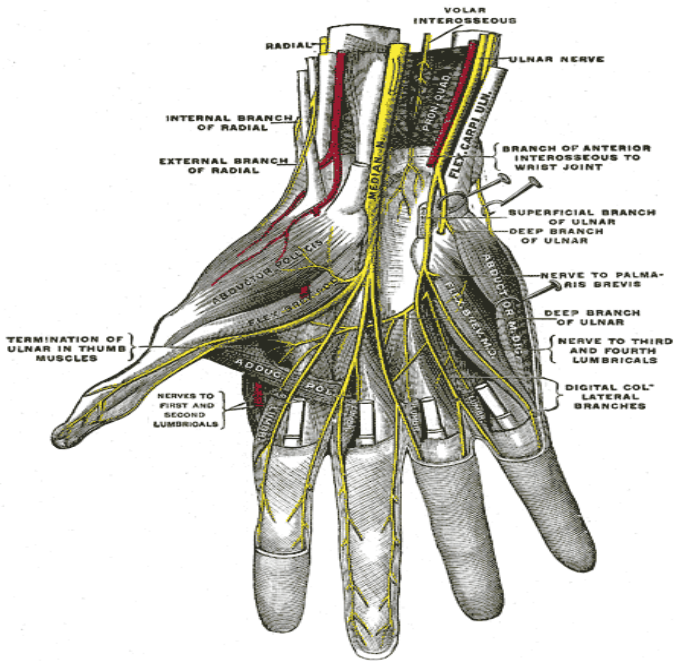
1.1.2 Anatomy of the carpal tunnel

Figure 1-1 Anatomy of the carpal tunnel. *Taken from Gray's Anatomy, initially published 1918. Copyright lapsed.*



The anatomy of the carpal tunnel is presented in the transverse and coronal planes in Figure 1-1 and Figure 1-2 respectively. The carpal tunnel is described as the space deep to the transverse carpal ligament (TCL) (also referred to as the flexor retinaculum or the anterior annual ligament), bordered posteriorly by the carpal bones. The TCL extends from the ulnar side of the wrist from both the hook of hamate in the distal row of the carpal bones and the triquetrum in the proximal row, to the scaphoid and trapezium on the radial side. Running through the carpal tunnel are the median nerve and nine flexor tendons including the flexor digitorum profundus (FDP) and flexor digitorum superficialis (FDS) tendons to the index, middle, ring and small fingers, as well as the flexor pollicis longus (FPL) tendon.[9] A number of anatomical variations have been described.[9]

Figure 1-2 Anatomy of the carpal tunnel. *Taken from Gray's Anatomy, initially published 1918. Copyright lapsed*.



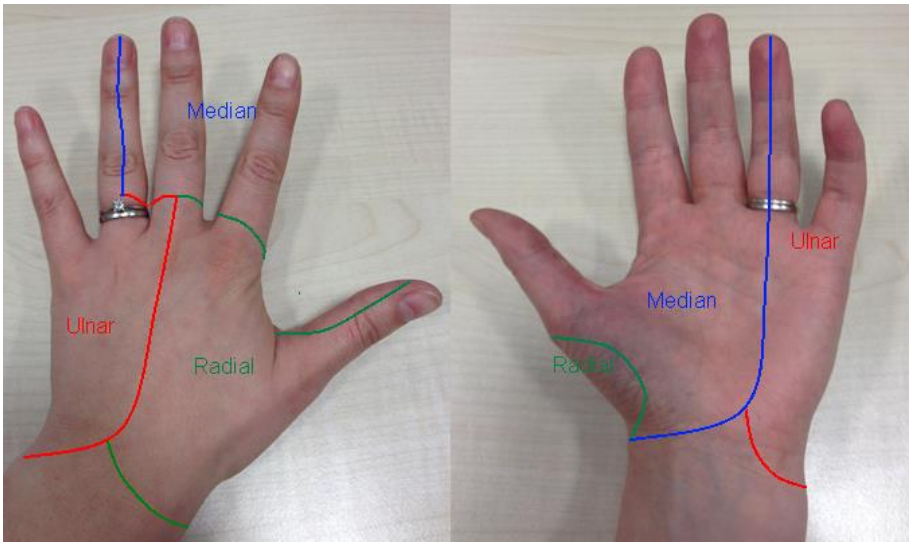
1.1.3 Anatomy of the median nerve

The median nerve originates from the brachial plexus. After entering the axilla it courses with the brachial artery into the cubital fossa. It gives off an articular branch as it passes the elbow joint. The nerve then arises from the cubital fossa and passes through the forearm giving off the anterior interosseous branch and palmer cutaneous branch. The palmar cutaneous branch of the median nerve supplies the cutaneous skin of the palm and usually arises approximately 6cm proximal to the transverse carpal ligament, so does not pass through the carpal tunnel. Sensation to the palm is therefore not usually affected in CTS, which, by definition, is caused by compression of the median nerve within the carpal tunnel. After passing through the carpal tunnel the median nerve gives rise to the:

- Digital cutaneous branches to the common palmer digital branch and the proper palmar digital branch, which classically provides sensory innervation to the three radial digits and the radial half of the 4th digit (see Figure 1-3)
- Motor innervation to the thenar eminence, first and second lumbricals (abductor pollicis brevis, opponens pollicis and flexor pollicis brevis) and the radial two lumbricals.

Motor deficit caused by compression of the median nerve at the carpal tunnel therefore includes weakness in abduction and opposition of the thumb and can effect grip strength.[10, 11]

Figure 1-3 Sensory innervation of the hand ©Keele 2013



1.1.4 Pathophysiology

The pathophysiology of CTS is likely to involve mechanical trauma within the carpal tunnel and a subsequent increase in pressure on and ischaemic injury to the median nerve.[11]

1.1.4.1 Mechanical trauma and increased pressure

Activities involving repetitive flexion and extension of the wrist are implicated in the pathological mechanism of CTS, with experimental work suggesting the greater the duration and level of pressure, the greater the dysfunction of the nerve.[12]

The normal pressure of the carpal tunnel lies between 2 and 10 mmHg.[11] Pressure can be exerted on the median nerve within the carpal tunnel by interstitial fluid and direct contact from adjacent tissues. Thickening of the synovium results from the effect of an increase in interstitial pressure whilst repetitive flexion and extension of the wrist creates the effect of direct contact pressure. The pressure of the carpal tunnel increases by 10-fold on wrist flexion and 8-fold on wrist extension. Wrist extension causes the volar carpal ligament to compress the carpal contents against the carpal bones. Increased pressure during wrist flexion is due to pressure from the TCL compressing the flexor tendons and bursa against the radial head.[13]

1.1.4.2 Nerve injury

The mechanism of nerve injury can be described as being acute or chronic. Acute compression neuropathies occur when there is a sudden increase in pressure causing the capillaries in the vasa nervorum to collapse, leading to subsequent ischaemia and a physiologic conduction block. This is rapidly reversible with a quick return to normal conduction once the compression is removed. Likely symptoms include short lived paraesthesia and numbness.

Chronic compression models are more relevant to entrapment neuropathies such as CTS and occur when there is a prolonged increase in pressure. Observations made during carpal tunnel release surgery (CTR), indicate the median nerve is often thinned in the area of entrapment with swelling of the nerve at the proximal edge of entrapment. Reasons for this observed swelling include: an accumulation of axoplasm, reactive neural oedema and fibrosis following chronic inflammatory changes.[13]

A feedback loop consisting of prolonged compression of the endoneural capillary system, subsequent changes in the blood nerve barrier, ischaemia and local metabolic changes ensues. This process leads to axonal degeneration and further inflammatory response, which then exacerbates the cycle of increased pressure and chemical irritation of the nerve .[11]

1.2 The epidemiology of carpal tunnel syndrome

1.2.1 Prevalence and incidence

CTS is the most frequently presenting of the entrapment neuropathies[14] and many studies have sought to define its prevalence and incidence. Such epidemiological studies have been diverse in their approach to the populations studied and case definitions of CTS applied.[15]

There is no 'gold standard' method of identifying CTS and no consensus on the most appropriate research case definition.[16] A systematic review by Boocock et al identified seven different research definitions of CTS proposed in the literature.[17] Descatha performed a comparison study to assess the agreement between the various definitions used to define CTS, by classifying 1107 newly hired workers by each case definition. The Kappa statistic was used to measure agreement between the definitions. The prevalence of CTS ranged from 2.5% to 11% with the percentage of misclassification between 1 to 10%. Levels of agreement between the definitions was described by the author as acceptable (Kappa 0.30 – 0.85). Despite acceptable agreement, the different definitions lead to a substantial range in reported prevalence.[18]

Table 1-1 below summarises studies that have reported a prevalence or incidence estimate for CTS to allow comparison of the study method and case definitions used, up until the time period described by the study presented in this thesis (2013). Table 1-2 further summarises the reported prevalence and / or incidence by gender, where available. Of the 15 studies identified, 11 used clinical codes recorded by a clinician at consultation or a clinical diagnostic approach to define an episode of CTS. The remainder required additional electrophysiological confirmation or were based on nerve conduction study (NCS) findings to elicit a CTS diagnosis. The reported prevalence ranged from 3720 to 5700 per 100,000 person years (12 studies). The reported incidence was less stable and ranged from 72 to 8200 per 100,000 (3 studies).

Of note, the most recent study set in UK primary care, utilised data from between 1992 and 2000.[19] The commissioning of services requires current evidence. Updating the data to describe the current

prevalence and incidence of patients presenting in primary care with CTS would therefore be of use to policy makers to help plan and commission services appropriately.

Table 1-1 Comparison of population studies reporting the prevalence and / or incidence of carpal tunnel syndrome

Study Identifier	Study method	Definition of CTS	Comments
De Krom et al. 1992	Survey of a random age sex stratified sample of the general population taken from the population register of Maastricht between 1983 and 1985	Questionnaire based on symptoms and signs	
Ferry et al. 1998	i) Cross sectional survey to estimate the point prevalence of hand symptoms (from a random sample of 1000 individuals from the UK general population, aged 18 to 75 years) and ii) nerve conduction testing of a weighted sample - Circa. 1998 (not stated) - point prevalence determined	Based on nerve conduction studies using defined cut offs	Subjects over 54yrs had a higher prevalence than younger participants. No difference between genders was noted.
Nordstrom et al. 1998	Prospective study conducted in the general population of the Marshfield Epidemiologic Study Area, Wisconsin, between 1991 and 1993	1. any diagnosis of possible, probable or definite CTS; 2. any diagnosis of probable or definite CTS; and 3. any diagnosis of possible , probable or definite CTS plus at least one of six clinical signs	A 3.5 fold increase in CTS incidence was noted compared with data from 20 years previously in the same study population
Atroshi et al. 2000	Survey of a random sample of the age sex stratified general population of Southern Sweden, in 1997	Diagnosis based on clinical examination and positive electrophysiological findings	The population prevalence of symptoms was 14.4%; the prevalence of clinically and electrophysiologically confirmed CTS was 2.7%
Papanicolaou, McCable & Firrell 2001	Cross-sectional study to evaluate prevalence of carpal tunnel syndrome in the General population of the United States	Katz hand diagram	After correcting for nonresponders the lowest possible estimate of CTS was 3.72%

Mondelli, Giannini & Giacchi 2002	Prospective study of patients referred to four electrodiagnostic laboratories in the Siena area, Italy. Mean annual incidence calculated from time period 1991 to 1998	Diagnosis based on clinical history and electrodiagnostic evidence of a reduced distal conduction velocity of the median nerve (American Academy of Neurology standards)	Of the patients presenting 79.7% were women. The mean age at diagnosis was 55.0 +/- 14.4 years (range 16 to 97)
Bland, Rudolfer 2003	Prospective collection of neurophysiological and clinical data of patients referred to two electromyography clinics in the UK between 1991 to 1993 and 1992 to 2001	Based on nerve conduction studies using defined cut offs	An increase in diagnosed cases was observed between the two data collection periods; attributed to referral of milder cases. Median nerve impairment was more severe in the elderly and men at all ages.
Latinovic, Gulliford & Hughes 2006	Population study based in a general practice database of consulting primary care patients from 253 practices between January 1992 and 31 December 2000.	Read and OXMIS codes for carpal tunnel syndrome	Most frequent in women aged 45-54. In 2000 operative treatment was undertaken for 31% of incident CTS presentations
Bonger et al. 2007	Analysis of the first and second Dutch National Survey of General Practice, conducted in 1987 and 2001	International Classification of Primary Care coded diagnosis	A crude increase in incidence over time was not statistically significant after subdividing by age and sex. Incidence rates were related to the job level in women, but not men
Dieleman et al. 2008	Population study based in a general practice database (Integrated Primary Care Information database): data of consulting primary care patients in the Netherlands between 1996 and 2003	ICPC coded diagnosis	Neuropathic pain was noted to affect almost 1% of the population. Mononeuropathies and carpal tunnel syndrome were the most common causes
Gelfman et al. 2009	Analysis of medical records linkage system 1981-1985 to 2000-2005 of residents of Olmsted County, Minnesota (Rochester Epidemiology Project)	Clinical coding with a sample verified by full record review	An increase in incidence was observed over the study period. An increase in young individuals seeking care for less severe CTS in the mid-1980's was followed in the 1990's by an increasing incidence in older people
Atroshi et al. 2011	Analysis of the Skane Health Care Register (inhabitants presenting to public health	Physician diagnosed	

	providers), incident cases identified between 2006 - 2008		
Jenkins et al. 2012b	Prospective audit of patients referred to a regional hand service based in secondary care in Scotland between November 2004 and May 2010	Symptoms of pain or paraesthesia in the median nerve distribution and one or more of: nerve conduction deficit, thenar muscle wasting or positive Tinel's or Phalen's sign	Mean age of presentation 55.1years (range 22 to 96, SD 13.5 years). Mean body mass index at presentation 29.5 kg/m2 CTS more common in: females (OR 1.9, 95% CI 1.5 to 2.5) Incidence varied significantly between deprivation groups: most deprived 81/100,000 and least deprived 62/100,000 (OR 1.3, 95% CI 1.1 to 1.6)
Jenkins et al. 2013	Prospective audit of patients referred to a regional hand service based in secondary care in Scotland between November 2004 and May 2010, who were employed	Clinical diagnosis based on history and examination, in most cases substantiated by nerve conduction studies	The greatest incidence as in caring and leisure occupations (197 per 100,000) and the lowest incidence was in the associate professional group (37 per 100,000)
Dale 2013	Pooled analysis of six prospective studies collecting data from >50 workplaces, over variable time frames	A pooled case definition was derived to include clinical and elctrodiagnostic criteria	7.8% of 4321 subjects studied had prevalent CTS, with an additional 204 subjects meeting the CTS criteria, leading to an incidence of 2.3 cases per 100 person years

Table 1-2 Summary of reported incidence and prevalence by gender

Study Identifier	Country of Origin Data collection (Prevalence or Incidence)	Prevalence or Incidence per 100,000, per annum			Female / male ratio
		All	Female	Male	
De Krom et al. 1992	The Netherlands 1983 - July 1985 (Prevalence)	5700	5800	600	9.66
Atroshi et al. 2000	Sweden 1997 (Prevalence)	3800	4600	2800	1.64
Papanicolaou, McCable & Firrell 2001	United States 2001 (Prevalence)	3720			4.8
Ferry et al. 1998	United Kingdom Not stated (Incidence)	8200	6400	8200	0.78
Nordstrom et al. 1998	United States 1991 - 1993 (Incidence)	346	373	318	1.17
Mondelli, Giannini & Giacchi 2002	Italy 1991 – 1998 (mean) (Incidence)	276	506	139	3.64
Bland, Rudolfer 2003	Kent, UK 1991 - 2001 (Incidence)	105	120.5	60	2
	Huddersfield, UK		61.5	30	2

Latinovic, Gulliford & Hughes 2006	United Kingdom 2000 (Incidence)		192.8	87.8	2.23
Bongers et al. 2007	The Netherlands (Incidence) 1987	130	190	60	3.17
	2001	180	280	90	3.11
Dieleman et al. 2008	The Netherlands 1996 - 2003 (Incidence)	233.1			
Gelfman et al. 2009	United States (Incidence) 1981-1985	258	337	177	1.90
	2001-2005	424	542	303	1.79
Atroshi et al. 2011	Sweden 2006 - 2008 (Incidence)		428	182	2.35
Jenkins et al. 2012b	Scotland 2004 - 2010 (Incidence)	72	98	43	2.28
Jenkins et al. 2013	Scotland 2004 - 2010 (Incidence)	103			
Dale 2013	United States (Incidence)	2300			

1.2.2 Disease associations

There are many cited aetiological factors associated with CTS including: obesity, occupational and recreational hand use[20] hypothyroidism, diabetes, autoimmune disease, rheumatological disease, arthritis, renal disease, trauma, infectious disease and substance misuse, late pregnancy although this usually only presents (transient) symptoms.[21] In some instances CTS may be a presenting feature of a condition such as diabetes or hypothyroidism but guidelines suggest routinely testing for such conditions only when other features lead to clinical suspicion.[22, 23]

1.3 Assessing carpal tunnel syndrome

Whilst there is no universally accepted 'Gold Standard' test for identifying a case CTS,[16] attempts have been made to develop standardised criteria for use in clinical practice and research purpose, based on history and examination findings.

1.3.1 The clinical assessment of carpal tunnel syndrome

Rempel et al used a consensus process to develop an approach to CTS diagnosis, for use in epidemiologic studies. Whilst the 12 medical researchers who contributed to the exercise felt that the ideal scenario for a CTS diagnosis to be made was to have both NCS study findings and symptom characteristics present, in the absence of NCS, combinations of symptoms and examination findings could be acceptable. Classic / probable CTS was defined as,

> *"numbness, tingling, burning or pain in at least 2 of digits 1, 2 or 3. Palm pain, wrist pain, or radiation proximal to the wrist is allowed."*[24] *pg 1450*

The basis for describing the anatomical distribution of symptoms was based on the work by Katz et al, where-by a self-administered hand diagram was developed to assist in the assessment of upper limb paraesthesias.[25]

Wainner et al in 2005 developed a clinical prediction rule of the likelihood of a CTS diagnosis. They performed standardised clinical testing (history, neurological examination, wrist-ratio index and provocative testing) on 82 consecutive patients referred for NCS. They used a visual analog scale, the Brigham and Women's Hopsital Hand Symptom Severity Scale and Function Status Scale (also referred to as the BCTQ, see below) and the Katz hand diagram[25] as self-reported outcome measures. Logistic regression identified five test variables (shaking hand for symptom relief, wrist-ratio >0.67, symptom severity score >1.9, diminished sensation in the median sensory field and age >45 years) that could be entered into the clinical prediction rule to produce likelihood ratios and post-test probabilities of CTS. Electrodiagnosis was accepted as gold standard for diagnosis but at the time of publication, the rule was still to be validated and tested for usability in a clinical setting.[26]

Graham et al developed standardised criteria for the diagnosis of carpal tunnel syndrome (also known as CTS-6), using a Delphi technique. The validation process was carried out using the decisions of two expert panels as a reference standard for CTS. One panel assessed case vignettes (used in preference to patients to maintain objectivity) and gave a binary outcome which was used to produce a logistic regression model of the highest-ranking criteria and another panel who estimated the probability of CTS in each of the same case histories. The correlation of the model and the panel was 0.71 [27] The statistically significant ($P < 0.05$) criteria were:

- Numbness in the median nerve distribution
- Nocturnal numbness
- Weakness / atrophy of the thenar musculature
- Tinel's sign positive
- Phalen's sign postive
- Loss of 2-point discrimination.[28]

Graham et al suggest that use of the standardised tool could aid epidemiological research by reducing the variability in criteria used to identify CTS cases. It was postulated that 'non experts' in primary care could use the tool to stratify potential CTS patients by the possibility of CTS, as calculated using the

model, into groups that could be treated non surgically, referred for surgery or referred for investigation / considered for having an alternative diagnosis.[27]

Graham et al went on to validate the diagnostic tool clinically and studied the value added by electrodiagnostic testing to the pre-test probability of CTS given by the CTS-6. They found that the average change in the pre and post-test probability was between -0.02 and -0.06 depending on the electrodiagnostic criteria used. They concluded that for the majority of patients (referred into tertiary care) considered to have CTS on the basis of history and examination alone, electrodiagnostic tests did not add any further clinically relevant diagnostic information.[16]

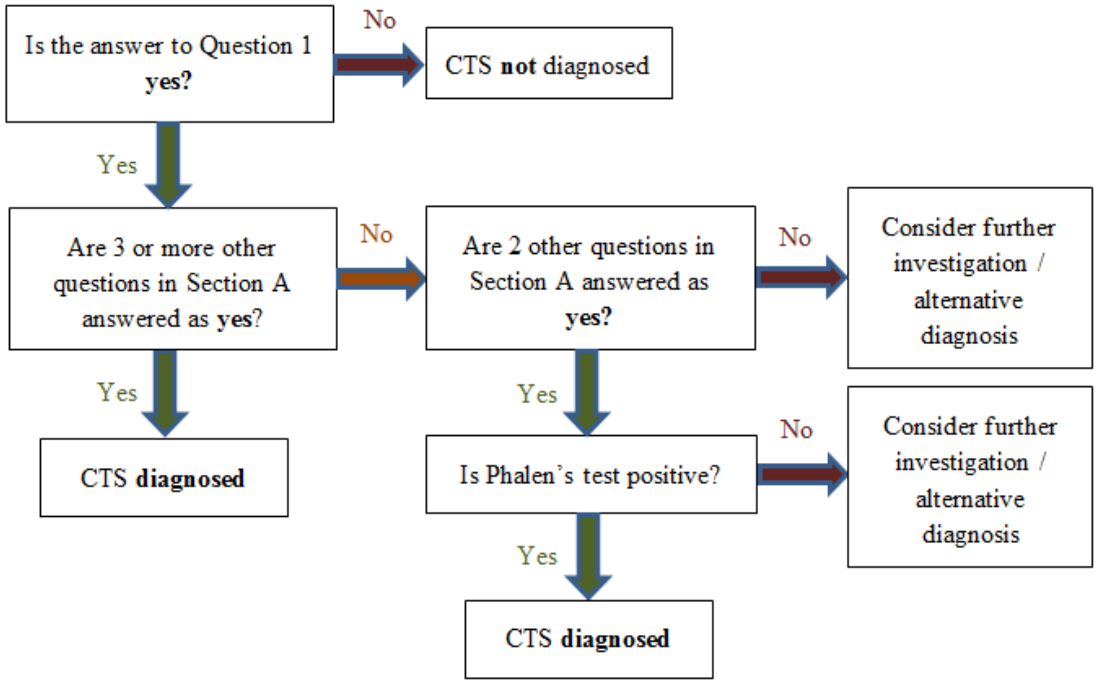
Guidelines from the American Academy of Orthopaedic Surgeons (AAOS) discuss how the history of the presenting complaint and physical examination findings assist in the diagnosis of CTS and can help plan management interventions.[21] Keith et al reported that after an extensive review of available literature, a high level of evidence was not available to assess the diagnostic utility and predictive value of such information.[21] However, when The AAOS updated their Clinical Guidelines in 2016; this primary approach to diagnosis by clinical assessment remained the same.[29] Despite a lack of high-level evidence for a standardised approach to diagnosis, expert opinion is generally used to suggest that symptoms, clinical examination and, in certain situations, electrodiagnosis can be combined to provide a satisfactory level of confidence in a CTS diagnosis.[21] This review could not however define which combination of tests could be used most accurately to identify CTS, due to the small number of studies of studies using a variety of case definitions.

Despite a number of recommendations in the literature, there remain no universally agreed and accepted criteria for the definitive diagnosis of CTS in routine clinical use.[30] Of note, none of the tools described above have been derived from a primary care population. Work prior to this thesis involved developing agreed clinical criteria with which to diagnose patients presenting in primary care with CTS, for the purposes of entry into a pragmatic randomised control trial, which will be referred to in later chapters.[31] The questions and associated flow diagram for use in the agreed clinical criteria are presented in Figure 1-4 and Figure 1-5.

Figure 1-4 Questions to be asked to a patient presenting with hand or wrist symptoms

1. Do you have numbness or tingling in your wrist, hand or fingers?
2. Do your symptoms spare your little finger?
3. Are the symptoms worse at night?
4. Do the symptoms wake you up at night?
5. Have you noticed your hand is weak; for example, have you found yourself dropping things?
6. Do you find shaking your hand, holding your hand or running it under warm water improves your symptoms?
7. Are the symptoms made worse by activities such as driving, holding a telephone, using vibrating tools or typing?
8. Have splints or injections helped with your pain if you have had it in the past?

Figure 1-5 Decision tree to be used in conjunction with Figure 1-4



1.3.1.1 Differential diagnoses to consider

Alternative diagnoses that may be considered in patients presenting with discomfort and / or altered sensation in the distal upper limb include: cervical radiculopathy, peripheral neuropathies, wrist/trapeziometacarpal arthrosis, wrist tendonitis/tenosynovitis, ulnar neuropathy, Raynaud's phenomenon, arterial injury or thrombosis, nerve laceration, neuroma, brachial plexus injury, other

nerve entrapment syndromes, pain syndromes, annular ligament injury, 'double crush syndromes' and motor neurone disease.[21]

1.3.2 Assessing the severity of carpal tunnel syndrome

Attempts have been made to formulate standardised clinical criteria with which to assess the severity of CTS and likelihood of treatment outcome (i.e. based on the patient's history and examination findings and without the input of further investigations).

The landmark paper which has influenced much of the more recent literature on the diagnosis, impact and outcome of CTS and its treatment was the development of a self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome (The Boston Carpal Tunnel Questionnaire - BCTQ) by Levine et al in 1993.[32] The questionnaire was initially developed using a clinical consensus exercise. It was then piloted and tested in two cohorts of patients: a prospective cohort study for determination of reproducibility, internal consistency, validity and responsiveness to change and a separate cohort of surgical patients for responsiveness to change. Levine et al concluded that the questionnaire was able to evaluate the course of CTS and the effectiveness of operative and non-operative interventions.[32]

In order to predict a satisfactory outcome from CTR, Kamath et al. (2003) developed a screening questionnaire based on the BCTQ[32] and tested the sensitivity of this screening questionnaire (now the Stothard questionnaire) in a prospective study of 58 patients referred to an NCS clinic, for electrodiagnostic testing. Symptomatic improvement after CTR was used as evidence of the 'true' diagnosis of CTS. The questionnaire was shown to be 85% sensitive with a positive predictive value (PPV) of 90% whereas electrodiagnosis was found to be 92% sensitive with a PPV of 92% in predicting response to surgery. It was suggested that the scored questionnaire could replace NCS; where if a patient scored more than five, they could be referred directly for surgery, to decrease waiting times and save money. The study was carried out in secondary care but the authors felt that it could be used by primary care physicians to diagnose CTS, which would be alleviated by surgery. They argue that the use of their objective questionnaire would also negate the medico-legal role of NCS prior to surgery.[33]

Atroshi et al also developed a brief measure of symptom severity, derived from the BCTQ. They subjected the 11 symptom severity items and 8 functional status items to factor analysis and item response theory. By comparison with a validation sample of 213 patients assessed using the *Quick*DASH questionnaire, they proposed a 6-item CTS symptom scale to be used as a brief measure of symptom severity.[34]

The trial referred to later in this thesis, used criteria presented by the British Society for Surgery to the Hand (BSSH) to classify the severity of CTS as being mild, moderate or severe. The following classification system was used to include patients with mild and moderate disease and exclude those with severe CTS:

- *Mild*: intermittent paraesthesia (nocturnal, position of hand, pregnancy, hypothyroidism)
- *Moderate*: constant paraesthesia (interference with activities of daily living, constant night waking)
- *Severe*: constant numbness or pain, wasting of thumb muscles and / or activities of daily living, weakness of thumb muscles[30]

1.3.3 Nerve conduction studies

Nerve conduction studies may be referred to under the umbrella terms of: electrophysiology; neurophysiology and electrodiagnosis. These terms can also be used to include electromyography (EMG), which involves the study of the motor innervation of muscles. For the purposes of consistency, the investigation of nerve conduction in the investigation and diagnosis of CTS will be referred to as nerve conduction studies (NCS).

CTS is a syndrome of signs and symptoms caused by compression of the median nerve in the carpal tunnel. Compression leads to demyelination, which reduces the performance of the nerve. The electrophysiological performance of a nerve can be quantified by NCS. The velocity of conduction from an artificial electrical impulse proximal to a potential lesion to a receiving electrode distally, can be

measured. Demyelination causes a reduction in the velocity of nerve conduction. The location of this slower conduction indicates where the compression or damage is occurring.

Electrophysiological measures were first used to define CTS in the 1950's[5] and modern methods of NCS have been reported to have a diagnostic sensitivity and specificity level of approximately 95% in clinical populations, when compared with direct ultrasound imaging, used as a confirmation of visualised nerve compression.[35] Early cases of CTS may have higher false negative rates than more severe cases, and may therefore be missed by nerve conduction studies.[36]

The clinical use of confirmatory testing in CTS remains controversial.[2] As already established, CTS is essentially a clinical syndrome that may be diagnosed following a good history taking and examination. However, the AAOS recommend nerve conduction studies are performed:

- To differentiate from other potential clinical diagnoses
- When thenar atrophy / persistent numbness is present, in order to differentiate from other peripheral nerve problems and to inform whether more severe nerve injuries require further diagnostic evaluation and / or warrant aggressive management
- If clinical diagnosis is suggestive of CTS and surgical management is being considered. [21]

If NCS are to be used, the AAOS recommend that the testing protocol should follow the American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation and American Association of Neuromuscular & Electrodiagnostic Medicine (AAN/AANEM/AAPMR) guidelines for diagnosis of CTS:

- Sensory nerve conduction velocity (NCV) studies to the median nerve with distal latency compared to the ulnar and radial nerve
- Median motor nerve conduction in most patients
- Needle EMG at the physicians discretion.[37]

Keith et al's review of electrodiagnostic tests could not determine that any method was clearly superior, due to the likelihood of spectrum bias caused by the inclusion of case control studies.[1] In this

situation diagnostic accuracy estimates from case-control studies using well-defined patient groups with and without disease, may not be applicable to the clinically presenting population. A further systematic review did not recommend NCS if symptoms of CTS are well defined.[38]

Most reports acknowledge a diagnostic role for NCS, however the debate remains as to whether they are necessary in all cases.[39] The Joint Royal College of Surgery and British Orthopaedic Association Commissioning Pathway suggest NCS should be a secondary care investigation done when there is:

- an equivocal clinical examination and history
- persistent or recurrent carpal tunnel syndrome
- an unclear diagnosis suggestive of a peripheral neuropathy.[40]

1.3.4 Other modalities of diagnostic investigation

Diagnostic ultrasound, pressure specified sensorimotor devices, computer aided tomography and magnetic resonance imaging have been suggested as diagnostic investigations for CTS. Imaging is not routinely performed to establish a CTS diagnosis, however may be used to investigate for differential diagnoses. Ultrasound has been shown to be a useful investigative tool as it can detect changes in the surface area of the median nerve as it passes underneath the flexor retinaculum.[41]

Keith et al concluded that there was no evidence in their review that such investigations currently offer superior diagnostic value to current practice and do not recommend them for use in the routine evaluation of patients with CTS.[21]

1.4 The treatment of carpal tunnel syndrome

Options for the treatment of CTS can be classified as being either surgical or conservative (non-surgical). Surgical treatment is usually offered to those with severe CTS, whilst conservative treatments are recommended as an initial treatment for those: who have symptoms without evidence of denervation of the median nerve; in whom surgery is contraindicated or have intermittent symptoms of non-severe (moderate and mild according to the RCS/BOS categories) CTS.[42] Conservative treatment

options include local corticosteroid injections (CSI), night splinting (NS), oral steroids, therapeutic ultrasound, electromagnetic field therapy, workplace adaptation and traditional cupping.[43] The majority of these treatment modalities are not routinely available in primary care. CSI and NS form the mainstay of interventions in the management of carpal tunnel syndrome, as indicated by national care pathways[22, 23] and guidelines,[40] thus will be the treatment options focused on in this thesis.

1.4.1 Wrist splints

The principle of resting (night) wrist splints is to immobilise the wrist in a neutral position, thereby alleviating pressure on the median nerve as it passes through the carpal tunnel. The splint may be worn solely at night, when most patients find their symptoms are most severe due to prolonged wrist flexion and hence increased pressure in the carpal tunnel, or at night as well as during daytime activities which trigger symptoms. Splints are available to purchase over the counter or custom-fitted splints may be provided by occupational therapists.[44]

Page et al conducted a Cochrane review of randomised and quasi-randomised trials comparing splinting with no treatment (or placebo) or with other non-surgical interventions. 19 studies were identified, randomising 1190 participants. Concerns with bias were noted regarding allocation concealment and blinding. The authors' conclusions suggest there is limited evidence that night splinting is more effective than no treatment in the short term (less than 3 months follow-up). The authors also reported insufficient evidence regarding the effectiveness and safety of one splint design over another. They did however suggest that evidence is insufficient and that more research is needed on the long-term effects of this intervention.[42]

Splinting may therefore be a treatment option for some patients but there is limited evidence regarding its effectiveness compared to no treatment, other conservative treatment options or surgery.

1.4.2 Local corticosteroid injections

Local (as opposed to systemic) corticosteroid injections are a common treatment option for mild to moderate CTS, or severe cases awaiting surgery and can be administered in primary care by trained clinicians.[31]

A Cochrane Review evaluating the effectiveness of CSI for CTS versus placebo injection or other non-surgical interventions concluded that CSI do provide improvement in symptoms after one month, although symptom relief beyond this period was not clearly demonstrated.[45] Of the 12 studies included in the review, seven used methylprednisolone as the injectate at a dose of between 15mg and 40mg.[46-52] Other drugs used in the included studies were: dexamethasone; betamethasone; triamcinolone and hydrocortisone. The authors were not able to identify a particular drug or dose of drug as being clearly superior.[45] A systematic review by Huisstede et al also concluded that evidence of short term benefit of CSI exists, but that mid and longer term follow up was required.[43]

A more recent RCT not included in the systematic reviews, assessed the clinical effectiveness of different doses of methylprednisolone injection in CTS. Three groups (37 patients in each) received 80mg of methylprednisolone, 40mg of methylprednisolone, or placebo. The mean change in symptom severity scores at 10 weeks was greater in the 80mg of methylprednisolone group and the 40mg of methylprednisolone group, when compared to placebo (-0.64 (95% CI -1.06 to -0.21; *P*=0.003) and -0.88 (95% CI -1.30 to -0.46; *P*<0.001)) respectively. There was no significant difference between the two doses at 10 weeks (0.24 (95% CI 0.24 to 0.69; *P*=0.29). The only group to show a significant reduction in the rate of surgery at 1 year was the 80mg of methylprednisolone group compared to placebo (0.24 (95% CI 0.24 (0.06 to 0.95; *P*= 0.41)). There were no serious adverse events recorded.[53] This trial provides some longer-term data suggestive that steroid injection may be clinically effective in reducing symptoms and the number of patients having surgery, but perhaps only at a dose of corticosteroid higher than those in regular clinical use. Further research is required to investigate whether steroid injections have the potential to reduce the rate of CTR, in the longer term, and at what dose.

Some guidance exists suggesting the inclusion of a local anaesthetic (LA) with the steroid when injecting into the carpal tunnel.[40] Regarding the use of LA, one trial has been identified in which 120

median nerves were randomly assigned to three treatment groups: 40mg of triamcinolone; 4ml of 1% procaine and 40mg of triamcinolone and 1% procaine. NCS and a visual analogue scale of symptoms were carried out at baseline, two months and six months after treatment. Improvement in some electrophysiological measures and the visual analogue scale were noted in all groups at two and six months (P<0.05). The only significant differences noted between groups were an improvement in some electrophysiological findings and visual analogue scale results in the combined group when compared with procaine alone at two and six months (p<0.05). There was no comment regarding patient acceptability or cost.[54] There appears to be clinical consensus within the literature that additional local anaesthetic does not add any clinical benefit to the procedure, but likewise is unlikely to cause harm.

1.4.3 Comparison of splinting versus corticosteroid injection and rationale for further study in this area

CSI and NS, the two mainstay treatment modalities used by clinicians and patients in a primary care setting, had been compared in three randomised control trials, other than the INSTINCTS trial, which will be discussed later in this thesis. [55-57] Sevim et al evaluated the effectiveness of CSI and NS in mild and moderate CTS. 120 patients with electrophysiologically confirmed CTS were randomised to either night splinting (60 patients), or beclomethasone injected proximally to the carpal tunnel (30 patients) or distally to the carpal tunnel (30 patients). After one year, clinical symptoms and NCS results were evaluated. The trial excluded patients who were non-compliant with splinting but suggested that the compliant cohort showed significant clinical and electrophysiological improvements whilst the injections groups did not.[55] Ucan compared the use of splinting, splinting plus local steroid injection and open CTR in patients with mild to moderate CTS with symptoms (and an electrophysiological diagnosis) for at least six months. The 57 hands included in the study were randomised to one of the three treatments (23 received injection, 23 received injection plus splinting, and 11 received CTR). Follow up was at three and six months with NCS, BCTQ and a patient satisfaction questionnaire. At 3 months all treatment modalities demonstrated improvement in patient reported and

electrophysiological outcomes, however at six months both measures deteriorated in the steroid and steroid with splinting group, whilst the CTR group continued to improve (BCTQ functional score *P*=0.03).[56] So et al also compared the efficacy of CSI with NS in 50 patients with CTS diagnosed using AAN criteria. They reported that at 4 weeks, both the CSI and NS groups showed an improvement in the symptom severity scale of the BCTQ (-0.670 +/- 0.614 and -0.38 +/- 0.475, *P*= 0.07 respectively), however only the CSI group showed improvement in their function and patient satisfaction score.[57]

These trials were relatively small and set in a secondary care environment using case definitions which included NCS findings. Ucan et al did not aim to compare splinting with injection alone.[56] It is therefore unlikely that these trials present robust evidence of the effectiveness of splinting versus injection generalisable to the primary care population, where patients can be assumed to present in the earlier stages of the condition and are more likely to have a milder symptom profile (if being treated as opposed to referred directly into specialised services). Clinicians are therefore unable to base their decisions as to which intervention is most appropriate on robust trial evidence. The INSTINCTS trial (Injection versus Splinting in Carpal Tunnel Syndrome) was designed to contribute to this evidence.[58, 59]

INSTINCTS was a pragmatic randomised clinical trial, recruiting from a primary care population, in order to further establish the comparative effectiveness of six weeks of night resting splint use with a single steroid injection.[58] As explained further in Chapter 2, this thesis will utilise data from the INSTINCTS trial to describe the prognosis of the trial population, develop a prognostic model predicting future patient reported outcome and to explore possible predictors of response to the two treatments investigated.

1.4.4 Carpal tunnel release surgery

Carpal tunnel decompression or release surgery (CTR) is a well-established treatment for CTS. It is considered to be the most effective treatment to alter the relationship between the median nerve and the carpal tunnel.[2] CTR is routinely carried out under local anaesthetic as day case surgery. Open and endoscopic approaches can be used to release the flexor retinaculum. Adjuncts to the release include a tenosynovectomy, neurolysis of the median nerve and lengthening or reconstruction of the flexor retinaculum.[60] A Cochrane review of surgical approaches did not find that either technique was more successful than the other and concluded the decision to use an open or endoscopic approach should be guided by surgeon and patient preference rather than evidence.[61]

Patient satisfaction with the outcome of surgery appears high.[2] A review of the surgical treatment of CTS reported that 70% - 90% of patients undergoing a CTR report a good outcome.[62] A retrospective cohort study observing patients after CTR for a mean of 13 years described that 88% of patients were either completely satisfied or very satisfied with their post-operative outcome. 74% reported their symptoms had completely resolved and 1.8% (113 patients) had undergone repeat surgery.[63] Surgery does carry a risk of complications including damage to nerves, arteries, tendons and the development of complex regional pain syndrome. Complication rates have been reported to be between 1 and 25% of patients.[2] Surgery should not therefore be considered a benign treatment option.

A systematic review by Turner et al, summarised predictors of an adverse surgical outcome and found prognostic factors included: diabetes; poor health status; thoracic outlet syndrome; double crush syndrome; alcohol misuse; normal nerve conduction studies; neurolysis; thenar wasting and workers compensation cases.[62]

CTR provides an effective mode of therapy for patients who have failed to respond to conservative treatment or who have severe CTS.[23] There is little evidence however that CTR is an appropriate initial management option for patients presenting in primary care with mild to moderate symptoms, especially in the absence of high-quality trial evidence that conservative management is ineffective. Surgery remains an expensive procedure relative to a CSI or splint and is unlikely to represent a cost-

effective management approach for all patients, if the much cheaper options are shown to be effective. In fact, commissioners are restricting access to referral and surgery in some healthcare localities due to this[64] and more robust evidence of the effectiveness and correct use of primary care options is required to potentiate benefits, reduce potential harms and maintain a cost effective approach to the primary care management of CTS.

1.5 The costs implications of carpal tunnel syndrome

The economic burden of CTS is likely to be high. An estimated $2 Billion is spent on the 400,000 to 500,000 cases of CTS treated with surgery in the United States each year.[65] CTS is a recognised occupational health condition and as such impacts upon the financial situation of workers and the workplace. Data from the US suggests the median number of days per person away from work due to CTS, when compared to other occupational and major disabling illnesses and injuries, is relatively high at 27 days.[66]

Hospital Episode Statistics, publicly available NHS healthcare data,[67] provide an estimate of the number of CTR's in an annual period. In England in 2012-13, 48,705 completed consultant episodes were recorded (mean age 59 years).[67] This figure underestimates the total number of contacts patients had with specialists as the data do not include patients having CTR in the community, as is becoming more common place, whereby trained GP's and allied health professionals are delivering surgical interventions in appropriate primary care settings. This further highlights the need for more research to be based in these evolving settings.

Miranda et al 2013, suggest an overall treatment cost for a patient having a CTR in their NHS Trust (including consultation) to be £877.60 (+/- £4.01).[68] If this is taken to be representative of the rest of the English population in 2013, an estimated £42,743,500 would have been spent in one year, on patients having CTR surgery.

Miranda et al further provide a helpful estimation of patient burden and cost when considering conservative versus surgical management. They retrospectively observed that 38% of the 149 patients

in their cohort experienced long term relief from conservative management whilst 62% progressed to surgery with an average symptom duration of 8 month (from initial clinic consultation). The authors did not identify any difference in treatment costs between groups (£824.82 +/- £49.79 injection group versus £877.60 +/- £4.01 surgery group, *P*=0.29) but did observe that patients who initially received conservative management required more clinic appointments and were treated for longer periods. Their entire surgical cohort reported long-term relief, leading them to conclude that although injections are an important first-line treatment; this is likely to be limited to particular patient groups.[68] It should also be recognised here that the figures quoted for patients receiving an injection include the mean number of outpatient appointments required and that the cost of a local corticosteroid injection to the department was £5.18.[68]

Conservative management in the community is not considered in these costings and as such substantial cost saving may be possible if referral and indeed surgery can be avoided by effective primary care management.

1.6 The prognosis of carpal tunnel syndrome

The prognosis of CTS, particularly in the presenting primary care population, has not been clearly established. A frequently cited study by Padua et al (2001) described the course of untreated CTS over a 10 to 15-month follow-up period. 196 patients who had not received treatment (274 hands) were assessed at baseline using clinical and electrophysiological methods. 27% of patients improved according to their electrophysiological classification and 34% improved symptomatically. The authors found clinical and electrophysiological measures improved more in patients with more severe initial impairment compared with those with milder initial impairment. The main predictors of a satisfactory clinical outcome were: a shorter symptom duration and younger age. Bilateral symptoms and a positive Phalen's test predicted poorer outcome.[69]

The outcome of surgically managed CTS will not be discussed in this thesis, but few studies have observed the prognosis of conservatively managed CTS and none of these have been set in the primary care population.

1.7 An introduction to the PROGRESS Framework

Prognosis has its etymological roots in the Greek *pro* – 'before' and *gignōskein* 'know'.[70] Prognosis therefore means foreseeing, predicting or estimating the likelihood of future events. Prognosis research can be defined as:

> *"…the investigation of future outcomes (endpoints) among people with a given baseline health state (startpoint), in order to improve health."*[71]*pg 1*

Overall prognosis research thus focuses on the average course of health-related conditions in groups of people.[71] Prognosis research is important for a number of reasons: it shapes the development of public health policy; allows research into the comparative effectiveness of health services; informs the development of potential new interventions and the trials required to test these; moves from the limitations of a diagnostic medical model to a prognostic one and can identify new conditions or phenotypes.[71]

The systematic reviews and empirical studies presented in this thesis will follow the PROGnosis RESearch Strategy (PROGRESS) Framework. This Framework includes four distinct but related research themes. The definition and underlying principles of these themes were developed by members of the Medical Research Council (MRC) funded PROGRESS Partnership, with the aim of,

> *"…explaining how [each of these four prognosis research themes] provide important evidence that can be used at multiple (translational) pathways toward improving clinical outcomes—from the discovery of new interventions, through to their evaluation and implementation in the clinical management of individual patients, and to examining the impact of interventions and healthcare policies on patient outcomes."* [71] *pg 2*

These four research themes will be described in further detail throughout the thesis but in summary are:

I. Overall prognosis research: which aims to describe and explain future outcomes in relation to current practice.[71]

II. Prognostic factor research: where a prognostic factor is any measure that is associated with a subsequent outcome, prognostic factor research examines the impact of such prognostic factors on overall prognosis.[72]

III. Prognostic model research: where a prognostic model includes multiple prognostic factors in combination to predict the risk of a future outcome, prognostic model research moves from predicting average risk to predicting the risk of an outcome at the level of the individual.[73]

IV. Stratified care research: where stratified care refers to the targeting of treatments according to baseline characteristics shared by a subgroup of patients, stratified care research aims to identify priority areas for stratification, identify predictors of treatment response and examine the effect of stratified care approaches in healthcare.[74]

These research themes will be followed in order to describe the overall prognosis of CTS, identify factors that predict its outcome and work to develop models that predict outcome for individuals. Data from a randomised trial will be used to explore whether a stratified approach may improve outcomes in patients with CTS treated conservatively in primary care.

1.8 Summary

CTS is a common condition causing distressing symptoms and functional deficit, as well as placing potential financial burdens on patients and the wider healthcare and socioeconomic environments. There is debate surrounding the methods used in its diagnosis. Prognosis is unclear, particularly for those patients treated conservatively. The initial management of CTS is likely to occur in primary care where the most common interventions are CSI and NS. More severe cases or those not responding to conservative approaches are likely to be treated surgically. There is some suggestion that referrals for and episodes of surgery are increasing.

Most research to date investigating the epidemiology, prognosis and management of CTS, has taken place outside of the primary care setting in patients with more severe disease. Chapter 2 will present the rationale, aims and objectives of the studies untaken as part of this thesis, which seeks to consider

the epidemiology, prognosis and non-surgical management of carpal tunnel syndrome, in primary care and thus addresses the gaps in the research highlighted above.

2 Aims, objectives and study design

Summary

This chapter presents the aims, objectives and methodological overview of the thesis. A summary of the overall structure, together with a brief outline of individual studies and chapters, is provided.

2.1 Thesis statement

CTS is a common condition affecting the distal upper limb, which can cause distressing symptoms and functional deficit. Current understanding regarding the epidemiology and prognosis of CTS, with specific focus on patients presenting in primary care, is lacking. Treatment options that can be delivered to patients in the primary care environment exist; yet guidance as to who is likely to fail to respond and / or require surgery is not available. As such, new evidence is required to explore ways in which treatments may be best targeted to individuals in order to improve clinical outcomes but also to identify patients who are more likely to require referral for consideration of surgery.

2.2 Aims and objectives

The initial aim of this PhD was to update the evidence describing patterns in the prevalence, incidence and management of CTS presenting in UK primary care and to estimate the proportions of patients receiving treatment in its various forms over time. Secondly, the studies in this thesis aimed to improve the primary care management of patients with CTS by identifying patients who are likely to respond to the different treatment options available in primary care and predict which patients are less likely to respond and eventually need surgery.

The specific objectives of the studies presented in this thesis were to:

1a. Estimate trends in the annual prevalence and incidence of CTS diagnosed in primary care between 1993 and 2013

1b. Estimate trends in healthcare use of patients with CTS between 1993 and 2013

2a. Summarise available evidence regarding the course of conservatively managed CTS and the predictors of its outcome

2b. Develop a prognostic model to predict poor outcome in conservatively managed CTS, as defined by (the first occurrence of) carpal tunnel release surgery, in a cohort of patients identified in the Clinical Practice Research Datalink

2c. Develop a prognostic model using individual patient data from a randomised controlled trial to predict future change in patient-reported CTS-symptoms following primary care management

3a. Summarise available evidence regarding predictors of response to common primary care treatments of CTS; in particular corticosteroid injection and night splinting

3b. Investigate if *a priori* defined candidate predictors of treatment effect (effect modifiers), predict a better outcome from either corticosteroid injections or night splinting in primary care patients with CTS

2.3 Methodological overview

To address the overall study objectives, the following designs and their corresponding PROGRESS study type were:

1a: Epidemiological analyses over time (using the Clinical Practice Research Datalink) to estimate prevalence and incidence of CTS

1b: Cross-sectional analyses over time (using the Clinical Practice Research Datalink) to describe trends in health care use

2a: Systematic literature search and narrative synthesis of cohort studies to summarise available evidence regarding the overall prognosis and predictors of future outcomes in patients with CTS treated conservatively *(PROGRESS I & II)*

2b: Retrospective cohort study using population data from the Clinical Practice Research Datalink to develop a model predicting treatment of CTS with carpal tunnel release surgery *(PROGRESS III)*

2c: Prospective analysis (prognostic model study) of individual participant data from a randomised controlled trial (secondary analysis of the INSTINCTS trial) *(PROGRESS III)*

3a: Systematic literature search and narrative synthesis of trials to summarise available evidence regarding predictors of response to treatment (local corticosteroid injection and night splinting) in patients with CTS *(PROGRESS IV)*

3b: Subgroup analysis of data from a randomised controlled trial to explore a priori defined predictors of treatment effect (local corticosteroid injection and night splinting) *(PROGRESS IV)*

2.4 Thesis structure

This thesis is divided into the following 9 chapters:

1. Introduction

This chapter provides an overview of CTS as a clinical condition. A background of its pathophysiology, clinical diagnosis and management is presented. The chapter contextualises CTS as a common bothersome condition with a paucity of evidence regarding its management in a primary care setting. The concept of the PROGRESS Framework is introduced.

2. Aims, objective and study design

3. The epidemiology of CTS: Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013 - an observational analysis using the Clinical Practice Research Datalink

The prevalence and incidence of CTS in the UK primary care population over a 20 year period are described, using data from the Clinical Practice Research Datalink (CPRD). The proportion of prevalent patients receiving interventions, including CSI and CTR, for each annual period between 1993 and 2013 are presented. Joinpoint regression is used to indicate significant changes in trends over time.

4. The prognosis of carpal tunnel syndrome: The clinical course and prognostic factors in conservatively managed carpal tunnel syndrome - a systematic review and narrative synthesis of cohort studies

Following a systematic search of the literature, this chapter provides a summary of the evidence regarding the clinical course of patients with CTS managed conservatively and identifies predictors of poor outcome.

5. The prognosis of carpal tunnel syndrome: Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care – a cohort study set in the Clinical Practice Research Datalink

A cohort derived from patients identified in chapter 3 is observed over a three-year period. Candidate predictors identified in the literature and through clinical consensus are used to develop a Cox regression model predicting surgical intervention.

6. The prognosis of carpal tunnel syndrome: Describing the course of symptoms and predicting outcome in patients with carpal tunnel syndrome receiving conservative management as part of a randomised controlled trial (Injection versus Night Splints in Carpal Tunnel Syndrome)

Candidate predictors tested in chapter 5 are limited by the need for them to be identifiable in consultation data. Further candidate predictors identifiable in clinical trial data are tested and used to develop a model predicting patient reported outcome (carpal tunnel related symptoms and functional limitations).

7. The management of carpal tunnel syndrome: Matching patients to treatments in carpal tunnel syndrome - A systematic review and narrative synthesis of trial evidence

In order to identify candidate moderators to be tested in chapter 8, a systematic search of clinical trials is conducted and evidence of potential moderators, as targets for inclusion in a sub-group analysis, described.

8. The management of carpal tunnel syndrome: Testing predictors of the effect of treatments for carpal tunnel syndrome in primary care – An exploratory analysis of data from the INSTINCTS (Injection versus Night Splints in Carpal Tunnel Syndrome) trial

An exploratory analysis of data from the INSTINCTS trial was conducted to explore the potential moderating effect of a small number of candidate predictors.

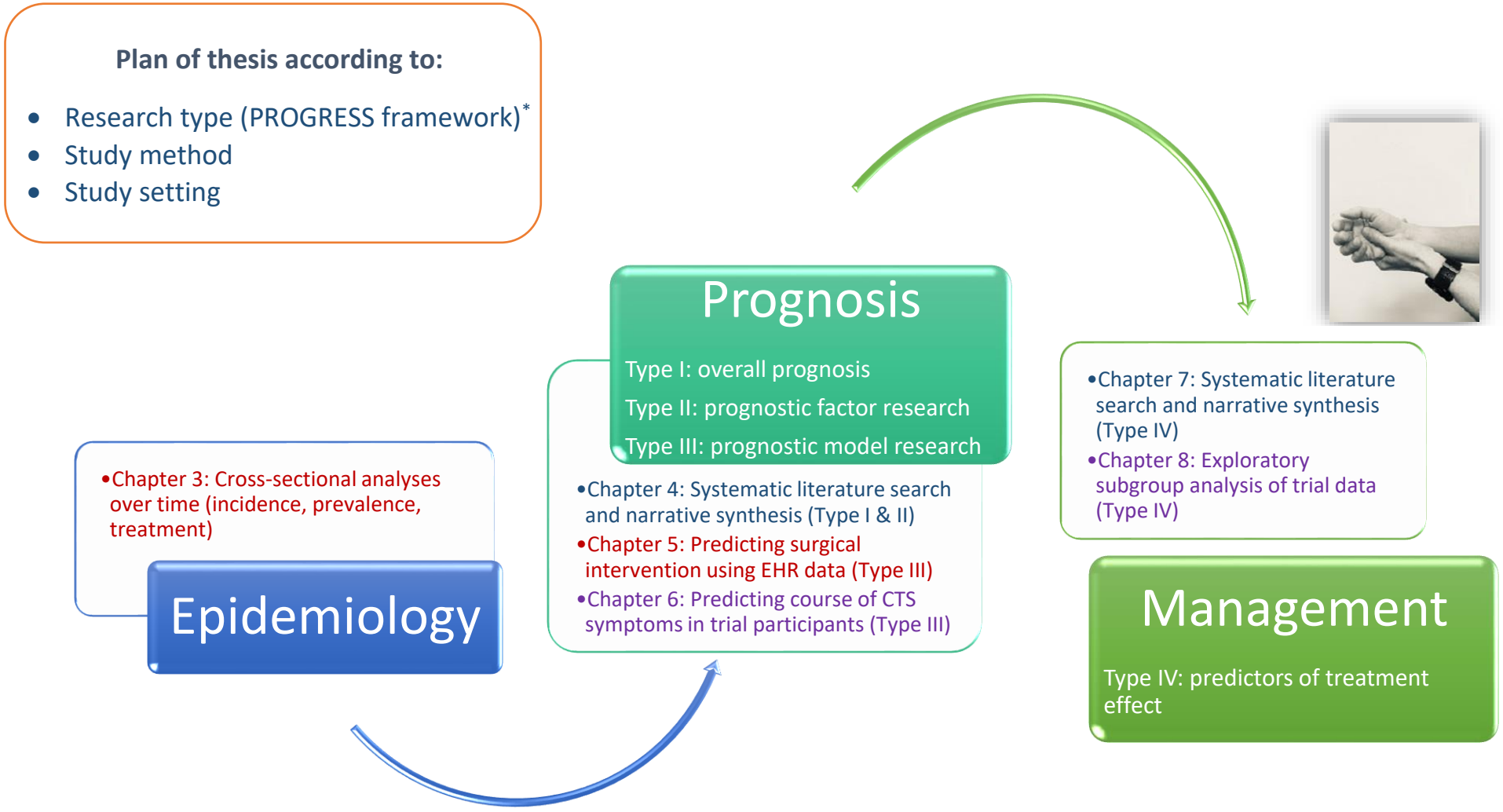
9. Summary, discussion, implications and conclusions

An overall summary and synthesis from each element of the thesis are presented. The clinical implications are described and recommendations for future research discussed.

2.5 Illustration of the thesis plan

Figure 2-1 below provides an illustrated overview of the chapters, study type, setting and their correspondence to the PROGRESS research framework.[75]

Figure 2-1 Illustration of the thesis plan



2.6 Summary

This chapter has presented the aims and objectives of this thesis and outlined the study designs and methodological approaches utilised. The overall thesis structure has been summarised. Chapter 3 will present epidemiological studies, using consultation data from primary care, to describe the trends in the prevalence, incidence and management of CTS over time. This in turn will contextualise the subsequent studies in the setting of UK primary care.

3 The epidemiology of carpal tunnel syndrome: trends in the prevalence, incidence and management of carpal tunnel syndrome between 1993 and 2013 - an observational analysis using the Clinical Practice Research Datalink

Summary

The aim of this chapter is to describe the epidemiology of CTS in the setting of UK primary care. Firstly, the trends in the annual prevalence and incidence of CTS diagnosed in primary care between 1993 and 2013 are estimated. Secondly, trends in the health care use of these patients are described. Joinpoint regression is used to identify and quantify significant changes in any trends identified.

Burton CL, Chen Y, Chesterton LS, van der Windt DA. Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records.BMJ Open 2018;8:e020166

3.1 Introduction

Prevalence is an absolute measure of the frequency of an existing disease in a given population at a point in or over a period of time. Prevalence estimates can help to inform healthcare planners about the needs of their community and calculate the levels of service required. The incidence of a disease indicates the proportion of newly developed or diagnosed cases of a disease and is a useful measure in analytical research when studying trends.[76, 77] Quantifying the burden of CTS in patients presenting in a primary care setting and describing their management will help to contextualise the subsequent studies presented in this thesis.

3.1.1 Using electronic health records in research

General practice consultation databases, which hold electronic patient records, are of growing importance in research as they provide data on healthcare use from large samples, generally accepted to be representative of the UK population.[78, 79] A number of national anonymised sets of routinely collected consultation data now exist including: the Clinical Practice Research Datalink (CPRD); the Health Improvement Network (THIN); the SAIL Databank and QResearch.[79, 80] There are also regional databases such as the Consultations in Primary Care Archive (CiPCA), which are based on a smaller number of general practices.(Jordan et al. 2006)

Over 98% of the UK population are registered with a General Practitioner (GP).[81] GP's and other primary care practitioners are the first point of contact for most patients presenting with non-emergency health-related issues. Patients can be referred from primary to secondary or other specialist care, if felt appropriate. The levels of care in the NHS can be described as service tiers: Tier 1 refers to primary care; Tier 2 is a combination of some specialist services and some community-based services (e.g. a community based physiotherapist managing patients in a primary care setting); Tier 3 is a multi-disciplinary outpatient team (e.g. an extended scope practitioner managing patients in a community based musculoskeletal clinic), based in the community and Tier 4 refers to specialised services based in secondary care (e.g. an orthopaedic surgeon managing patients in a hospital outpatient clinic). GP's can be considered to be the 'gatekeepers' of the UK National Health Service NHS).[82]

The electronic information held in consultation databases relate to patients and their interactions that have taken place in general practice, for example: demographic information; prescription details; symptoms; diagnoses; tests and immunisations as well as referral data and data collected from secondary care correspondence (usually key diagnoses and treatments). Databases can therefore be considered to represent current and previous healthcare activity and have therefore been used as the setting for a wide range of research methodologies including: the assessment of epidemiological

trends; health economic analyses; prognosis research; comparative effectiveness research and randomised controlled trials.[82]

3.1.2 The use of codes in general practice consultation data

Coded clinical terms are used to define episodes of care and should be used to record patients' interactions on the computer systems used in primary care, such as EMIS (Egton Medical Information Systems Ltd). Codes allow patient information to be captured, stored and retrieved in clinical language.

The ever-expanding library of clinical terms used in practice can be assigned Read codes and include: categories of signs and symptoms, treatments and therapies, investigations, occupations, diagnoses and appliances. Read Codes therefore make up a hierarchical 'thesaurus' of terms, stored by the computer. In practice, clinical staff are expected to enter at least one morbidity code for each patient contact.

Other coding systems do exist. Oxford Medical Information Systems (OXMIS) codes were developed concurrently with Read codes in the 1980's, however these have since been mapped to their Read code equivalents, which have been used almost exclusively by UK based GP's since the mid 1990's. Read Codes (CTV3) have since been merged with the College of American Pathologist's SNOMED RT (Reference Terminology) to form SNOMED CT (Clinical Terms).[83] SNOMED CT is currently being phased in across primary care and should be applied across the NHS before April 2020.[84]

3.1.3 The quality of general practice consultation data

For research set in consultation databases to be valid, the clinical information they contain needs to be of consistently high quality. CPRD, stipulates data quality criteria for patients (acceptable 'research useable' patients) and for practices ('up to standard' data) to be fulfilled. A hierarchy of data quality exists. Objectively recorded information such as prescriptions being the most accurate. Quality then decreases as coding becomes more subjectively applied, as found in the coding of diagnoses and the recording of lifestyle / socio-economic data.[79] Whilst entry standards are imposed on practices, individual GP's do exhibit variability in the codes that they use to record symptoms or diagnoses.[79]

A systematic review of 49 studies based in consultation data by Khan et al, which commented on the validity, accuracy, concordance and recording of terms, showed that most diagnoses coded in CPRD were well recorded with a positive predictive value of 80% or above. However, acute diagnoses (e.g. acute liver failure) were found not to be as well recorded.[85] The review further identified differences in date between actual and coded diagnoses, which whilst small led the review authors to recommend that such discrepancies be considered when observing time dependent outcomes.[85]

Jordan et al reported that whilst trends across age and sex groups were similar, GPRD (now CPRD) gave a lower prevalence for any musculoskeletal condition, rheumatoid arthritis and osteoarthritis than other databases.[86] Jordan et al suggest that this may have been due to there being no requirement in GPRD for each chronic condition in each consultation to be coded. They therefore suggest caution in interpreting trends in prevalence.[86]

As well as the quality of the data available, the problem of missing data should be considered when using consultation databases in research. Understanding missing data can be complex. For example, body mass index may be recorded more frequently in patients with diabetes, and blood pressure in those with cardiovascular disease. Such data is therefore likely to be 'missing not at random'. Likewise, absence of a Read code does not necessarily indicate absence of disease and there is a risk that information stored in free text may be missed.[82]

Despite these potential limitations, the benefits of using consultation databases in research include: the very large amount of coded patient information held including morbidity and lifestyle variables; the long-term follow-up available, and in the case of CPRD, the potential to link with other healthcare data sources such as Hospital Episode Statistics (HES) and postcode linked deprivation measures.[87] The strengths of having a large sample size over a prolonged period should be weighed against the risk of the data quality being less satisfactory, when compared to the alternatives which would include manually intensive clinical record searches at a patient level or potentially expensive and limited purposively designed observational data collection.[79]

Following an initial pilot study in the locally held CiPCA, CPRD was used to estimate the trends in the epidemiology and healthcare use of patients with CTS diagnosed in primary care, over time. The next section will briefly describe the pilot study and how it was used to inform the methods of the larger CPRD study.

3.2 Pilot study using the Consultations in Primary Care Archive

3.2.1 A summary of the aims, methods and findings of the pilot study

The aim of the pilot study was to develop and test the methods and procedures necessary to perform analysis in the larger CPRD database. The pilot study would also produce epidemiological data from the local North Staffordshire population, which could potentially be compared with the results of the national database (this comparison has not taken place as part of this thesis).

Adults aged 18 years and over were included, and a series of descriptive analyses conducted to estimate the prevalence and incidence of CTS in each annual period between 2000 and 2010. Read code and prescription linkage to treatments of corticosteroid injection (CSI) and splinting (NS) for CTS were developed and used to estimate the healthcare use of patients with CTS over time. Evidence of CTR was identified from the patient record using a pre-defined list of Read codes.

Read codes to be used to identify CTS diagnoses were agreed through clinical consensus with other practicing clinicians, as described more fully in 3.3.3.1. Individuals with a diagnosis of CTS or a code for treatment of CTS were identified in each calendar period. Individuals with no previous consultation for CTS in the two-year period preceding the index diagnostic consultation were identified as incident cases. The denominator for prevalence and incidence was the mid-year registered adult population for each annual period. Crude estimates (with 95% confidence intervals) were directly standardised to the general age-sex population structure of the UK.

The standardised prevalence increased marginally over the observe period from 20 per 10,000 (95% CI 17 to 23) in 2000 to 24 per 10,000 (95% CI 21 to 27) in 2010, with a noticeable peak around 2004.

The total incidence remained largely stable at around 16 per 10,000 person years. The female: male ratio of incident cases decreased from 2.1 in 2000 to 1.7 in 2010. The median age of the incident population was 54 years for males and 53 years for females, across the years.

Between 2000 and 2010, the proportion of prevalent individuals having surgery appeared to have increased from 10% to 26%. The median age of male and female cohorts receiving surgery, increased over time. The female: male ratio of those having surgery fluctuated over time but averaged at 1.2.

3.2.2 Implications of the pilot study

The pilot study demonstrated that estimating epidemiological trends using general practice consultation data was both feasible and produced results comparable with the literature summarised in 1.2.1. The observed population (registered population in CiPCA practices) was however relatively small when compared with CPRD (124,000 versus 11.3 million patients, over the total period of the data collection). CiPCA also represents a single healthcare locality. Experience from working with recruitment centres from across the country for the INSTINCTS trial highlighted the variability in clinical practice in the management of CTS. There was therefore a substantial risk that CiPCA would not be representative of the national population. In order to observe a larger population, representative of the UK population, over a longer time period, the study was further developed and conducted in the CPRD.

3.3 Trends in the prevalence, incidence and management of carpal tunnel syndrome between 1993 and 2013 - an observational analysis using CPRD: Methods

3.3.1 Population and setting: the Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) is a live database of anonymised medical records from general practices, initiated in 1987. CPRD holds the information of over 11.3 million patients from 674

practices in the UK. 4.4 million active (alive and registered) patients currently contribute information to the datalink, which equates to 6.9% of the UK population.[82] CPRD is broadly representative of the UK general population in terms of age, gender and ethnicity.[82] The datalink includes coded health data, including data on: demographics; symptoms; tests; diagnoses; therapies; health-related behaviours and referrals to secondary care. 75% of contributing practices contribute to the CPRD linkage scheme. Patient level data can therefore be linked with Hospital episode Statistics (HES); Mortality data (via Office for National Statistics); Index of Multiple Deprivation and Townsend scores and disease registers. Whilst general practice consultation databases have their limitations when used for research as described above, their potential for epidemiological research is substantial and to date over 2,300 research studies based in CPRD have been published.[82, 87]

3.3.2 Ethics and data governance

The CPRD has National Research Ethics Service Committee approval for observational research using primary care data and data linkages. CPRD is a joint project run by the Medicines and Healthcare Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). CPRD is owned by the Department of Health and operates within the MHRA. CPRD operates within UK and European laws of information governance and strives to protect patient confidentiality.

In order to access data, researchers must have a protocol approved by the Independent Scientific Approvals Committee (ISAC). The protocol for this study (14_167) was approved on 16th September 2014 and can be found in Appendix A.

3.3.3 Selection of Cases

3.3.3.1 Identification of codes

In order to identify the Read codes used to record a clinical diagnosis of CTS, a list of possible codes was generated using a Clinical Terminology Browser. The candidate codes are shown in Table 3-1.

Table 3-1 Candidate Read codes for carpal tunnel syndrome

Read code	Term Details
F340.	Carpal tunnel syndrome / CTS
7N081	[SO]Median nerve
F346.	Median nerve entrapment
7N08H	[SO]Median nerve - hand
7N08D	[SO]Median nerve - forearm
F341.	Other median nerve lesions
F3410	Median nerve neuritis
F3411	Median nerve compression in forearm
F3412	Anterior interosseous nerve lesion
F341z	Median nerve lesions NOS
7N08K	[SO]Median nerve, thenar motor branch

General Practitioners from the Primary Care Centre Versus Arthritis were approached by email and asked which code or codes they would use in clinical practice to code a patient with a diagnosis of CTS, which they were clinically confident about. They were also asked to add any other terms they would use. 8 GP's responded and reported that F340 was the only code that they would use in the clinical scenario posed. 1 GP commented that he would use 85BE to code that he had delivered an injection to the carpal tunnel. 1 GP commented that he would use hand pain / wrist pain / hand symptom / wrist symptom NOS if the patient 'did not obviously have CTS.'

3.3.3.2 Inclusion criteria

The study population consisted of men and women over 18 years of age. It was decided not to include patients under the age of 18 years as firstly, CTS in a paediatric population is rare[88] and a code for CTS unlikely to be accurate and secondly, would have limited the data available as not all practices contribute data from minors to CPRD. Patients were required to have *'up to standard'* and *'acceptable patient'* data, for two years prior to an incident episode and at the point of diagnosis for a prevalent episode. These terms are defined by CPRD. The *'up to standard'* metric is based on the continuity of recorded data, including the recording of deaths, and is set at the most recent date at which a practice

meets the quality criteria. The *'acceptable patient'* metric is based on the presence of a registration status; the patient record itself and there being a valid age and gender.[82]

When carrying out pilot work within CiPCA, a review of free text comments (available in CiPCA but not CPRD) highlighted the fact that Read codes relating to surgery were frequently used to code consultations pertaining to CTS. For example, to code consultations where wounds were reviewed or fit notes issued. It was also noted that surgical codes could be the only code used to identify a patient with CTS. For example, a patient may initially be coded using a more general hand pain code (hence not identified by the inclusion criteria) and then have a CTS specific surgery code attributed to them following referral and eventual surgery. The same was true of carpal tunnel injection, although the numbers were much smaller. In line with the methodology used by Latinovic et al[19] in their GPRD based study, individuals with a code for CTS, carpal tunnel release or a carpal tunnel injection were included as CTS cases. Table 3-2 shows the final set of Read codes selected to identify patients with CTS. All Read codes required conversion to the 'medcodes' utilised by CPRD. All recorded episodes of care (e.g. GP consultations, telephone consultations, administration entries) were considered in the inclusion criteria.

Table 3-2 Read codes selected to identify prevalent cases of CTS

Read code	Term Details
F340	Carpal tunnel syndrome
85BE.00	Injection of carpal tunnel
70560	Carpal tunnel release
70564	Endoscopic carpal tunnel release
7056011	Carpal tunnel decompression

3.3.3.3 Distinguishing prevalent and incident cases

The prevalence of individuals consulting with CTS was calculated per annum. The numerator for prevalence was the number of patients with a record of a CTS diagnosis or evidence of an episode of CTR or a CSI, in each calendar year. In order to determine annual incidence, the numerator was the number of patients with a record of CTS or evidence of CTR or CI, without a prior record of these codes

during a run-in-period of two years. This two-year run-in period was based on expert consensus that aimed to estimate the period of time within which it was felt unlikely that a patient with ongoing bothersome symptoms would not have consulted. CTS may have presented as a new episode in the contralateral wrist sometime after the index presentation, hence it was not felt possible to use the criteria as 'no previous recorded episode' to define incidence.

The denominator population for calculating the prevalence was the total up-to-standard person-years contributed to CPRD by patients over the age of 18 years of age, for each annual period between 1st January 1993 and 31 December 2013. As all incident patients were required to have at least 2 calendar years registration prior to the event date, the denominator population were also required to have registration at the mid-point of the year, two calendar years before the index year, in order to be able to apply the same criteria to both the numerator and denominator populations.

3.3.3.4 Identifying episodes of healthcare use

3.3.3.4.1 Carpal tunnel release surgery

Episodes of CTR were identified using Read codes as shown in Table 3-3. In addition to the codes used to define prevalence and incidence, 're-release of carpal tunnel' and 'revision of carpal tunnel release' were included as a surgical episode (if the first code used to record surgery). These terms were not included in prevalence or incidence definitions as they may not have indicated an episode of 'idiopathic' CTS but rather iatrogenic symptoms following previous (unsuccessful) surgery. Of note revision codes contributed less than 1% of the total surgical codes used.

Table 3-3 Read codes used to identify an episode of carpal tunnel injection and carpal tunnel release surgery

Read Code	Term details
85BE.00	Injection of carpal tunnel
7056000	Carpal tunnel release
7056200	Re-release of carpal tunnel
7056400	Endoscopic carpal tunnel release
705A100	Revision of carpal tunnel release
7056011	Carpal tunnel decompression

The pilot study demonstrated that that substantial variation in the number of surgical episodes per patient existed. This variation was felt likely to be due to the issue of surgical intervention codes being used as consultation codes, following the initial episode. For example, a patient attending for sickness certification following surgery may be attributed a further surgical code. Repeat use of codes may however have indicated a true repeat surgical episode if the patient had a 'redo' procedure due to complications, or had the contralateral hand operated on. It was not however possible to distinguish between these. It was therefore decided to only count the first episode of CTR in a patient's records. This approach was acknowledged to risk the rate of surgery being underestimated.

3.3.3.4.2 Corticosteroid injection

Corticosteroid injections used as a treatment for CTS were identified in two ways. Firstly, the Read code (85BE: Injection of carpal tunnel) was used to identify coded episodes of treatment delivery. However, there was concern that the exact procedural code may not have been applied ('Injection of steroid' or 'Injection of steroid into wrist joint' are also available to use but are less specific). Therefore, a further method of identifying CTI was developed.

When a drug is used in primary care, it is usual practice to code the intervention and generate a prescription in the patient's notes to demonstrate that a drug has been prescribed and / or administered. Even if a drug has been used from practice stock, a prescription is required to allow the cost of the drug to be reclaimed. An episode of CSI should therefore be linked with a prescription for

a locally injected corticosteroid. These drugs are listed in Chapter 10.1.2.2 of the British National Formulary.[89] CPRD data includes all such prescriptions and the date they were prescribed. This should therefore allow the patient's unique identification number to be linked with the details of a prescription including the BNF Chapter and the date of issue of the prescription.

All prescriptions from Chapter 10.1.2.2 were identified. These prescription data were then merged with a database listing all patients identified by Read code as having a diagnosis of CTS (using the F340 diagnostic code). In order to link a prescription of a locally injected corticosteroid with a consultation tagged as a being related to CTS, a further database was produced to show patients who had been prescribed a corticosteroid within four weeks of a consultation for CTS. The four-week period was decided on through consensus between three GP's who routinely perform CSI's based on the assumption that the consultation should either be coded as a CTS or CSI or that the injection would be prescribed within 4 weeks of a consultation, where a decision had been made to inject.

The database containing entries coded with an episode of CSI and the database containing linked prescriptions were then merged. An episode of CSI was therefore defined as an episode with either a coded consultation for a CSI or evidence of a prescription for a locally injected corticosteroid issued within a 4-week period of a coded consultation for CTS. As it is clinically possible and even likely that some patients benefit from more than one injection, clinical consensus set the total number of injections that a patient may have over the timespan of their registration, at four.

3.3.3.4.3 Wrist splinting

Several Read codes for the provision of splints are available as listed in Table 3-4. It was known from the pilot study that these codes were used infrequently. It was decided to reaffirm this finding in CPRD. It is unlikely that a separate code for the recommendation of splinting would be used in a consultation. Splints are neither prescribed nor distributed in general practice. If they were recommended, it is likely that the suggestion to a patient to source them form a pharmacy or online provider would be recorded in free text, which is not available in CPRD data.

Table 3-4 Read codes used to identify an episode of wrist splinting

Read code	Term details
8O1C	Provision of splint
8O1C0	Provision of working splint wrist brace
8D562	Passive wrist extension splint
8D563	Active wrist extension splint
8O1C0	Provision of working splint wrist brace
8O1C	Provision of splint

3.3.3.4.4 Nerve conduction studies

The data for NCS was based on Read coded entries, as per Table 3-5 and additional investigation entries in the patient record. Up to two episodes were allowed over the full follow-up period (one episode per hand). It is acknowledged that access to NCS varies by region or healthcare locality. Locally, one would have to refer to the local musculoskeletal interface service (tier 3) to access such investigations. Only highly diligent coders might include a code for this from an outpatient letter so, along with CSI, NCS are unlikely to be completely identified in CPRD.

Table 3-5 Read codes used to identify an episode of nerve conduction studies

Read code	Term details
8HRE	Referral for nerve conduction studies
70652	Nerve conduction studies

3.3.3.4.5 Referrals

Using the Read codes shown in Table 3-6, coded episodes of referrals were sought using data from CPRD. In addition, the referrals database was also searched and merged with the coded CTS tagged consultation data. A referral to the destinations in Table 3-6 were assumed to be linked to CTS if it occurred within 2 weeks of the index CTS consultation.

Table 3-6 Read codes used to identify an episode of referral

Read code	Term details
8H54	Orthopaedic referral
8H4B	Referred to rheumatologist
8HTd	Referral to rheumatology clinic
8HRE	Referral for nerve conduction studies
70652	Nerve conduction studies
8H	Further care
8H77	Refer to physiotherapist
8H7J	Refer to occupational therap.
8H55	Neurosurgical referral
8H46	Neurological referral
8H59	Referral to plastic surgeon

The number of referrals to each speciality or intervention was recorded and the demographics of the referred cohort, described. In addition, it was be assumed that patients with a surgical episode must have had a referral from primary care, therefore patients with a surgical episode without a referral code, were included in the referral data.

3.3.3.4.6 Sickness certification

Unlike CiPCA which stores sickness certification (or fit note) data, CPRD does not have such a feature. Read codes as shown in Table 3-7 were therefore matched to CTS consultations and recorded if the dates of the events corresponded.

Table 3-7 Read codes used to identify an episode of sickness certification

Read Code	Term details
9D1	MED3 doctor's statement
9D11	MED3 issued to patient
9D17	MED3 NOS
9D19	MED 3 issued by hand not fit
9D1C	MED3 (2010) issued to patient

3.3.4 Statistical methods

Crude age and sex specific annual prevalence and incidence were determined for each calendar year between 1993 and 2013. Due to lower numbers of patients in the initial years of CPRD (1987 to 1992), results are reported from 1993 onwards. For confidence interval calculation, a Poisson distribution was used.

In order to consider the effect of a changing population structure over the study time-frame, crude values for prevalence and incidence were directly standardised to the age-sex population structure (aged 18 years and above) of the UK in 2013, using population estimates provided by the website of the Office of National Statistics.[90] There was no substantial difference between crude and standardised rates, hence the standardised values were presented as a sensitivity analysis and the crude figures reported in the main analysis. This was done in order to maintain consistency between the different parts of the study; episodes of healthcare use were described as the percentage of the crude prevalent population undergoing the intervention in question.

Emerging trends were described and Joinpoint regression used to identify when significant changes occurred in the underlying trend (a joinpoint). This process assisted the exploration of the influence of changes in practice over the observed period.

3.3.4.1 Joinpoint regression

Joinpoint regression is a statistical modelling approach to the analysis of trends. JOINPOINT REGRESSION PROGRAM (version 4.3.1.0) was used to conduct the analysis. This software utilises trend data and fits the simplest joinpoint model that the data will allow. A model with zero jointpoints would indicate there being no significant change in the trend being observed. The software then tests whether further joinpoints can be added to the model. The user is able to test whether an apparent change is statistically significant. The tests of significance use a Monte Carlo Permutation method and the estimated variation for each point is provided.[91] For the purposes of this study, the maximum

number of joinpoints was set at five (the maximum allowed). The best fitting model according to the software package was selected.

3.4 The prevalence of carpal tunnel syndrome in CPRD: Results

Table 3-8 presents the total number of individuals presenting in primary care with a CTS coded episode per annum, between 1993 and 2013 along with the total person years contributing to CPRD and the associated crude prevalence. The final column demonstrates the female: male ratio. Table 3-9 further presents the median age and age range of patients with CTS. Figure 3-1 demonstrates the change in population prevalence, by age and gender groups over time and Figure 3-2 demonstrates the prevalence of CTS stratified by age and gender at the end of the observed period in 2013. The associated numerical data represented in these graphs can be found in Appendix B1. Table 3-10 and Figure 3-3 illustrate the Joinpoint regression results for trends in prevalence of CTS over time.

Table 3-8 Crude prevalence of carpal tunnel syndrome (n/10,000 person years) per calendar year, as presented in UK primary care (CPRD)

Year	Number of person years	Number of prevalent individuals	Total crude prevalence per 10,000 person years, (95% confidence interval)	Female prevalence per 10,000 person years, (95% confidence interval)	Male prevalence per 10,000 person years, (95% confidence interval)	Female: male
1993	1117443	2909	26.03 (25.10 to 27.00)	37.52 (35.96 to 39.13)	13.69 (12.72 to 14.71)	2.74
1994	1198256	3188	26.61 (25.69 to 27.55)	37.23 (35.73 to 38.79)	15.21 (14.23 to 16.25)	2.45
1995	1286800	3343	25.98 (25.11 to 26.88)	36.64 (35.20 to 38.12)	14.58 (13.65 to 15.56)	2.51
1996	1437567	3706	25.78 (24.96 to 26.62)	36.75 (35.38 to 38.16)	14.09 (13.23 to 15.00)	2.61
1997	1681756	4190	24.91 (24.17 to 25.68)	34.87 (33.64 to 36.14)	14.34 (13.53 to 15.18)	2.43
1998	1899393	4884	25.71 (25.00 to 26.45)	36.57 (35.38 -37.79)	14.22 (13.46 to 15.01)	2.57
1999	2289158	5696	24.88 (24.24 to 25.54)	35.21 (34.14 to 36.30)	14.01 (13.32 to 14.72)	2.52
2000	2787457	6998	25.11 (24.52 to 25.70)	34.82 (33.86 to 35.81)	14.90 (14.26 to 15.57)	2.34
2001	3057458	8137	26.61 (26.04 to 27.20)	36.46 (35.52 to 37.42)	16.31 (15.67 to 16.98)	2.23
2002	3385511	9722	28.72 (28.15 to 29.29)	39.33 (38.40 to 40.28)	17.64 (17.00 to 18.29)	2.23
2003	3552908	11124	31.31 (30.73 to 31.90)	43.61 (42.66 to 44.59)	18.53 (17.90 to 19.18)	2.35
2004	3712172	12622	34.00 (33.41 to 34.60)	47.20 (46.23 to 48.19)	20.33 (19.68 to 20.99)	2.32
2005	3808183	12741	33.46 (32.88 to 34.04)	46.37 (45.42 to 47.34)	20.09 (19.45 to 20.74)	2.31
2006	3857487	12718	32.97 (32.40 to 33.55)	45.82 (44.88 to 46.78)	19.69 (19.07 to 20.33)	2.33
2007	3904068	13222	33.87 (33.29 to 34.45)	46.35 (45.41 to 47.31)	20.99 (20.35 to 21.65)	2.21
2008	3897624	14030	36.00 (35.40 to 36.60)	49.12 (48.15 to 50.11)	22.46 (21.79 to 23.14)	2.19
2009	3894989	14500	37.23 (36.60 to 37.81)	50.68 (49.69 to 51.68)	23.35 (22.68 to 24.05)	2.17
2010	3842773	14166	36.86 (36.26 to 37.48)	49.75 (48.76 to 50.75)	23.57 (22.88 to 24.27)	2.11
2011	3769676	13529	35.89 (35.29 to 36.50)	47.98 (47.00 to 48.97)	23.36 (22.67 to 24.07)	2.05
2012	3714877	13388	36.04 (35.43 to 36.66)	47.57 (46.59 to 48.56)	24.05 (23.35 to 24.78)	1.98
2013	3473094	12532	36.08 (35.45 to 36.72)	47.19 (46.18 to 48.21)	24.49 (23.75 to 25.25)	1.93

Table 3-9 Age and gender of patients with prevalent carpal tunnel syndrome between 1993 and 2013

Year	Female age range	Female median age (25th and 75th percentile)	Male age range	Male median age (25th and 75th percentile)
1993	18.20 to 98.70	49.33 (38.29, 61.50)	18.47 to 92.90	52.61 (41.50, 66.37)
1994	18.10 to 95.09	49.45 (39.44, 62.25)	19.32 to 94.72	52.8 (42.31, 66.15)
1995	18.13 to 94.70	50.18 (38.55, 62.17)	20.32 to 95.99	52.19 (41.45, 64.24)
1996	18.11 to 93.64	50.23 (39.69, 62.06)	18.81 to 95.96	52.63 (41.09, 65.70)
1997	18.56 to 95.81	50.65 (39.86, 62.05)	19.46 to 95.34	53.37 (42.39, 66.94)
1998	18.23 to 99.72	50.71 (39.76, 62.06)	18.22 to 99.72	53.84 (43.00, 67.22)
1999	18.13 to 100.09	51.49 (40.20, 62.07)	18.56 to 95.13	54.20 (44.17, 66.38)
2000	18.30 to 101.55	51.90 (40.94, 63.57)	19.12 to 97.22	55.13 (43.79, 67.33)
2001	18.00 to 99.84	52.76 (41.50, 64.57)	18.6 to 98.18	55.16 (44.18, 68.17)
2002	18.02 to 102.20	52.85 (41.02, 64.07)	18.18 to 99.23	54.70 (44.28, 66.83)
2003	18.20 to 97.18	53.61 (41.81, 64.58)	18.64 to 96.66	55.35 (44.41, 67.67)
2004	18.02 to 97.17	54.53 (42.78, 64.67)	18.48 to 95.98	56.06 (44.57, 67.97)
2005	18.36 to 103.25	54.42 (42.50, 64.94)	18.28 to 96.07	57.51 (45.24, 69.57)
2006	18.03 to 101.93	54.49 (42.64, 66.17)	18.29 to 95.83	57.90 (45.49, 69.93)
2007	18.21 to 99.78	53.68 (42.35, 65.77)	19.18 to 98.72	53.68 (42.35, 65.77)
2008	18.42 to 102.67	53.84 (42.79, 65.81)	18.48 to 96.81	57.55 (46.44, 70.30)
2009	18.06 to 100.15	54.00 (42.68, 66.63)	18.22 to 96.63	58.42 (46.90, 70.45)
2010	18.17 to 99.16	54.08 (42.61, 66.95)	18.45 to 97.81	57.43 (46.37, 70.50)
2011	18.06 to 98.46	53.96 (42.76, 67.48)	18.16 to 95.85	58.08 (47.07, 71.06)
2012	18.11 to 98.97	53.66 (42.62, 66.98)	18.94 to 97.90	58.62 (47.51, 70.88)
2013	18.27 to 100.73	54.12 (43.50, 67.31)	18.19 to 102.85	59.08 (47.51, 71.71)

Figure 3-1 Graph to show the population prevalence of CTS by age and gender between 1993 and 2013

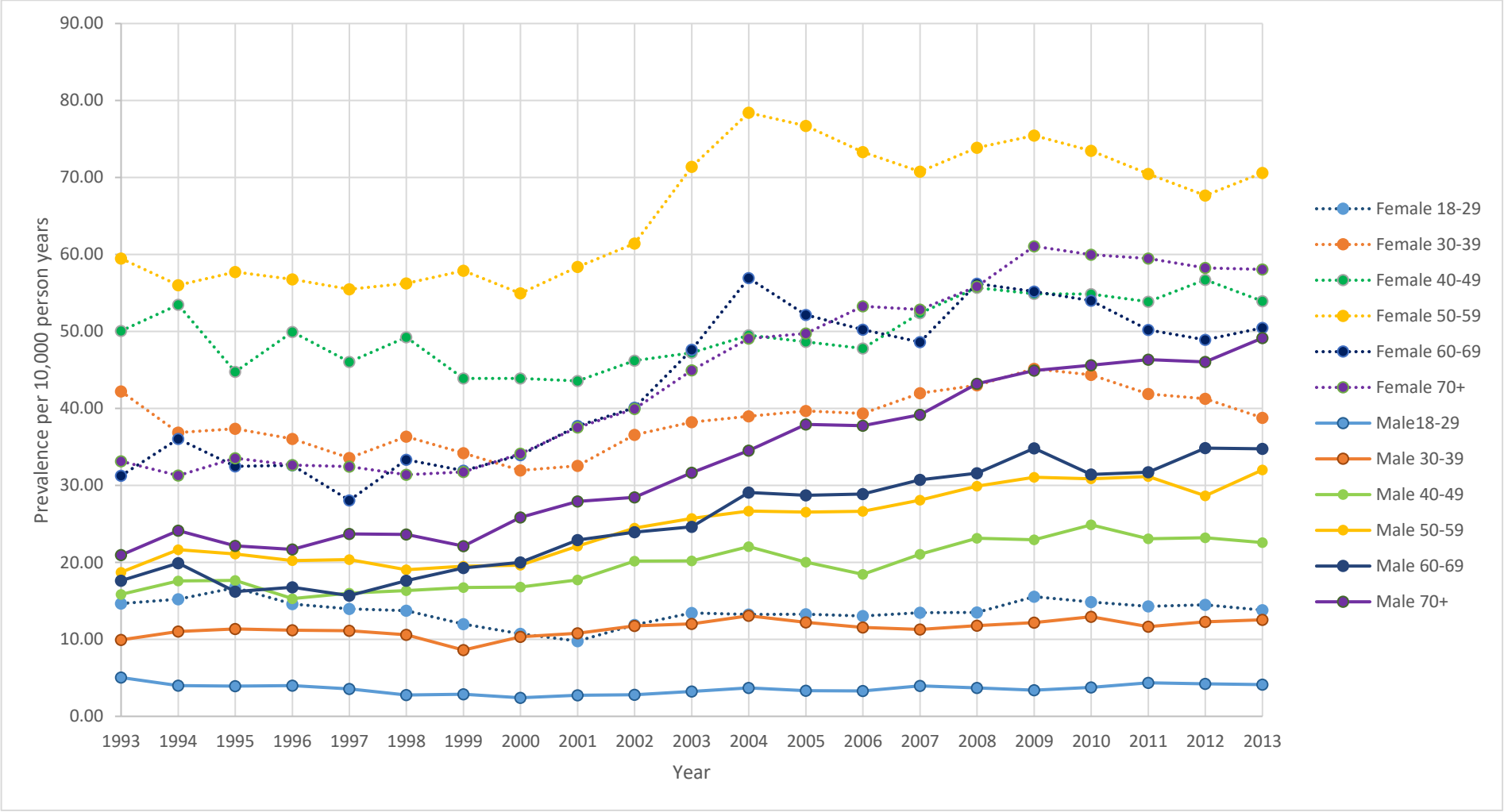


Figure 3-2 Bar graph to show the crude prevalence of carpal tunnel syndrome in 2013 in age gender stratified groups

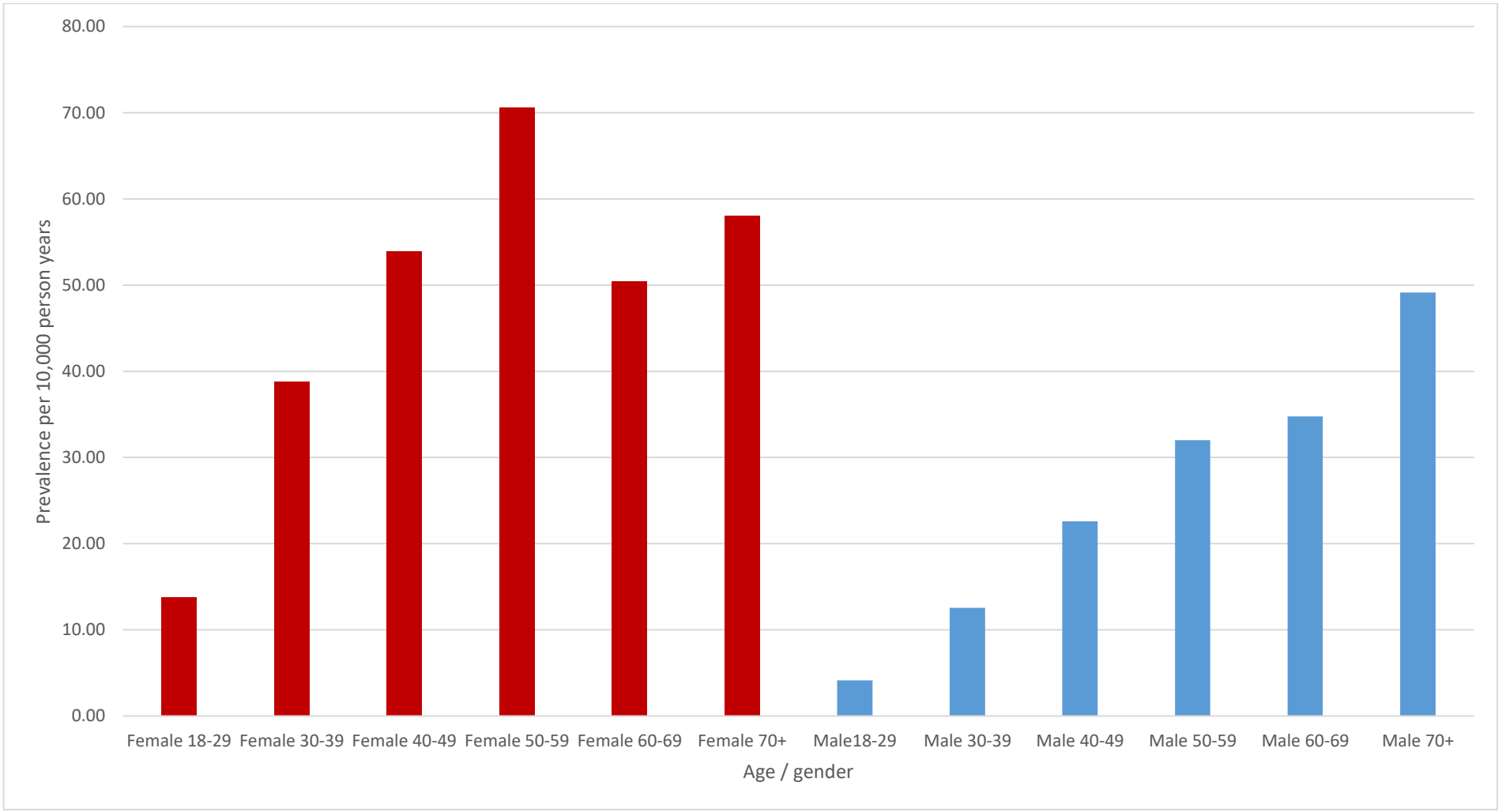
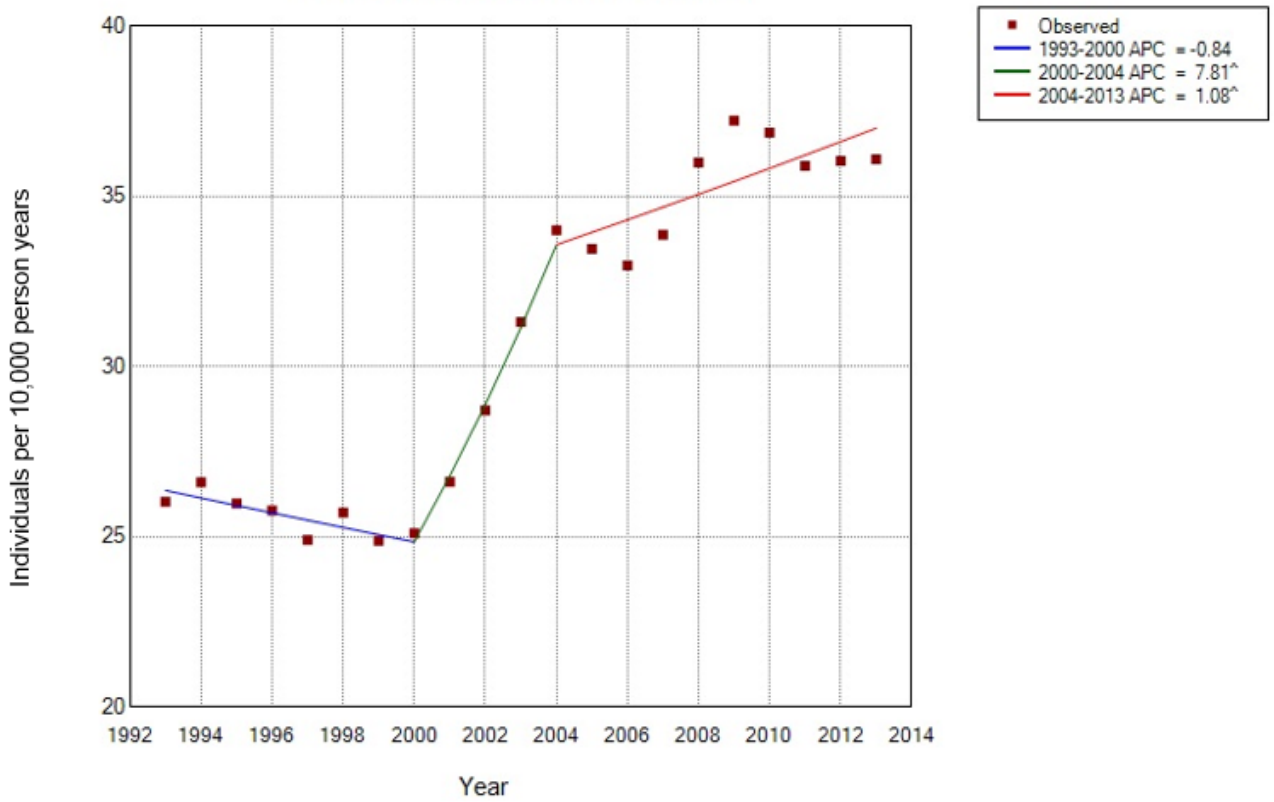


Figure 3-3 Joinpoint analysis plot of the crude prevalence of carpal tunnel syndrome between 1993 and 2013



^APC = annual percentage change, which is significantly different from zero, significance level $p < 0.05$

Table 3-10 Joinpoint analysis of crude prevalence

Segment	Lower Endpoint	Upper Endpoint	Annual percentage change	Lower 95th confidence interval	Upper 95th confidence interval	Test Statistic (t)	Prob > |t|
1	1993	2000	-0.8	-2.6	1.0	-1.0	0.3
2	2000	2004	7.8	3.1	12.7	3.7	< 0.0
3	2004	2013	1.1	0.4	1.8	3.4	< 0.0

Table 3-8 and Table 3-9 present the prevalence (crude estimates) of patients presenting in primary care with carpal tunnel syndrome between 1993 and 2013 and the demographics of that population. The denominator population for prevalence increased from 1,117,433 person years in 1993 to 3,473,094 person years in 2013. The total prevalence in 1993 was 26.03 per 10,000 person years (95% CI 25.10 to 27.00), and in 2013, 36.08 per 10,000 person years (95% CI 35.45 to 36.72). As shown in Figure 3-3 and corresponding Table 3-10, the prevalence of CTS appeared to decrease between 1993 and 2000 (annual percentage change APC = -0.8, 95% confidence interval -2.6 to 1.0). It then increased between 2000 and 2004 (APC = 7.8, 95% CI 3.1 to 12.7) and then increased at a slower rate between 2004 and 2013 (APC = 1.1, 95% CI 0.4 to 1.8). The female to male ratio reduced over time from 2.74 in 1993 to 1.93 in 2013. The median age of female and male patients with CTS increased from 49 and 53 years respectively in 1993 to 54 and 59 years respectively in 2013. Figure 3-1 and Figure 3-2 further illustrate the crude prevalence of CTS over time stratified by age and gender. The prevalence of CTS appears to increase with age in the male population, whereas the prevalence in female population is bimodal with a peak in the 50 to 59 age group and a further peak in the 70+ year age group.

3.5 The incidence of carpal tunnel syndrome in CPRD: Results

Table 3-11 presents the total number of individuals presenting in primary care with a new episode of CTS, per annum, between 1993 and 2013 along with the total person years contributing to CPRD and the associated crude incidence. The final column demonstrates the female: male ratio. Table 3-12 further presents the median age and age range of patients with incident episodes of CTS. Figure 3-4 demonstrates the change in population incidence, by age and gender groups over time and Figure 3-5 shows the incidence of CTS by age and gender in 2013. The associated numerical data represented in these graphs can be found in Appendix B2. Table 3-13 and Figure 3-6 show the Joinpoint regression results of crude incidence over time.

Table 3-11 Crude incidence of carpal tunnel syndrome (n/10,000 person years) per calendar year, as presented in UK primary care (CPRD)

Year	Number of person years	Number of incident individuals	Total crude incidence per 10,000 person years, (95% confidence interval)	Female incidence per 10,000 person years, (95% confidence interval)	Male incidence per 10,000 person years, (95% confidence interval)	Female: male
1993	783330	1584	20.22 (19.24 to 21.24)	28.72 (27.09 to 30.42)	11.17 (10.14 to 12.29)	2.57
1994	868616	1797	20.69 (19.74 to 21.67)	28.52 (26.97 to 30.13)	12.38 (11.34 to 13.69)	2.30
1995	1003593	1963	19.56 (18.70 to 20.45)	27.53 (26.12 to 29.00)	11.12 (10.20 to 12.10)	2.48
1996	1065068	2142	20.11 (19.27 to 20.98)	28.39 (27.00 to 29.84)	11.37 (10.47 to 12.33)	2.50
1997	1150299	2306	20.05 (19.24 to 20.88)	28.39 (27.05 to 29.79)	11.25 (10.39 to 12.16)	2.52
1998	1300074	2696	20.74 (19.95 to 21.52)	29.65 (28.57 to 31.22)	11.37 (10.56 to 12.23)	2.61
1999	1497673	3030	20.23 (19.52 to 20.10)	28.53 (27.35 to 29.75)	11.54 (10.77 to 12.34)	2.47
2000	1682027	3462	20.58 (19.90 to 21.28)	28.66 (27.54 to 29.81)	12.15 (11.41 to 12.93)	2.36
2001	2019596	4391	21.74 (21.10 to 22.40)	29.72 (28.68 to 30.79)	13.46 (12.74 to 14.20)	2.21
2002	2456761	5718	23.27 (22.68 to 31.78)	31.78 (30.78 to 32.79)	14.47 (13.80 to 15.17)	2.20
2003	2669111	6772	25.37 (24.77 to 25.98)	35.13 (34.14 to 36.14)	15.33 (14.67 to 16.02)	2.29
2004	2779821	7868	28.30 (27.68 to 28.94)	39.22 (38.19 to 40.27)	17.10 (16.42 to 17.81)	2.29
2005	3164506	8113	25.64 (25.08 to 26.20)	35.55 (34.63 to 36.48)	15.49 (14.88 to 16.12)	2.30
2006	3307051	8337	25.21 (24.67 to 25.76)	34.91 (34.02 to 35.82)	15.27 (14.68 to 15.89)	2.29
2007	3343009	8865	26.52 (25.97 to 27.08)	35.76 (34.86 to 36.67)	17.07 (16.45 to 17.71)	2.09
2008	3341299	9437	28.24 (27.68 to 28.82)	38.23 (37.30 to 39.17)	18.06 (17.42 to 18.72)	2.12
2009	3383196	9918	29.32 (28.74 to 29.90)	39.73 (38.79 to 50.68)	18.69 (18.04 to 19.36)	2.13
2010	3357338	9634	28.70 (28.13 to 29.27)	38.70 (37.77 to 39.64)	18.46 (17.82 to 19.13)	2.10
2011	3269296	9083	27.78 (27.21 to 28.36)	37.11 (36.19 to 38.05)	18.20 (17.54 to 18.87)	2.04
2012	3222880	9011	27.96 (27.39 to 28.54)	36.44 (35.52 to 37.88)	19.23 (18.56 to 19.93)	1.89
2013	3015670	8346	27.68 (27.09 to 28.28)	35.95 (35.01 to 36.92)	19.12 (18.43 to 19.84)	1.88

Table 3-12 Age and gender of patients with incident carpal tunnel syndrome between 1993 and 2013

Year	Female age range	Female median age (25th and 75th percentile)	Male age range	Male median age (25th and 75th percentile)
1993	19.40 to 96.11	49.51 (38.96 to 62.70)	18.72 to 89.90	51.49 (41.70 to 64.64)
1994	18.10 to 95.09	50.18 (39.86 to 63.18)	19.32 to 94.72	52.93 (43.39 to 65.78)
1995	18.13 to 94.70	50.81 (39.72 to 62.54)	20.32 to 95.57	52.79 (42.31 to 63.83)
1996	18.22 to 93.64	50.81 (40.10 to 63.76)	18.81 to 95.96	52.45 (40.79 to 65.83)
1997	19.10 to 95.81	51.27 (40.32 to 63.93)	21.30 to 95.30	55.05 (44.67 to 67.46)
1998	18.23 to 99.72	51.02 (40.22 to 63.26)	19.60 to 97.22	54.35 (43.79 to 67.61)
1999	18.13 to 100.09	52.15 (40.72 to 63.63)	20.51 to 91.48	55.04 (45.16 to 66.92)
2000	18.30 to 98.61	52.58 (41.83 to 65.00)	20.64 to 91.03	55.44 (44.45 to 68.14)
2001	18.00 to 99.60	53.23 (42.02 to 65.58)	18.60 to 94.66	55.37 (44.84 to 67.96)
2002	18.02 to 102.2	53.79 (42.16 to 65.70)	18.18 to 96.04	54.69 (44.47 to 67.36)
2003	18.35 to 96.35	54.51 (42.93 to 65.57)	18.64 to 96.08	55.62 (44.69 to 68.11)
2004	18.02 to 97.17	55.42 (43.82 to 65.88)	18.48 to 95.98	56.79 (44.96 to 68.17)
2005	18.36 to 99.51	54.91 (43.22 to 66.07)	18.28 to 96.07	57.94 (46.21 to 69.97)
2006	18.22 to 101.87	54.97 (43.55 to 67.25)	18.29 to 95.46	58.18 (46.15 to 69.89)
2007	18.21 to 99.76	53.93 (43.12 to 66.39)	19.18 to 96.49	58.14 (46.52 to 69.75)
2008	18.48 to 96.46	54.58 (43.89 to 66.75)	18.48 to 96.46	57.91 (47.14 to 70.10)
2009	18.11 to 99.27	54.88 (43.53 to 67.40)	18.22 to 96.63	59.19 (47.21 to 70.73)
2010	18.17 to 97.80	54.88 (43.71 to 67.55)	18.45 to 93.60	57.35 (46.63 to 70.29)
2011	18.21 to 98.46	54.72 (43.78 to 68.42)	18.21 to 95.12	58.93 (47.80 to 70.91)
2012	18.11 to 98.83	54.30 (43.52 to 67.39)	18.94 to 97.90	59.14 (48.05 to 70.76)
2013	18.27 to 100.73	55.02 (44.70 to 68.50)	19.21 to 102.85	58.84 (48.07 to 70.79)

Figure 3-4 Incidence by age and gender between 1993 and 2013

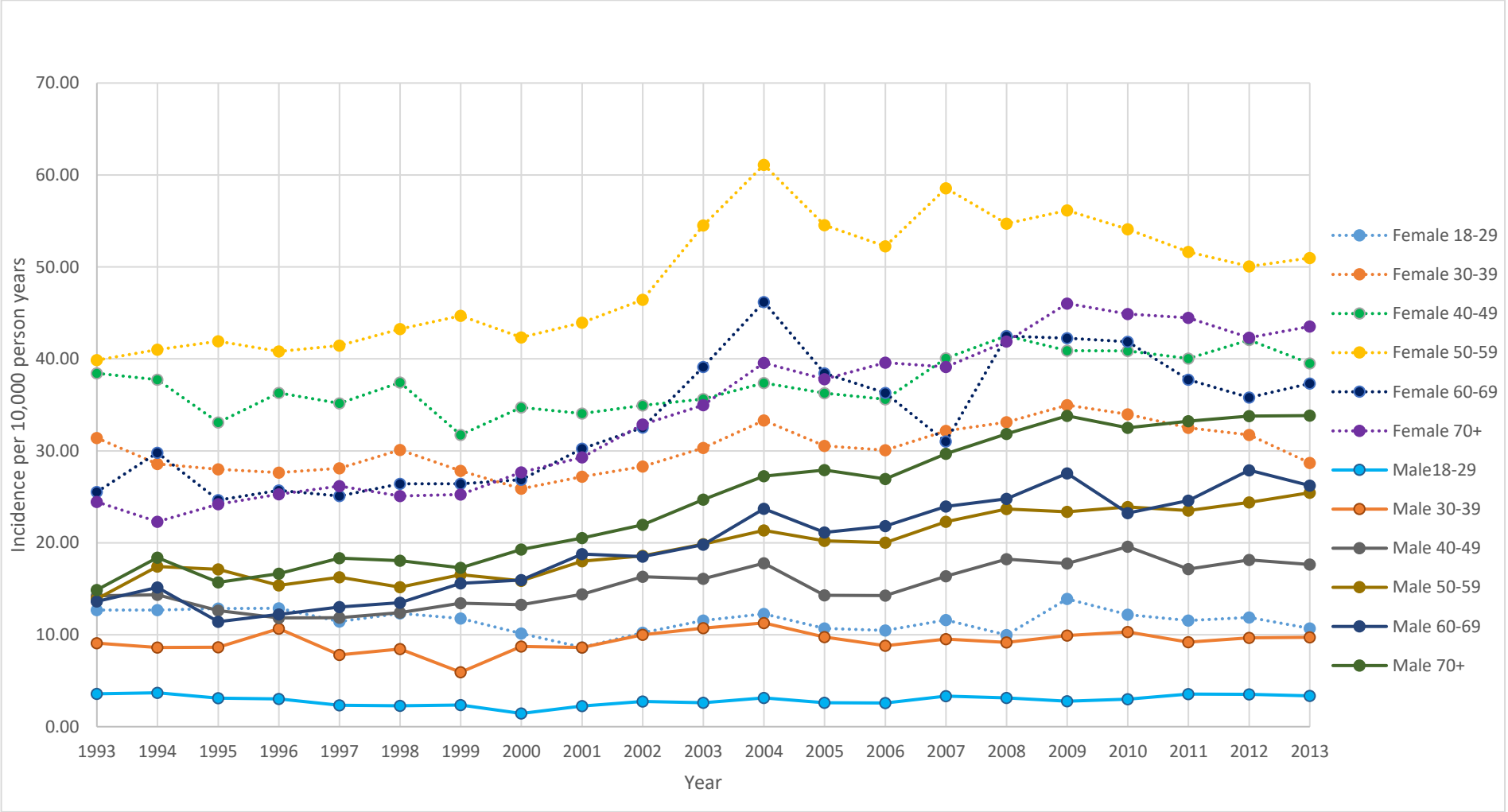


Figure 3-5 Crude incidence of carpal tunnel syndrome in 2013 in age stratified groups

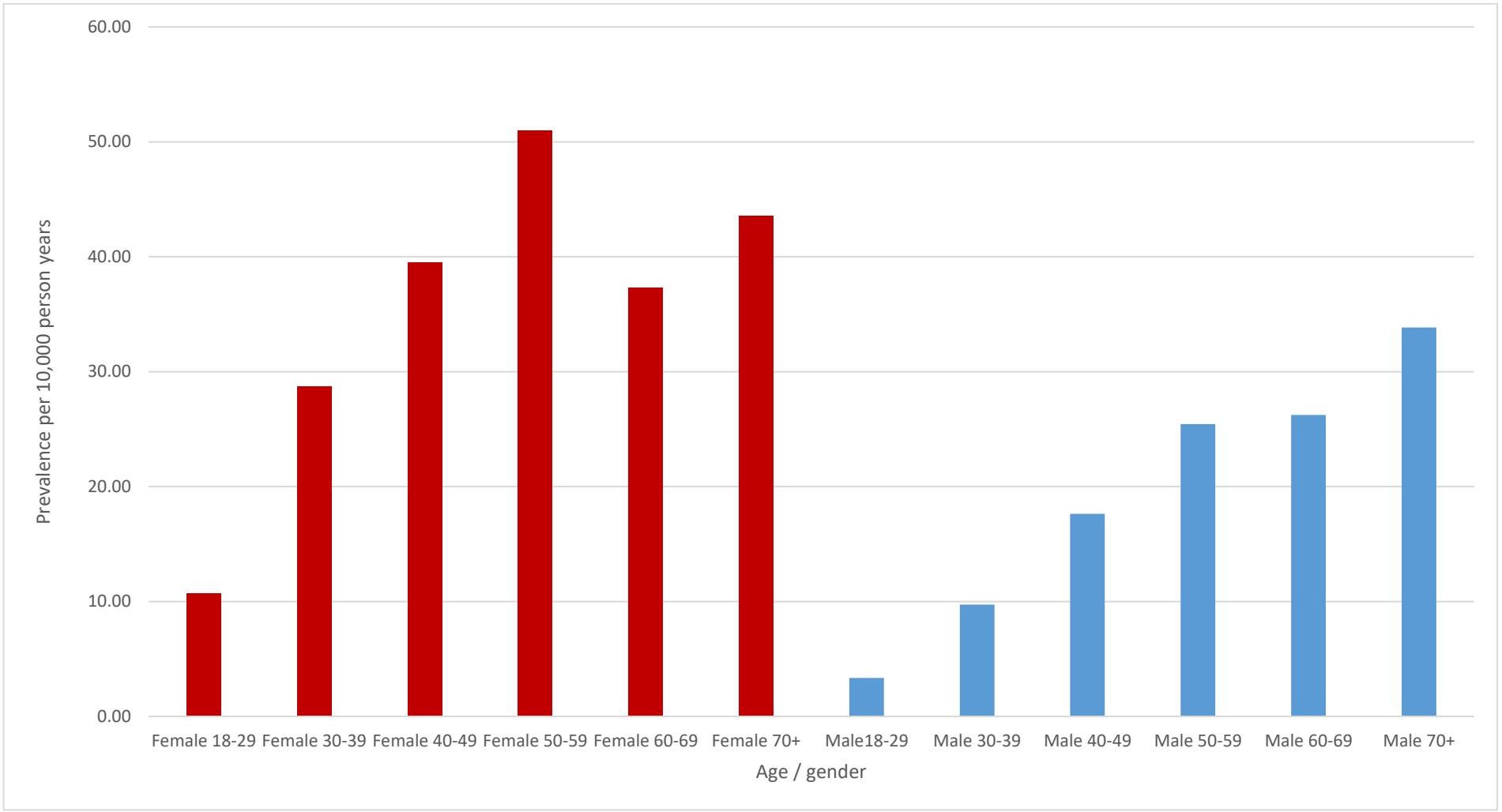
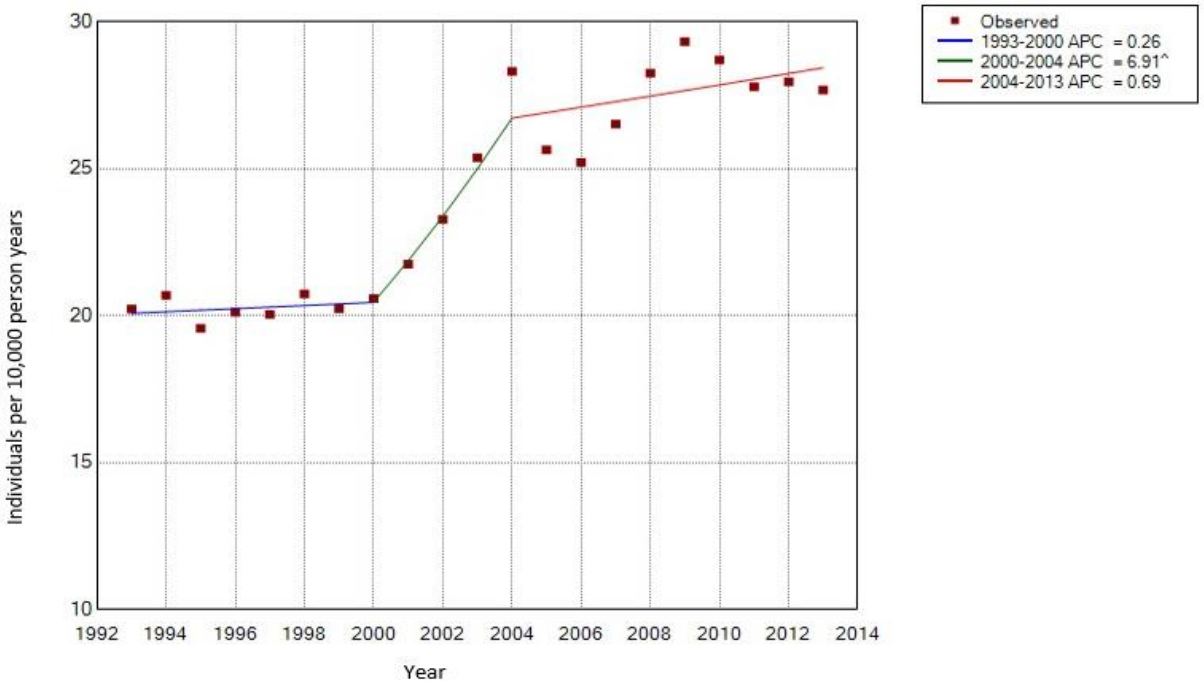


Figure 3-6 Jointpoint analysis plot of the crude incidence of carpal tunnel syndrome between 1993 and 2013



^APC = annual percentage change, which is significantly different from zero, significance level p< 0.05

Table 3-13 Joinpoint analysis data of crude incidence

Segment	Lower Endpoint	Upper Endpoint	Annual percentage change	Lower 95th confidence interval	Upper 95th confidence interval	Test Statistic (t)	Prob > |t|
1	1993	2000	0.3	-2.3	2.9	0.2	0.8
2	2000	2004	6.9^	0.5	13.7	2.3	<0.0
3	2004	2013	0.7	-0.2	1.6	1.7	0.1

Table 3-11 presents the annual incidence (crude estimates) for patients presenting in UK primary care with carpal tunnel syndrome between 1993 and 2013 and the demographics of the population. The denominator population for incidence, which is dependent on patients having 2 years up to standard data prior to the midpoint of the year in question, increased from 783,330 person years in 1993 to 3,015,670 person years in 2013. The crude incidence in 1993 was 20.22 per 10,000 person years (95% CI 19.24 to 21.24)) and 27.68 per 10,000 person years in 2013 (95% CI 27.09 to 28.28). As shown in Figure 3-4 and Table 3-13, the results of the best fitting Joinpoint regression model suggest the incidence increased between 1993 and 2000 (APC = 0.3, 95% CI -2.3 to 2.9). It then increased more quickly between 2000 and 2004 (APC = 6.9, 95% CI 0.5 to 13.7), before slowing between 2004 and 2013 (APC = 0.7. 95% CI -0.2 to 1.6). The female to male ratio reduced over time from 2.57 in 1993 to 1.88 in 2013. The median age of female and male patients were noted to increase from 50 and 51 years respectively in 1993 to 55 and 59 years respectively in 2013. Table 3-12, Figure 3-4 and Figure 3-5 further illustrate the incidence of CTS over time by age and gender. As with prevalence, the incidence of CTS appears to increase with age in the male population, whilst the incidence in women is bimodal with a peak in the 50 to 59 age group and a further peak in the 70+ year age group.

3.5.1 Age and sex standardised estimates of the annual prevalence and incidence of CTS

To test the effect of any change in the population structure over time on the observed crude estimates, a sensitivity analysis was performed. The crude estimates were directly standardised against the population structure in 2013, as provided by the Office of National Statistics. Table 3-14 below presents these standardised estimates for prevalence and incidence in each calendar year. As the results were so similar (the 95% confidence intervals overlap in most instances), further analyses are not presented to prevent repetition, however the Joinpoint plots for standardised estimates can be found in Appendices B3 and B4.

Table 3-14 Age and sex standardised and crude prevalence and incidence estimates for each calendar year between 1993 and 2013

Year	Age sex standardised prevalence (per 10,000 person years, 95% CI)	Crude prevalence (per 10,000 person years, 95% CI)	Age sex standardised incidence (per 10,000 person years, 95% CI)	Crude incidence(per 10,000 person years, 95% CI)
1993	26.27 (26.13 to 26.42)	26.03 (25.10 to 27.00)	19.95 (19.83 to 20.07)	20.22 (19.24 to 21.24)
1994	26.83 (26.69 to 26.98)	26.61 (25.69 to 27.55)	20.46 (20.34 to 20.59)	20.69 (19.74 to 21.67)
1995	25.90 (25.77 to 26.05)	25.98 (25.11 to 26.88)	19.20 (19.08 to 19.33)	19.56 (18.70 to 20.45)
1996	25.64 (25.50 to 25.78)	25.78 (24.96 to 26.62)	19.61 (19.49 to 19.74)	20.11 (19.27 to 20.98)
1997	24.64 (24.20 to 25.07)	24.91 (24.17 to 25.68)	19.42 (19.30 to 19.55)	20.05 (19.24 to 20.88)
1998	25.42 (25.88 to 25.56)	25.71 (25.00 to 26.45)	20.05 (19.93 to 20.18)	20.74 (19.95 to 21.52)
1999	24.57 (24.44 to 24.71)	24.88 (24.24 to 25.54)	19.51 (19.39 to 19.64)	20.23 (19.52 to 20.10)
2000	24.77 (24.63 to 24.91)	25.11 (24.52 to 25.70)	19.73 (19.61 to 19.86)	20.58 (19.90 to 21.28)
2001	26.22 (26.08 to 26.36)	26.61 (26.04 to 27.20)	20.75 (20.63 to 20.88)	21.74 (21.10 to 22.40)
2002	28.22 (28.07 to 28.37)	28.72 (28.15 to 29.29)	22.22 (22.10 to 22.36)	23.27 (22.68 to 31.78)
2003	30.81 (30.65 to 30.96)	31.31 (30.73 to 31.90)	24.28 (24.15 to 24.42)	25.37 (24.77 to 25.98)
2004	33.51 (33.35 to 33.67)	34.00 (33.41 to 34.60)	27.00 (26.86 to 27.14)	28.30 (27.68 to 28.94)
2005	32.98 (32.82 to 33.14)	33.46 (32.88 to 34.04)	24.56 (24.42 to 24.70)	25.64 (25.08 to 26.20)
2006	32.55 (32.39 to 32.70)	32.97 (32.40 to 33.55)	24.14 (24.00 to 24.27)	25.21 (24.67 to 25.76)
2007	33.48 (33.32 to 33.64)	33.87 (33.29 to 34.45)	25.52 (25.38 to 25.66)	26.52 (25.97 to 27.08)
2008	35.59 (35.43 to 35.76)	36.00 (35.40 to 36.60)	27.07 (26.92 to 27.21)	28.24 (27.68 to 28.82)
2009	36.81 (36.64 to 36.98)	37.23 (36.60 to 37.81)	28.19 (28.05 to 28.34)	29.32 (28.74 to 29.90)
2010	36.40 (36.24 to 36.66)	36.86 (36.26 to 37.48)	27.53 (27.39 to 27.68)	28.70 (28.13 to 29.27)
2011	35.28 (35.12 to 35.44)	35.89 (35.29 to 36.50)	26.59 (26.45 to 26.74)	27.78 (27.21 to 28.36)
2012	35.50 (35.34 to 35.67)	36.04 (35.43 to 36.66)	26.75 (26.61 to 26.89)	27.96 (27.39 to 28.54)
2013	35.45 (35.29 to 35.61)	36.08 (35.45 to 36.72)	26.34 (26.01 to 26.49)	27.68 (27.09 to 28.28)

3.6 The management of carpal tunnel syndrome in CPRD: Results

The CiPCA pilot study suggested that consultation coding for injections and splinting were inadequate and unlikely to represent the true number of interventions that occurred in primary care. This was retested in CPRD using the methods described in 3.3.3.4.2 with results again showing the frequency of recorded use being less than what would be expected. Although the results for CSI and NS will be presented, the focus of this section is therefore on the use of carpal tunnel release surgery. CTR is of particular interest as it firstly indicates that patients either have had severe CTS or have not responded to the treatments available to them in primary care and secondly as access to this procedure is restricted in some areas.[64]

3.6.1 Use of carpal tunnel release surgery over time

Table 3-15 presents the rate and percentage of prevalent patients with CTS who had recorded episode of CTR in each calendar year between 1993 and 2013 and the associated demographics of this population. 71% of patients with any CTR code had a single (as opposed to multiple) CTR code in their record. As it was not possible to verify whether further codes were true 'redo' or contralateral episodes, as opposed to the code being reused in the consultation data, it is possible that the number of surgical episodes is underestimated. Figure 3-7 represents the rate of surgery by gender over time and Figure 3-8 demonstrates the Joinpoint regression of this data with the associated statistics in Table 3-16.

Table 3-15 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of carpal tunnel release surgery per calendar year

Year	Episodes per 10,000 person years	% prevalent individuals having surgery	% prevalent females having surgery	% prevalent males having surgery	Female median age (25% and 75% percentile)	Male median age (25% and 75% percentile)
1993	5.04	19.35	18.78	21.03	53 (43 to64)	55 (44 to 69)
1994	5.70	21.42	20.62	23.52	53 (43 to 68)	58 (45 to 70)
1995	6.19	23.81	23.40	24.92	53 (42 to 67)	55 (44 to 70)
1996	5.41	20.99	20.48	22.43	53 (44 to 65)	52 (40 to 65)
1997	5.70	22.89	22.14	24.81	53 (45 to 67)	56 (42 to 69)
1998	5.73	22.28	21.28	25.00	53 (44 to 65)	53 (44 to 65)
1999	6.24	25.09	24.60	26.38	54 (44 to 67)	56 (46 to 70)
2000	6.41	25.54	24.84	27.23	54 (44 to 68)	56 (45 to 69)
2001	6.88	25.87	25.95	25.68	55 (45 to 68)	58 (46 to 71)
2002	7.02	24.46	24.19	25.09	57 (46 to 71)	55 (45 to 68)
2003	8.26	26.39	25.88	27.66	56 (45 to 67)	57 (46 to 71)
2004	9.34	27.48	27.38	27.74	56 (46 to 67)	57 (47 to 68)
2005	9.70	29.00	28.31	30.65	57 (47 to 68)	58 (46 to 71)
2006	9.36	28.40	28.31	28.61	57 (47 to 68)	60 (48 to 72)
2007	9.71	28.66	28.26	29.59	56 (46 to 69)	59 (48 to 71)
2008	10.53	29.25	29.00	29.82	56 (46 to 68)	60 (49 to 72)
2009	10.92	29.32	28.73	30.66	56 (46 to 70)	61 (49 to 72)
2010	10.40	28.22	27.57	29.62	57 (47 to 71)	61 (48 to 73)
2011	9.47	26.37	26.11	26.93	57 (47 to 70)	61 (49 to 73)
2012	9.48	26.31	25.89	27.19	57 (47 to 71)	60 (49 to 73)
2013	9.89	27.41	26.47	29.30	57 (48 to 70)	62 (51 to 74)

Figure 3-7 Episodes of carpal tunnel surgery as a percentage of prevalent cases in each year, over time

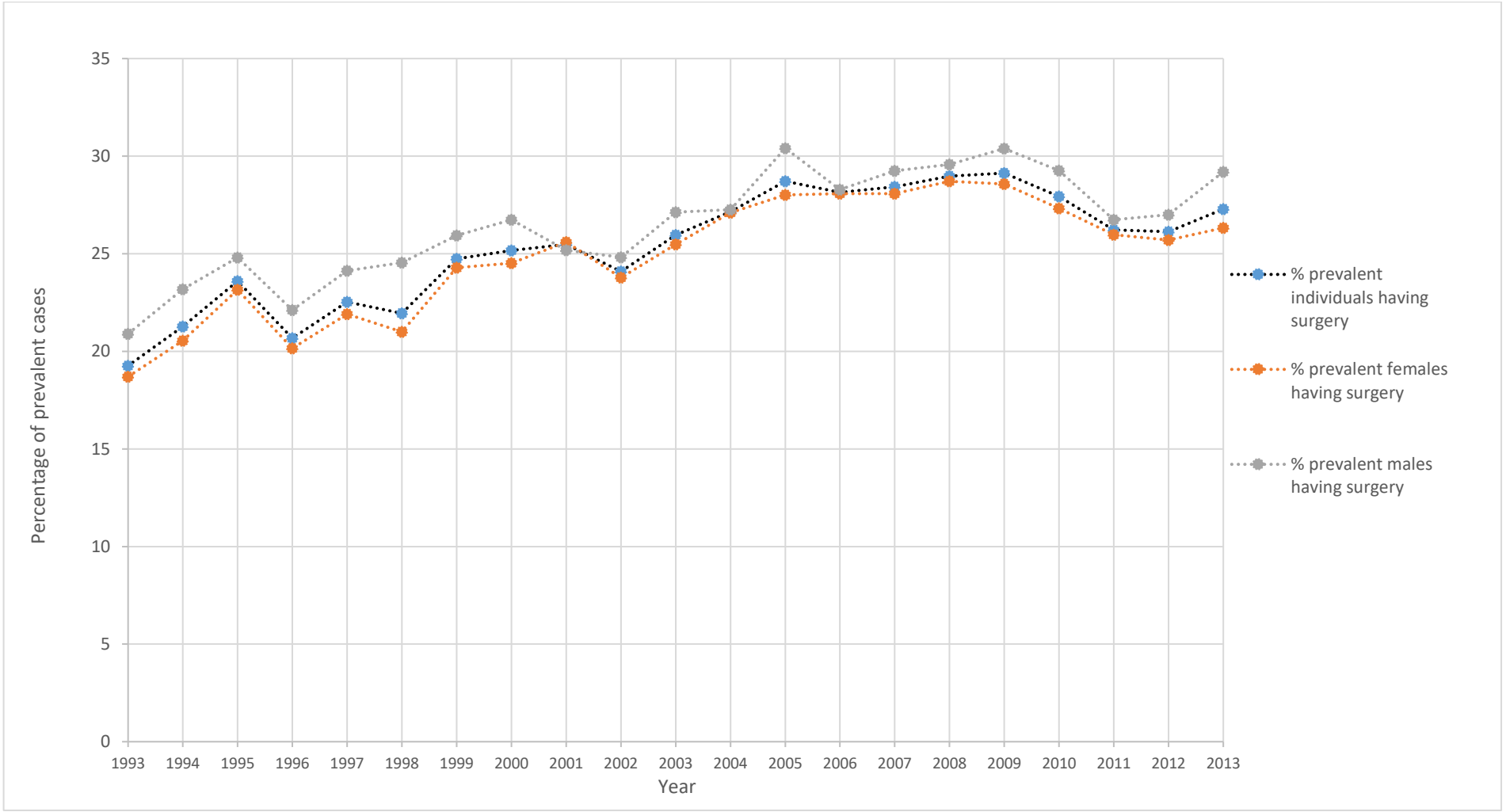
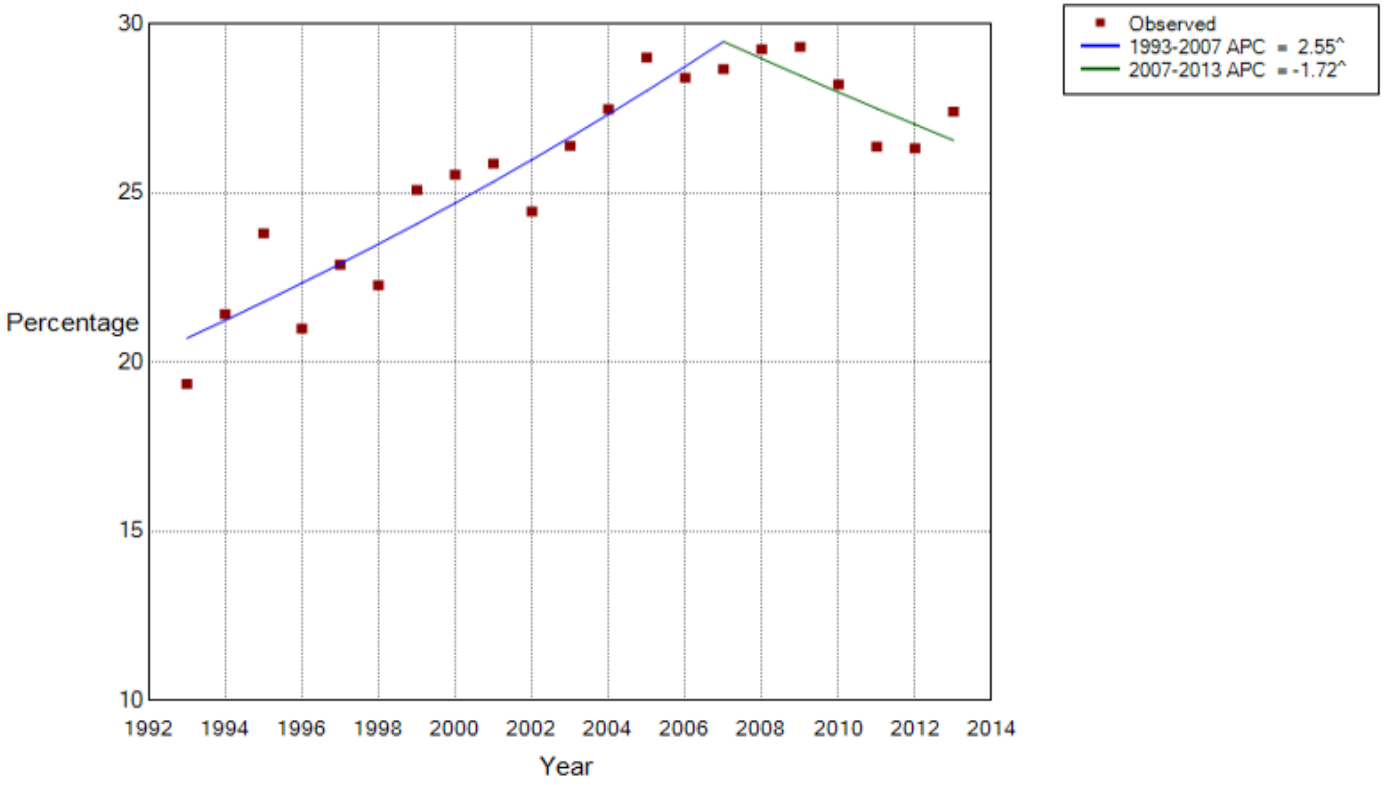


Figure 3-8 Joinpoint analysis plot of the percentage of prevalent patients with a recorded episode of carpal tunnel release, in each calendar year syndrome, between 1993 and 2013



^APC = annual percentage change, which is significantly different from zero, significance level $p < 0.05$

Table 3-16 Joinpoint analysis of trends in the proportion of prevalent patients with a recorded episode of carpal tunnel release

Segment	Lower Endpoint	Upper Endpoint	Annual percentage change	Lower 95th confidence interval	Upper 95th confidence interval	Test Statistic (t)	Prob > |t|
1	1993	2007	2.6	1.9	3.2	8.2	0.0
2	2007	2013	-1.7	-3.1	-0.3	-2.6	<0.0

Table 3-15, Figure 3-7 and Figure 3-8 show that the proportion of prevalent patients receiving carpal tunnel release surgery, increased over the observed time period from 19.35% in 1993 to 27.3 % in 2013. This increase was observed in both female and male populations and in every year apart from 2001, the percentage of males having surgery was greater than the percentage of females. Although the ratio of female and male populations receiving surgery fluctuated on a year on year basis, the general trend was a reduction in the female: male ratio (2.57 in 1993 and 1.7 in 2013), suggesting proportionally more men were having surgery compared to women. The median age of both male and female populations also appeared to increase, as shown in Table 3-15, from 55 and 53 years old in 1993 (male and female respectively) to 62 years old in the male population and 57 years old in the female population, in 2010, after which the increase in age appeared to plateau. The increase in age was more apparent in the male population.

As shown in Figure 3-8 and corresponding Table 3-15, the trend in the percentage of patients with a coded episode of CTR increased between 1993 and 2007 (annual percentage change APC = 2.6, 95% CI 1.9 to 3.2). It then decreased between 2007 and 2013 (APC = -1.7, 95% CI -3.3 to -0.3).

3.6.2 Use of carpal tunnel injections over time

Using both Read coded and linked prescription data Table 3-17 and Figure 3-9, show the proportion of prevalent patients who were given a carpal tunnel injection in each calendar year. Figure 3-10 shows the results of the Joinpoint regression of trends in the use of injections for CTS, with the associated statistics in Table 3-18.

Table 3-17 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of corticosteroid injection per calendar year

Year	Episodes per 10,000 person years	% prevalent individuals with an injection	% prevalent females with an injection	% prevalent males with an injection	Female median age (25% to 75 percentile)	Male median age (25% to 75% percentile)	Female : Male
1993	1.77	6.33	6.54	5.70	52 (40 to 69)	57 (44 to 72)	2.63
1994	1.54	5.43	5.07	6.36	51 (44 to 68)	55 (45 to 70)	2.30
1995	1.43	5.23	4.84	6.28	50 (38 to 65)	50 (38 to 65)	2.52
1996	1.38	5.10	4.62	6.42	51 (39 to 67)	55 (40 to 75)	2.54
1997	1.62	5.89	5.23	7.61	55 (44 to 74)	54 (44 to 74)	2.31
1998	1.44	4.89	4.54	5.87	53 (41 to 70)	55 (44 to 66)	2.32
1999	1.67	6.06	5.64	7.17	53 (41 to 69)	59 (46 to 72)	2.47
2000	1.49	5.32	5.05	5.97	56 (43 to 72)	56 (46 to 76)	2.24
2001	1.38	4.68	4.21	5.78	57 (44 to 73)	58 (48 to 73)	2.36
2002	1.63	5.19	5.09	5.44	56 (43 to 72)	59 (44 to 72)	2.24
2003	1.82	5.31	5.22	5.54	57 (44 to 70)	58 (43 to 73)	2.29
2004	1.82	4.83	4.77	4.99	58 (47 to 72)	57 (46 to 73)	2.37
2005	1.76	4.87	4.89	4.84	58 (45 to 73)	62 (46 to 77)	2.21
2006	2.06	5.67	5.50	6.18	59 (48 to 75)	61 (48 to 75)	2.38
2007	2.20	5.79	5.91	5.50	60 (46 to 76)	61 (47 to 73)	2.17
2008	2.33	5.79	5.70	5.99	57 (46 to 74)	61 (44 to 75)	2.19
2009	2.33	5.43	5.38	5.54	59 (48 to 75)	61 (46 to 73)	2.10
2010	2.82	6.70	6.87	6.33	57 (46 to 74)	57 (46 to 73)	2.03
2011	3.27	8.06	7.91	8.37	58 (47 to 73)	63 (48 to 77)	2.07
2012	3.20	7.75	7.49	8.29	56 (46 to 75)	63 (49 to 75)	1.96
2013	3.23	7.97	7.80	8.32	58 (48 to 74)	64 (48 to 76)	1.82

Figure 3-9 Episodes of carpal tunnel injection as a percentage of prevalent cases in each calendar year, over time

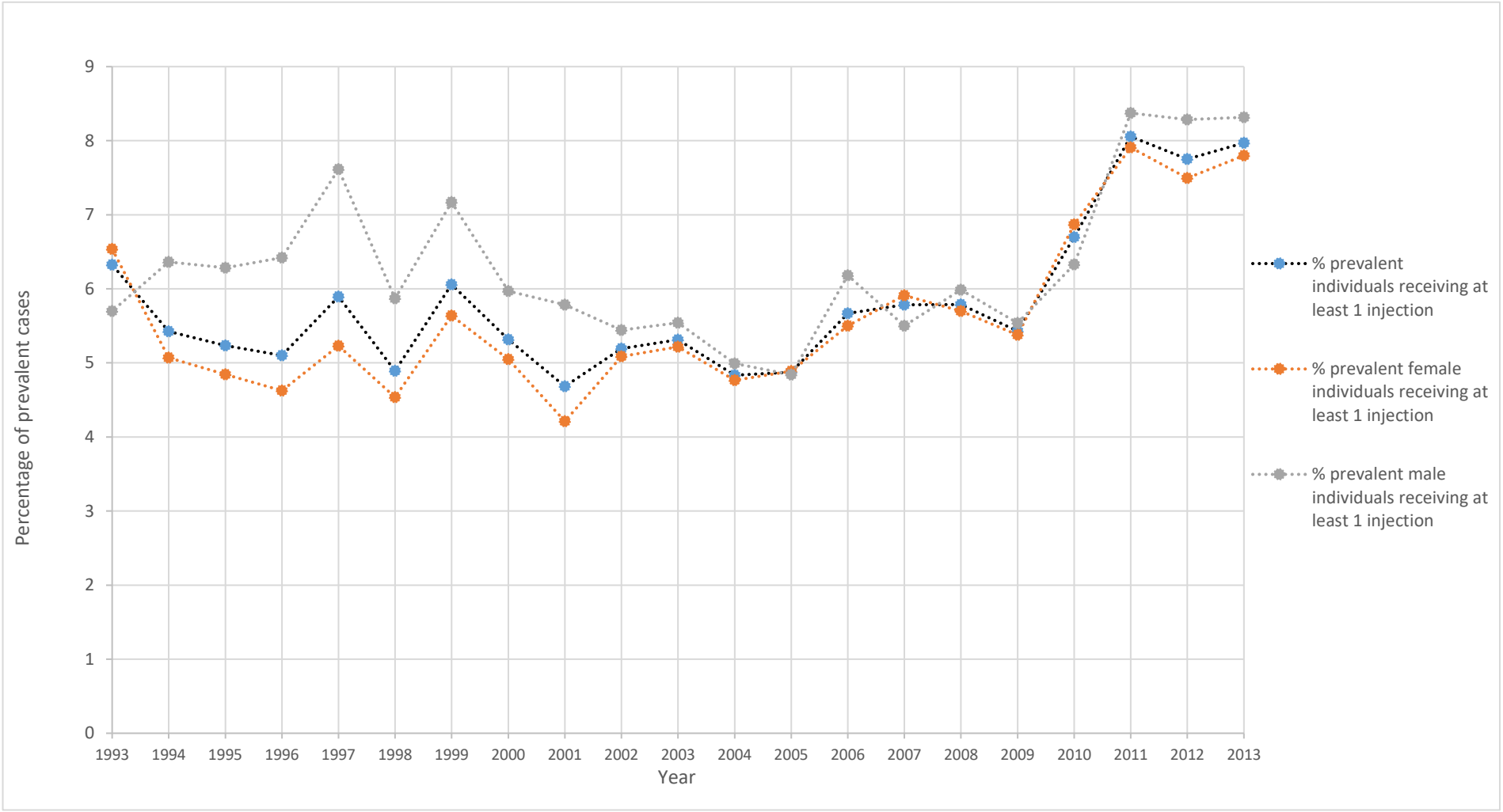
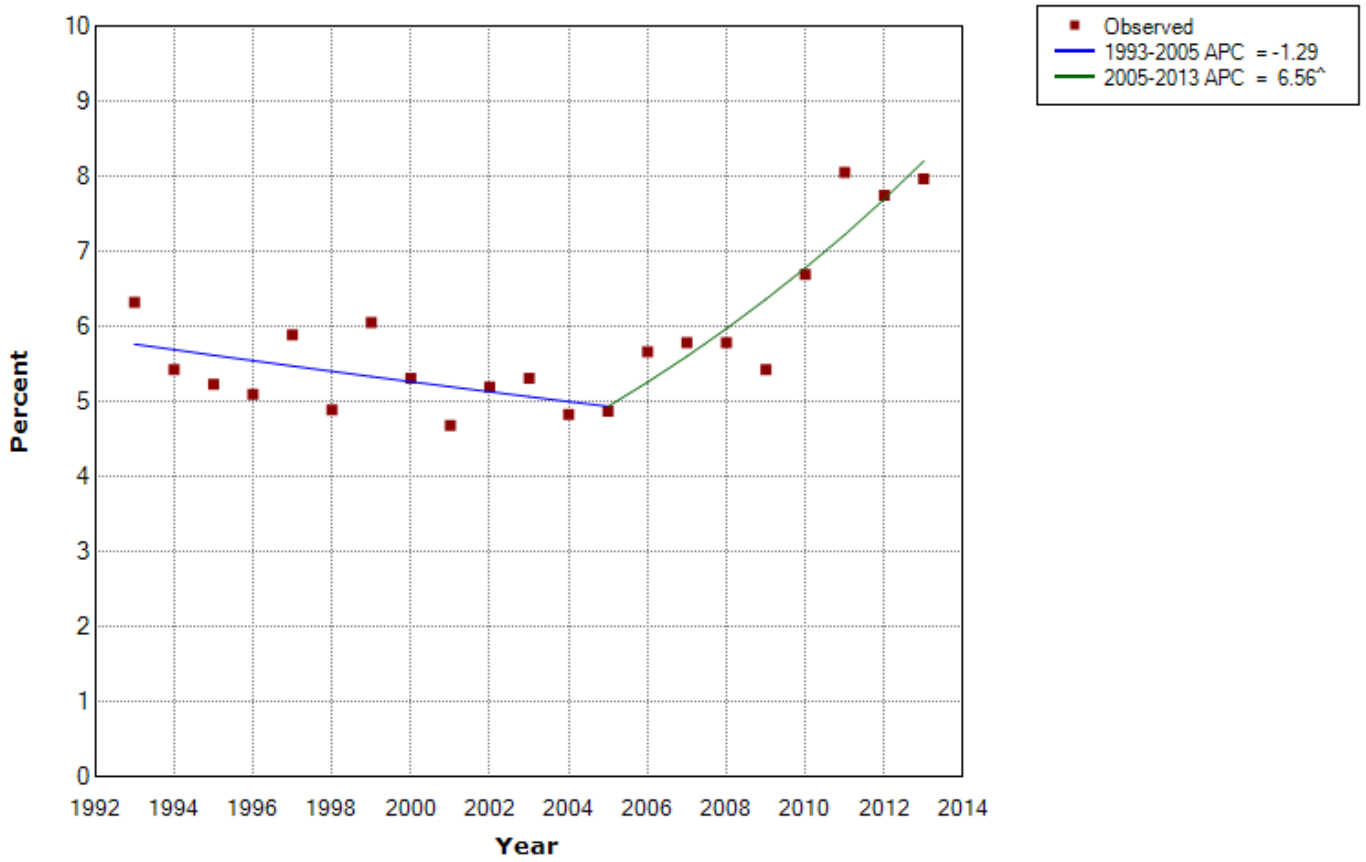


Figure 3-10 Joinpoint analysis plot of the percentage of patients with a prevalent episode of carpal tunnel syndrome receiving a corticosteroid injection, over time



^APC = annual percentage change, which is significantly different from zero, significance level p<0.05

Table 3-18 Joinpoint analysis of trends in the proportion of prevalent patients with a recorded episode of carpal tunnel injection

Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	1993	2005	-1.3	-3.2	0.7	-1.4	0.2
2	2005	2013	6.6	4.3	8.8	6.3	<0.0

The percentage of prevalent patients receiving an injection varied between 5% and 8% and was similar between males and females. Figure 3-10 suggests that there was a change in the use of CSI over time, in that its use appeared to reduce between 1993 and 2005 (APC = -1.29, 95% CI -3.2 to 0.7) and then increase between 2005 and 2013 (APC = 6.56, 95% CI 4.3 to 8.8).

3.6.3 Use of nerve conduction studies over time

The crude data for the total, male and female population with a recorded episode of NCS is presented in Table 3-19 and Figure 3-11. Figure 3-12 further shows the Joinpoint regression of trends in this data with the associated statistics in Table 3-20.

Table 3-19 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of nerve conduction studies per calendar year

Year	Episodes of NCS per 10,000 person years	% prevalent individuals with evidence of NCS	% prevalent females with evidence of NCS	% prevalent males with evidence of NCS
1993	0.72	2.75	2.67	2.99
1994	0.98	3.70	3.68	3.75
1995	1.11	4.28	4.35	4.08
1996	1.38	5.37	5.03	6.32
1997	1.52	6.09	6.22	5.73
1998	1.05	4.07	4.06	4.12
1999	1.00	4.02	3.65	4.99
2000	1.10	4.39	4.37	4.44
2001	1.44	5.41	4.95	6.48
2002	1.21	4.23	4.15	4.41
2003	1.53	4.90	4.89	4.92
2004	1.71	5.03	4.49	6.34
2005	1.94	5.80	5.71	6.01
2006	2.04	6.19	6.28	5.97
2007	2.69	7.96	7.50	9.00
2008	2.94	8.15	7.75	9.07
2009	3.43	9.21	8.39	11.03
2010	3.63	9.84	9.40	10.79
2011	3.70	10.31	9.70	11.61
2012	3.64	10.09	9.27	11.78
2013	3.98	11.04	9.92	13.31

Figure 3-11 Episodes of nerve conduction studies, as a percentage of prevalent cases in each calendar year, over time

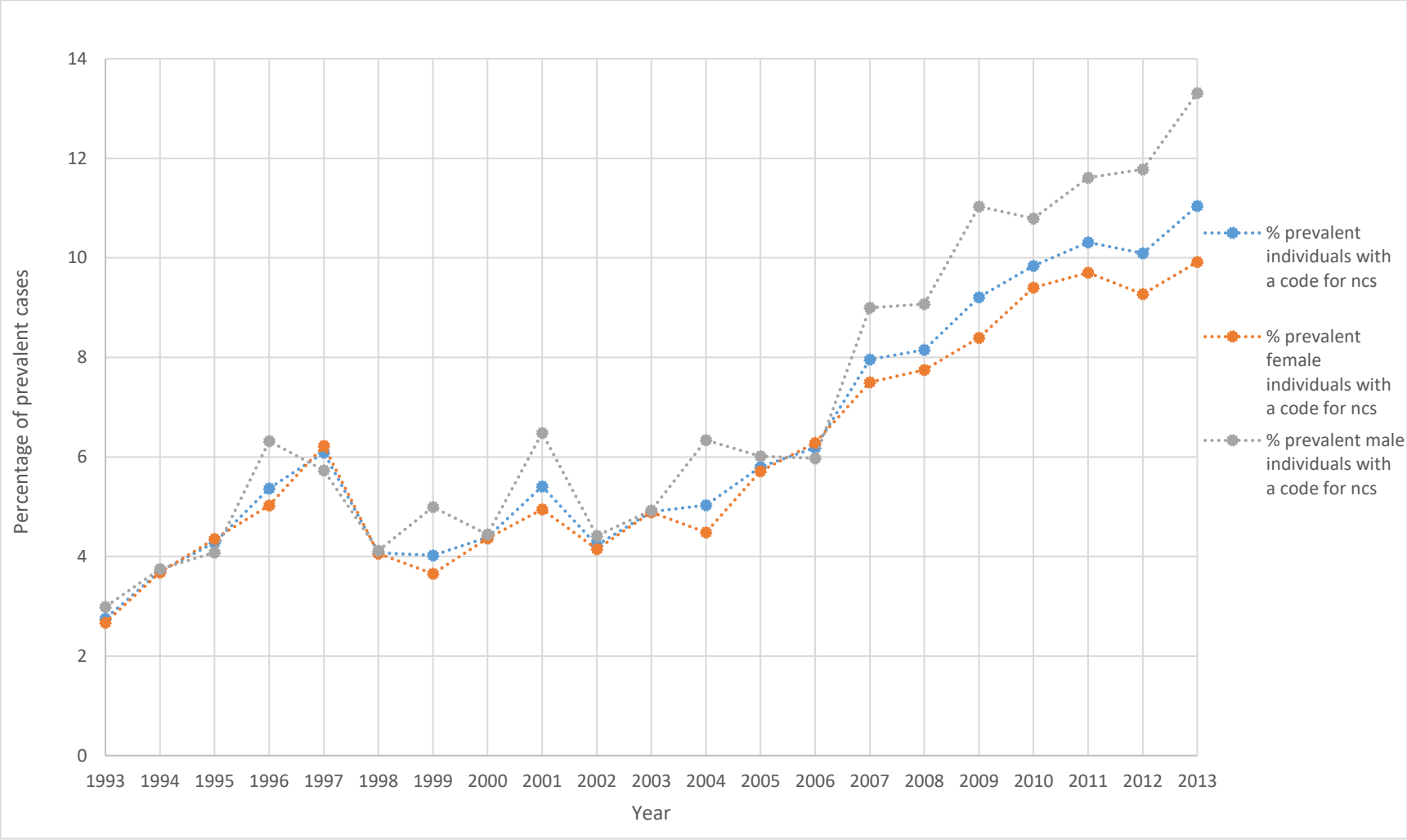
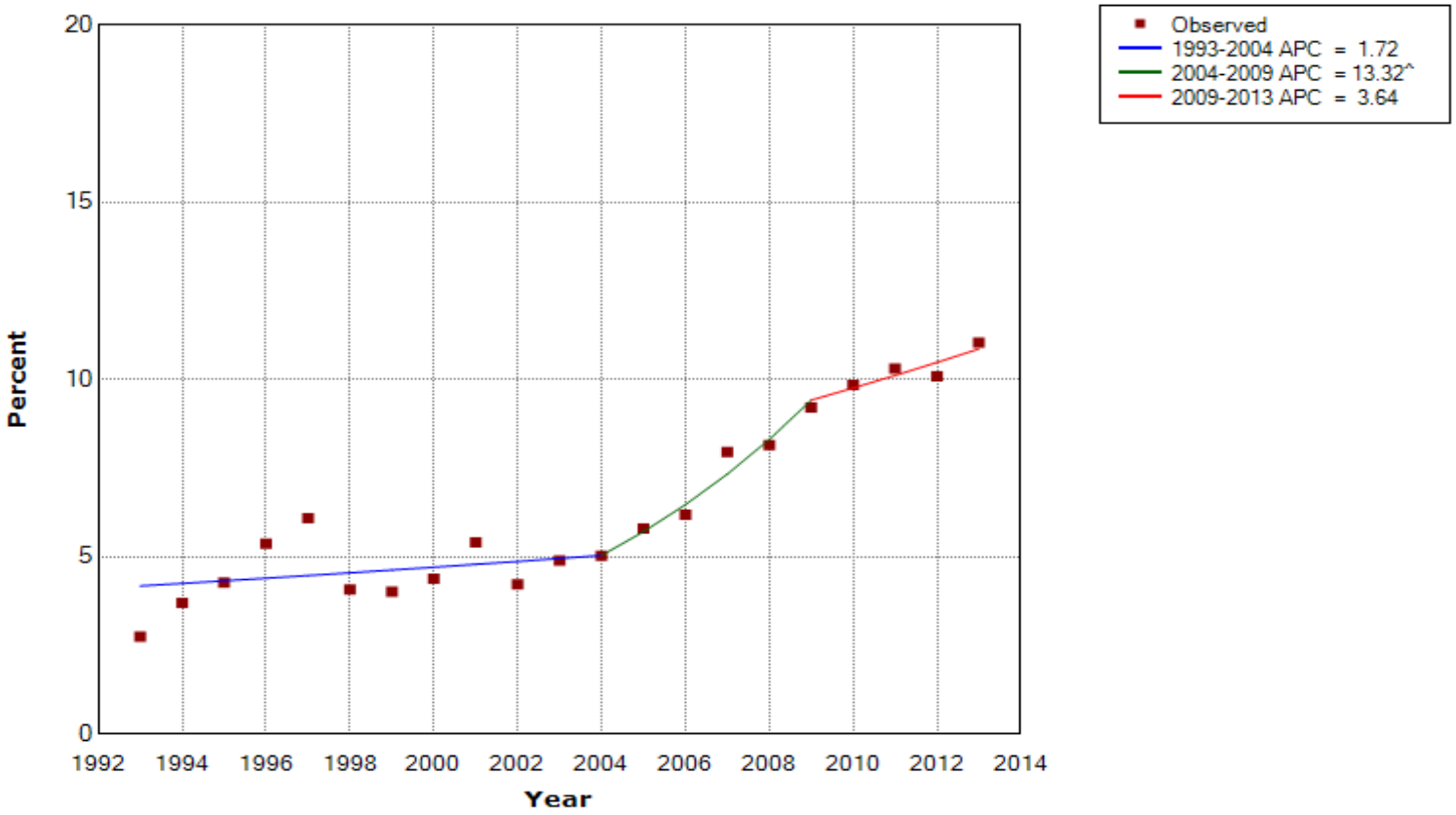


Figure 3-12 Joinpoint analysis plot of the percentage of prevalent individuals with a coded episode of nerve conduction studies, per year



^APC = annual percentage change, which is significantly different from zero significance level p<0.5

Table 3-20 Joinpoint analysis data of prevalent patients with a recorded episode of nerve conduction studies

Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	1993	2004	1.7	-1.8	5.3	1.1	0.3
2	2004	2009	13.3^	4.6	22.8	3.4	<0.0
3	2009	2013	3.6	-2.8	10.5	1.2	0.2

Figure 3-11 and Figure 3-12suggest an increase in the use of NCS, over the observed period (1.72 APC between 1993 and 2004; 13.32 APC between 2004 and 2009 and 3.64 between 2009 and 2013).

3.6.4 Referrals for carpal tunnel syndrome over time

The crude data for the total, male and female population with a coded referral or linked referral episode are shown in Table 3-21 and Figure 3-14. Figure 3-15 further demonstrates the Joinpoint regression of this data with the associated statistics shown in Table 3-20.

Table 3-21 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of referral per calendar year

Year	Episodes of referral per 10,000 person years	% prevalent individuals with a referral	% prevalent females with a referral	% prevalent males with a referral
1993	5.15	19.80	19.38	21.03
1994	5.84	21.96	21.01	24.43
1995	6.41	24.68	24.18	26.02
1996	5.59	21.69	21.47	22.32
1997	5.90	23.68	22.94	25.58
1998	6.11	23.77	22.90	26.14
1999	6.86	27.58	26.83	29.58
2000	7.07	28.15	27.62	29.45
2001	7.63	28.67	28.58	28.88
2002	8.20	28.54	28.26	29.19
2003	9.32	29.76	29.27	30.97
2004	10.59	31.16	31.30	30.81
2005	10.91	32.60	32.13	33.71
2006	10.46	31.73	31.61	32.04
2007	10.78	31.82	31.40	32.76
2008	11.73	32.59	32.42	32.98
2009	12.27	32.95	32.25	34.52
2010	11.64	31.58	31.09	32.65
2011	11.23	31.30	31.08	31.76
2012	11.46	31.80	31.31	32.80
2013	11.93	33.08	32.27	34.70

Figure 3-13 Proportion of referrals to each discipline in each calendar year

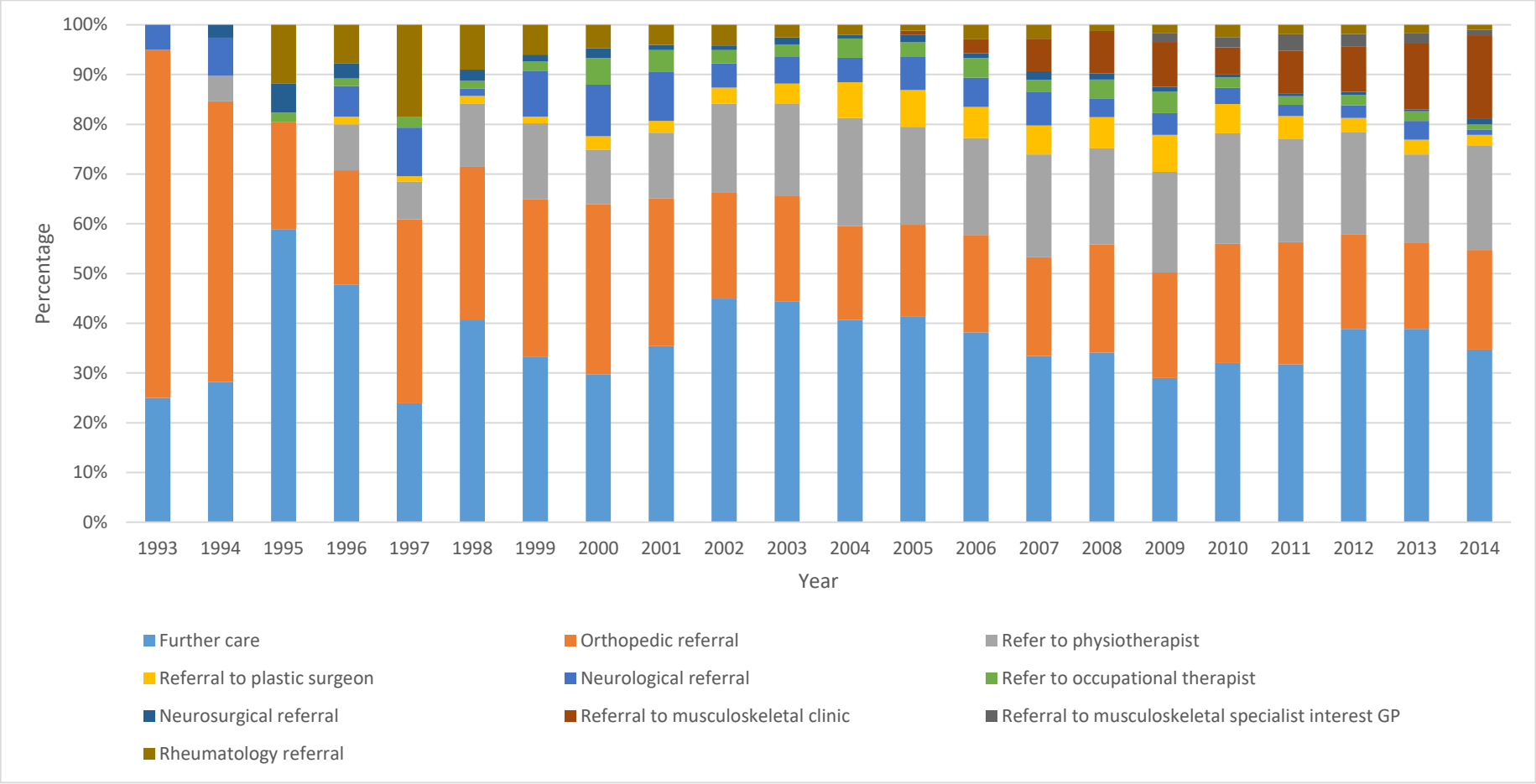
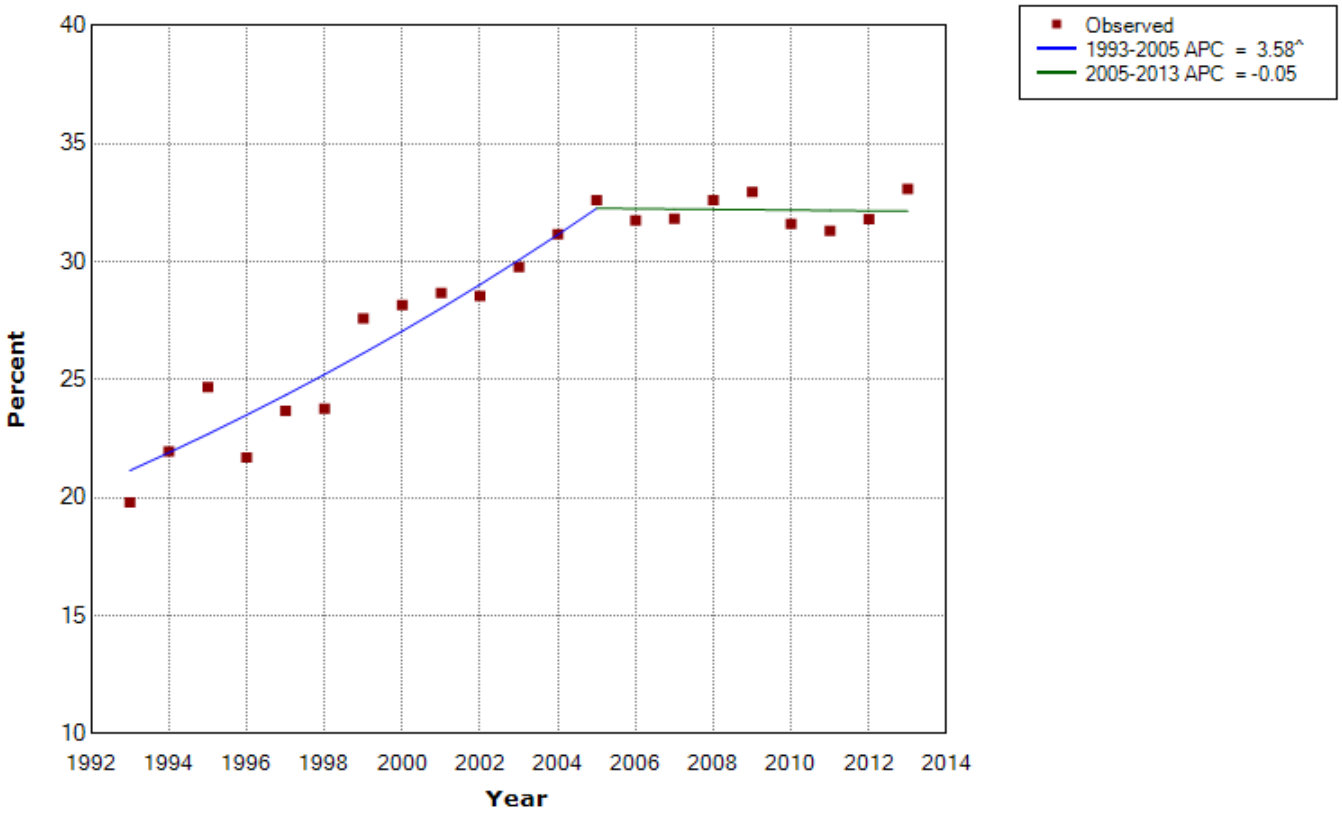


Figure 3-14 Referrals for CTS, as a percentage of prevalent cases in each calendar year, over time

Figure 3-15 Joinpoint analysis of the percentage of prevalent individuals with a referral



^APC = annual percentage change, which is significantly different from zero significance level <0.5

Figure 3-16 Joinpoint analysis data of prevalent patients with a recorded episodes of referral

Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	1993	2005	3.6	2.8	4.4	9.7	<0.0
2	2005	2013	-0.0	-0.8	0.7	-0.1	0.9

Figure 3-14 and Figure 3-15 show an increase in referrals over the observed study period, which appeared to plateau over the latter part of the study. Figure 3-13 shows that that orthopaedic surgeons and physiotherapists received the most referrals, and that the type of referral changed over time. Referrals to musculoskeletal clinics began in 2005 and continued to increase until the end of the observed period. In 2009, referrals specifically to GP's with a specialist interest began to be recorded. Coded referral destinations may not be entirely accurate in that all local musculoskeletal clinic referrals are coded through 'Choose and Book' as orthopaedic referrals. Figure 3-15 illustrates the increase in referral rate of patients with CTS between 1993 and 2005 (APC 3.6%, 95% CI 2.8 to 4.4), followed by a plateau between 2005 and 2013 (APC -0.0, 95% CI -0.8 to 0.7). Only 8.6% of the patients with a surgical code, also had a referral code. It is therefore not feasible to calculate the proportion of patients referred, who received surgery.

3.6.5 Sickness certification for carpal tunnel syndrome over time

With the provisos stated in the methods around identifying sickness certification in CPRD, all Read coded episodes of sickness certification were included. The proportion of patients with a diagnosis of CTS who received a sick note is presented in Table 3-22 and Figure 3-17 and Figure 3-18 further demonstrates the Joinpoint regression of this data with the associated statistics given in Table 3-23.

Table 3-22 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of sickness certification, per calendar year

Year	Episodes of sickness certification per 10,000 person years	% prevalent individuals with sickness certification	% prevalent females with sickness certification	% prevalent males with sickness certification
1993	1.76	6.77	6.54	7.46
1994	1.75	6.59	6.20	7.61
1995	1.56	6.01	5.95	6.17
1996	1.72	6.66	6.09	8.26
1997	1.63	6.54	6.69	6.16
1998	1.77	6.90	6.86	7.01
1999	1.90	7.65	7.45	8.19
2000	2.18	8.69	8.61	8.88
2001	2.52	9.46	9.41	9.60
2002	2.93	10.19	10.40	9.72
2003	3.44	10.99	11.39	10.00
2004	4.02	11.84	11.75	12.03
2005	3.84	11.47	11.70	10.91
2006	3.58	10.86	10.67	11.32
2007	3.59	10.59	10.25	11.35
2008	3.86	10.71	10.39	11.44
2009	3.70	9.95	9.56	10.83
2010	3.74	10.16	10.04	10.41
2011	3.36	9.37	9.34	9.44
2012	3.30	9.16	9.04	9.40
2013	3.26	9.04	8.61	9.90

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Figure 3-17 Coded episodes of sickness certification, as a percentage of prevalent cases in each calendar year, over time

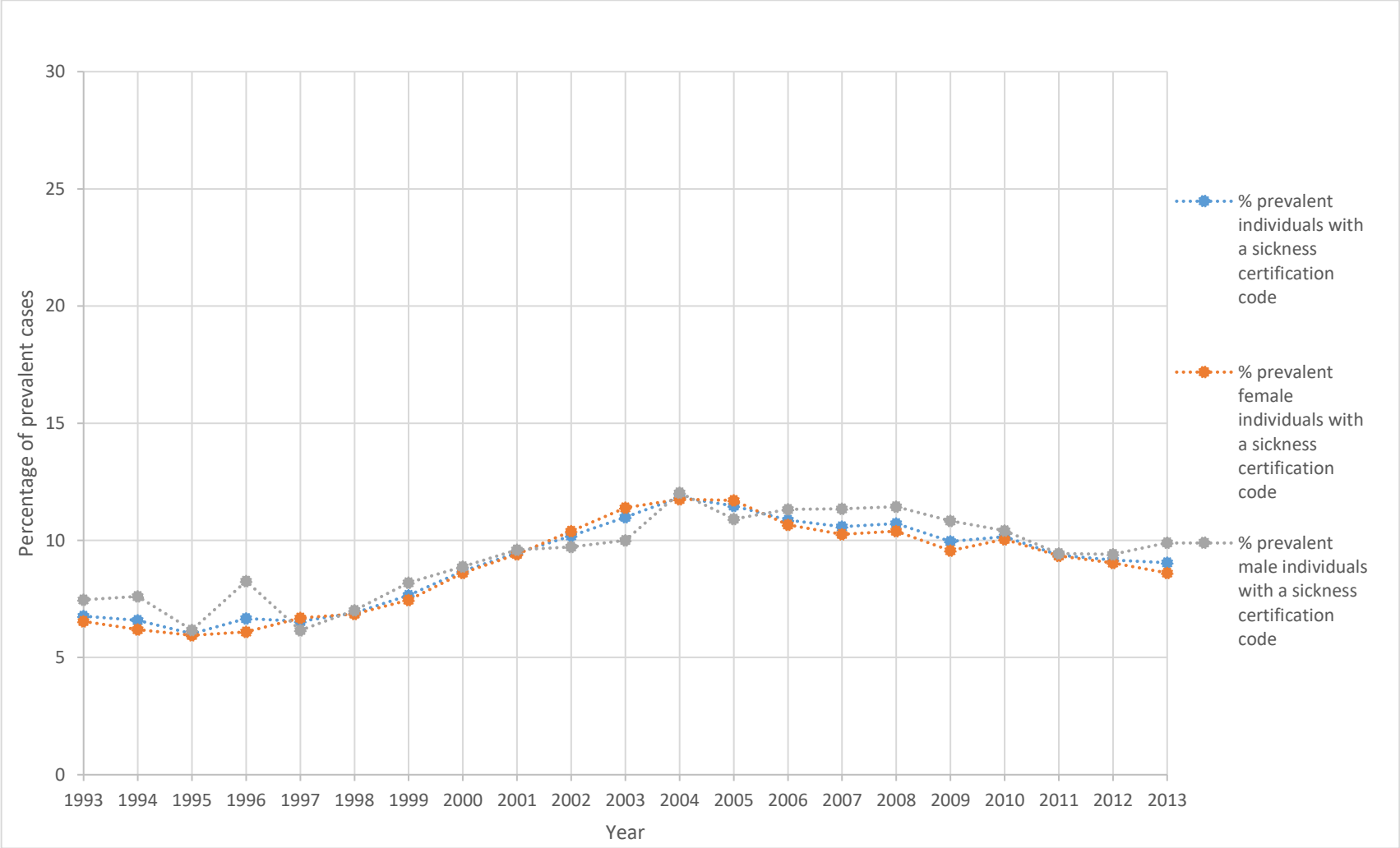
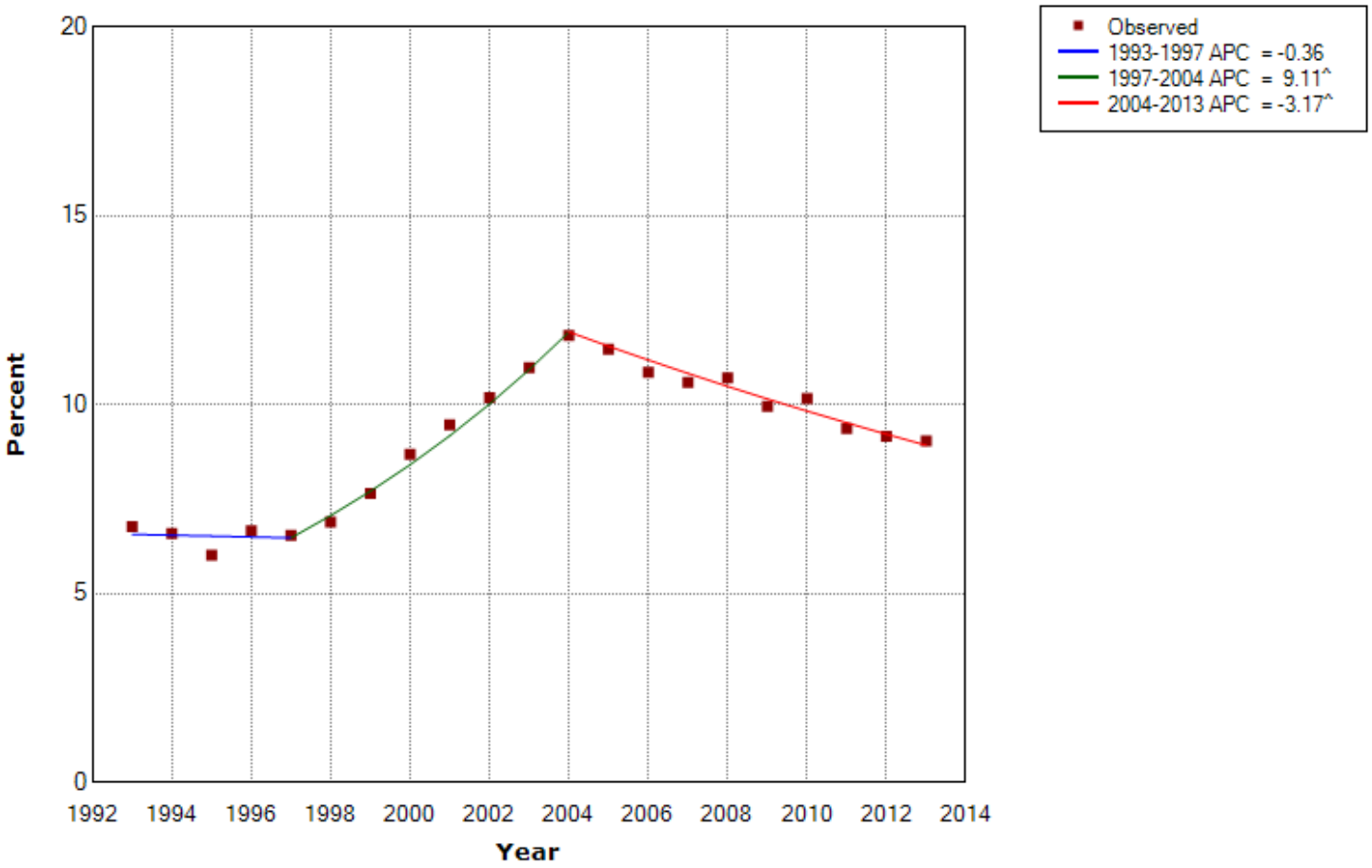


Figure 3-18 Joinpoint analysis of episodes of sickness certification as a percentage of the prevalent population, per year



APC = annual percentage change, which is significantly different from zero significance level $p < 0.5$

Table 3-23 Joinpoint of the percentage of prevalent patients with a recorded episode of sickness certification

Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	1993	1997	-0.4	-3.3	2.7	-0.3	0.8
2	1997	2004	9.1	7.4	10.9	11.8	< 0.0
3	2004	2013	-3.2	-4.0	-2.3	-8.0	< 0.0

Figure 3-17 and Figure 3-18 suggest that the use of sickness certification in patients with a diagnosis of CTS increased between 1997 and 2004 (APC 9.1, 95% CI 7.4 to 10.9) before decreasing over the remainder of the observed period (APC -3.20, 95% CI -4.0 to -2.3).

3.6.6 Use of wrist splints for carpal tunnel syndrome over time

CPRD may substantially underestimate the number of patients to whom splinting is recommended for reasons previously mentioned (not a prescribed item and clinicians would not ordinarily add a specific Read code if they were recommending an approach to self-care). The frequencies and proportion of patients with prevalent CTS with an indication in CPRD of splinting, are shown in Table 3-24.

Table 3-24 Rate and percentage of patients with carpal tunnel syndrome with a recorded episode of splinting, per calendar year

Year	Total number of coded splinting episodes (n<3)	Total number of coded splinting episodes in female patients (n<3)	Total number of coded splinting episodes in male patients (n<3)	% prevalent individuals with a code for wrist splinting	% prevalent female individuals with a code for wrist splinting	% prevalent male individuals with a code for wrist splinting
1993	0.00	0.00	0.00	0.00	0.00	0.00
1994	0.00	0.00	0.00	0.00	0.00	0.00
1995	1.00	1.00	0.00	0.03	0.04	0.00
1996	2.00	2.00	0.00	0.05	0.07	0.00
1997	3.00	0.00	3.00	0.07	0.00	0.26
1998	0.00	0.00	0.00	0.00	0.00	0.00
1999	4.00	1.00	3.00	0.07	0.02	0.19
2000	2.00	0.00	2.00	0.03	0.00	0.10
2001	7.00	7.00	0.00	0.09	0.12	0.00
2002	10.00	5.00	5.00	0.10	0.07	0.17
2003	6.00	6.00	0.00	0.05	0.08	0.00
2004	25.00	18.00	7.00	0.20	0.20	0.19
2005	19.00	10.00	9.00	0.15	0.11	0.24
2006	16.00	14.00	2.00	0.13	0.11	0.05
2007	33.00	30.00	3.00	0.25	0.33	0.07
2008	19.00	11.00	8.00	0.14	0.11	0.19
2009	28.00	21.00	7.00	0.19	0.21	0.16
2010	8.00	7.00	1.00	0.06	0.07	0.02
2011	69.00	54.00	15.00	0.51	0.59	0.35
2012	59.00	49.00	10.00	0.44	0.54	0.23
2013	28.00	21.00	7.00	0.22	0.25	0.17

3.7 The prevalence and incidence of carpal tunnel syndrome in CPRD: Discussion

3.7.1 Summary of main findings

The prevalence of carpal tunnel syndrome in patients presenting in UK primary care, increased over the observed study period between 1993 (26.03 per 10,000 person years, 95% CI 25.10 to 27.00) and 2013 (36.08, 95% CI 35.45 to 36.72), with a peak in 2009 (37.23, 95% CI 36.60 to 38.81). The ratio of female to male patients decreased over time, from 2.74 in 1993 to 1.93 in 2013. A similar increasing pattern in the incidence of CTS was also observed between 1993 (20.22, 95% CI 19.24 to 21.24) and 2013 (27.68, 95% CI 27.09 to 28.28), with a peak in 2009 (29.32, 95% CI 28.74 to 28.82). A decrease in the female: male ratio was observed over time (2.57 in 1993 and 1.88 in 2013). The median age of female and male patients recorded with a diagnosis of CTS increased over the study period.

3.7.2 Interpretation of results

Figure 3-3 and Figure 3-6 demonstrate a significant increase in the prevalence and incidence of CTS over the study period. The initial 6 years of CPRD data (1987 to 1993), in keeping with the population of CPRD, included small numbers of patients leading to wide confidence intervals in prevalence and issues calculating incidence (e.g. when no male patients were present in the prevalence group in 1987). From 1990 the population size of CPRD increased and the results become more stable between years. Data was therefore presented from 1993 onwards. At the time of data acquisition, 2013 was the most recent data available.

Incidence was calculated based on prevalence, meaning the trends over time are understandably similar. The difference between the two measures is because prevalent patients who were still experiencing symptoms would present in consecutive annual periods, whereas incident patients would only present in the index year (unless being represented more than two calendar years following, as a new presentation). Incidence figures may also be slightly lower due to the criterion applied requiring patients to have two years full registration from the midpoint of the incident year. The denominator

population used for calculating incidence had the same criterion applied, which should have minimised this effect.

Table 3-8 and Table 3-11 present the crude estimates of prevalence and incidence. These estimates were then directly standardised to the age sex structure of the 2013 UK population. This process controls for any change in the age and sex structure of the population over the observed period. The crude and standardised rates are very similar, as shown in Table 3-14, suggesting that the population structure did not change over the observed period in a way that would impact the trends observed in the prevalence and incidence of CTS.

Joinpoint analysis identifies and estimates the magnitude and significance of changes in trends. Prevalence decreased non-significantly (at a level of $P< 0.05$) between 1993 and 2000 before increasing significantly between 2000 and 2004 and at a slower rate between 2004 and 2013. Incidence was steady between 1993 and 2000 but increased significantly between 2000 and 2004 before plateauing out between 2004 and 2013.

Joinpoint analysis points to events occurring at the 'Joinpoints' i.e. in 2000 and 2004, which may be related to the trends being observed. CPRD, as discussed in 3.1.3, relies on data being of sufficient quality in order to produce valid research. *Information for Health* was the UK Government's information technology strategy for the NHS.[92] It envisioned that by 2005 the person-based electronic health record, would have been fully implemented.[93] Although associations with such events cannot be established using Jointpoint regression, it may be speculated that with the increasing use of IT systems in primary care and attention to coding, episodes of CTS were more frequently and accurately recorded. This would not however explain the continuing increase in the trend post 2005.

Between 2000 and 2004, the Labour Government was implementing the second phase of its *War on Waiting*, i.e. the reduction of waiting times. For example, the target for the maximum wait for a day-case procedure (i.e. a CTR) was reduced from 18 months to six months.[94] Anecdotally, the managers of the local orthopaedic team recall a time in 2004 when the carpal tunnel release list was 'blitzed' and a large number of patients were operated on to 'clear the waiting list.' The peak in prevalence seen in

2004 may therefore be explained by the fact that patients requiring surgery were 'accumulating' between 2000 and 2004. They then received an effective treatment, which reduced the rate of further presentations in primary care for ongoing symptoms and hence the corresponding prevalence. This effect would not however be expected to impact upon the incidence, which disregards repeat patient presentations in subsequent annual periods, unless patients with a less specific initial code received treatment and appeared as an incident episode following a condition specific intervention.

The change in trends in 2004 may also represent a change in service. The introduction of the Quality and Outcomes Framework (QOF) occurred with the introduction of the General Medical Services (GMS) contract in 2004. QOF can be considered to be a form of 'performance related pay' for practices. Although there has never been a domain for musculoskeletal health, the importance of coding to develop and maintain registers and evidence patient outcomes, may have influenced coding behaviour and in turn led to an increase in the more frequent and more specific use of the CTS Read code.

At the same time as the introduction of QOF, Primary Care Trusts (PCT's) were given a role in commissioning services, with the aim of better meeting the needs of the local population. The ability of PCT's to commission new services heralded locally the development of the Musculoskeletal Interface Clinic (MIC), which acts as a 'one stop shop' for patients with musculoskeletal problems. A referral to this clinic from primary care may also be a reason why prevalent patients with persisting symptoms stopped presenting in primary care as they had open follow up in the MIC.

These three factors (changes in coding behaviour, a reduction in waiting times, and service redevelopment) may all contribute to the change in trends of CTS presentations between 2000 and 2004 but given the increase in incidence as well as prevalence during this period, there are likely to be additional reasons.

CTS is associated with certain occupations. Blue-collar workers involved in manufacturing, construction, meat and fish-processing and work involving chain saws and white-collar workers in personal service industries, have been observed to be more likely to develop CTS.[95] A change in the occupational structure of the population may therefore influence the prevalence of CTS. CTS as an

occupational condition may also influence consultation rates, if patients were pursuing a legal claim against their employer.

The median age and gender ratios are similar to those presented in previous studies, as summarised in Table 1-2. The apparent trend of the female: male reducing over time, has not been previously commented on in the literature. The trend may pertain to the aetiology of the condition and its association with occupation. A social shift in occupations, either attracting more males than females, or attracting males into a previous more female orientated environment, may lead to a change in the gender ratio affected by CTS, if the occupation was associated with exacerbating CTS. This however remains conjecture and would require more precise observational studies to provide evidence for this hypothesis, since occupation is not recorded in CPRD, and trends in occupation cannot be derived from the presented data.

As described in previous studies, CTS shows a peak in prevalence and incidence in women of middle age (50–59 years age group), potentially due to hormonal changes around the time of the menopause), while in the male population, the prevalence and incidence of CTS increased with age. Gelfman et al also described an increasing number of older people presenting with CTS.[96] The increase in the prevalence and incidence of CTS in the older-aged male groups, may partially account for the observed decrease in the female-to-male ratio, over time.

The aetiology of CTS was discussed in 1.2.2. A change in the prevalence of these factors, for example increasing rates of obesity[97] and diabetes,[98] may subsequently contribute to an increase in the incidence of CTS.

3.7.3 Findings in relation to other studies

Table 1-1 and Table 1-2 summarise the prevalence, incidence and gender ratios of CTS observed and demonstrate the substantial differences that exist between studies; including the case definition of CTS used, methodology applied and population and setting observed. Comparing this study to others

is therefore difficult in that it is not clear how similarities and differences in design explain variability in results.

As discussed in 1.2.1, the prevalence of CTS in any given population is likely therefore to depend on the definition of CTS applied.[18] The case definition in the study presented in this chapter was derived from clinician recorded diagnosis and treatment codes applied, which are very likely to have been based on clinical findings alone but may also have included those who had further investigations (NCS) and those who received definitive condition-specific treatment (CSI and / or CTR). Hence, this study used a pragmatic approach, across a large population that included all patients presenting to their GP with symptoms. These study methods assume that patients with symptoms present in primary care and receive a definitive code. CPRD will not capture patients with chronic symptoms who do not present in primary care or who are not attributed a code.

The studies which are most similar to the one presented in this thesis are those of Latinovic et al and Bongers et al, both of which utilised primary care data in their methodology. A comparison is made in Table 3-25. Bongers et al noted an increase in incidence in the Dutch primary care population from 190 (female) and 60 (male) per 100,000 population in 1987, to 280 (female) and 90 (male) per 100,000 population in 2001.[99] Latinovic et al's results were similar stating an incidence in the UK primary care population in 2000 of 192.8 (female) and 87.8 (male) per 100,000 population.[19] The female: male were 2.23[19] and 3.17 (1987) and 3.11 (2001).[99]

As Latinovic et al was set in the General Practice Research Datalink, the forerunner to CPRD, one would expect similar results to be found. However, the results of the current study appear to show a higher incidence, more similar to the study by Bongers et al, set in The Netherlands. This is likely to be due to the different method of determining incidence. Latinovic et al selected only the first episode of CTS, whereas the current study required a two-year clear period prior to an incident episode being recorded. If the first ever criteria had been used, the incidence found by the current study would be slightly lower, but would still not match that of Latinovic et al. Further possible explanations of why the figures are not the same include the use of slightly different Medcode lists, the use of linked

prescription data, a different population (Latinovic only included practices with up to standard data for the entire 1992 to 2000 period) and a different criterion for determining the denominator population was applied. In this study, in order for the numerator and denominator populations to be treated equally, the denominator population for incidence had to have contributed up to standard data for the period 2 calendar years prior to the index year (measured at the midpoint). All these factors are likely to have contributed to the different rates observed between the studies.

Table 3-25 Comparison of the incidence of carpal tunnel syndrome in other studies based in primary care data

Study	Location Year	All patients per 100,000 person years	Female per 100,000 person years	Male per 100,000 person years	Female: male
Latinovic, Gulliford Hughes 2006	United Kingdom 1992 2000		170.0 192.8	64.8 87.8	2.62 2.23
Bongers et al. 2007	The Netherlands 1987 2001	130 180	190 280	60 90	3.17 3.11
Current study	United Kingdom 1992 2000	189.6 197.3	264.8 274.1	110.2 166.2	2.40 1.65
Current study (first ever criteria)	1992 2000	175.9 186.7	243.6 260.0	104.1 109.9	2.34 2.37

Not all studies have identified increasing trends of CTS. One observational study by Roquelaure et al (2017) used multiple sources of data to observe the incidence of CTS in different situations. Hospital discharge data was used to estimate surgically treated CTS. The Pays de la Loire surveillance program of musculoskeletal disorders was used to estimate CTS compensated for as an occupational disease and the French National Health insurance system to estimate work-related diseases, over an 8-year period (2004 to 2011). A decrease in the annual incidence rates of surgically treated CTS (3.35 to 2.98 per 1000 person years) and work related CTS (5.04 to 3.08 per 1000 employed person years) was observed but the incidence of CTS compensated for as an occupational disease increased over the study period (1.52 to 2.34 per 1000 person years).[100] Whilst the authors acknowledge that certain population groups may not contribute to the data-sets (e.g. non-salaried workers and agricultural workers) and that compensation schemes would collect bilateral CTS as two episodes, they report that these factors are likely to have remained stable over the observed period and that the trends over time remain valid. They conclude that a series of occupational and non-occupational changes brought in over the course of the study reduced the likelihood of developing CTS, whereas campaigns increasing the awareness of 'upper extremity musculoskeletal disorders' in the workplace may have

prompted patients to seek compensation.[100] The population described in this CPRD study is not likely to be very similar to the population observed in Roquelaure et al since it seems older / non-working patients were not identified, unless they had surgery.

3.8 The management of carpal tunnel syndrome in CPRD: Discussion

3.8.1 Summary of main findings

The proportion of patients with prevalent CTS having surgery in each calendar year increased over the study period from 19.35% in 1993 to 27.41% in 2013, with the median age of those having surgery also increasing by 4 years for women and 7 years for men. The ratio of female: male having surgery reduced from 2.63 in 1993 to 1.74 in 2013, suggesting that an increasingly greater proportion of prevalent male patients had surgery than their female counterparts. The coded use of CSI was relatively stable between 1993 and 2005 (APC = -1.29) with an increase in use between 2005 and 2013 (APC = 6.56). The use of splints, as expected, was poorly coded however results suggest that the use of NCS, referral to specialist care and sickness certification generally increased over the study period.

3.8.2 Interpretation of results

Definitive treatment options for patients with carpal tunnel syndrome in primary care are limited to CSI and wrist splinting. The availability of CSI is dependent on a competent injector operating within the practice and splinting is normally recommended to patients as a 'selfcare option' i.e. whilst referrals may be made to an orthotist or occupational therapist, it is often the case that the patient is expected to acquire a splint from a pharmacist or online provider.

Splinting was therefore poorly coded and as such further analysis was felt not to be sensible. The percentage of prevalent patients receiving a CSI was also relatively low and substantial uncertainty exists as to whether the results are truly representative of practice. However, two methods were employed to attempt to capture episodes of injection: the use of Read codes and linked prescription data. Injections delivered outside of primary care are unlikely to have been coded.

Figure 3-10 suggests an increase in the use or coding of CSI from 2005 until the end of the study period (APC 6.6). This may be associated with a move to full electronic patient records, meaning that a greater proportion of prescriptions issued for stock drugs were recorded in the patient record, as opposed to be written out manually. It may also represent a true increase in the use of CSI at a time where GP's were adapting to the new GMS contract and directly enhanced services, that in effect pay GP's to perform minor procedures (nb this is no longer the case).

Along with splinting, CSI is a mainstay of primary care treatment and one would assume that all patients having surgery were very likely to have had an injection or tried splinting first, plus those who responded and did not require surgery. It is highly likely therefore that injections simply were not picked up by the methods applied or, patients who do receive CTI's tend to receive them outside of primary care, e.g. the musculoskeletal interface clinic.

If conservative treatment options were unsuccessful or not available, referral to specialist services would be necessitated in order to access further investigation and management. Figure 3-14 and Figure 3-15 demonstrate an overall increase in referrals over the study period, particularly between 1993 and 2004. This preceded a period where referrals were almost the same each year (2005 and 2013, APC -0.05), noting patients may have received more than 1 referral code in each annual period.

This observation is interesting, particularly in the current climate of financial hardship within the NHS and the drive to scrutinise referrals and reduce costs. Referral of care and clinical responsibility between professionals is a complex area and involves a balance between several competing interests, particularly the GP acting as the clinical advocate of the patient as well as the gatekeeper of NHS resources. The referral process has a direct consequence on the patient's experience of care as well as being a major cost-driver in the NHS. A 'good' referral should be: clinically necessary; to the most appropriate destination first time and use the correct process. Rates of referral can be influenced by population health needs, GP attitudes towards risk and patient pressure and expectation.[101]

At a national level, GP referrals to outpatient services increased by 19 percent between 2005 and 2009.[102] Whilst the significant increase in referrals in this study preceded this, explanations for such an

increase could include: a true clinical need whereby patients have a better outcome if referred out of primary care; patient demand for referral being greater; fewer GP's being able to offer CSI (although this would be contrary to the findings of this study) or a change in the phenotype of CTS meaning that symptoms were more severe and required consideration of surgery. It is also possible that the increase in Tier 3 type MIC's meant that GP's were more likely to refer patients into a service where a block contract exists (meaning that the cost is already covered by a block payment and covers the complete care of the patient). It may be that GP beliefs are such that patients receive better care in these clinics and that the need for them to provide injections (which takes time within an already time burdened day), is removed. It is likely that the reasons behind the observed trends are a combination of these factors.

Figure 3-13 demonstrates the destination of referrals in each year. The first time a referral to a musculoskeletal clinic was coded was in 2005 and to a GP with specialist interest, in 2009. This highlights the introduction of Tier 3 services; however the coding is unlikely to be truly representative of the referral destinations.

Access to nerve conduction studies varies between locality and often requires the patient to have been referred into further care. Figure 3-11 and Figure 3-12 demonstrate an increase in the use of NCS over the observed study period. Interestingly, the proportion of patients having NCS increased at a time when referrals were not increasing. Perhaps GP's had access to NCS and were using this as a means of investigation; avoiding referral or at least delaying it. It may also be that, whilst clinical guidelines did not change, new referral or treatment pathways demanded NCS in order to quantify severity and ration further treatment. It may also be a reflection on coding practice.

It is also possible that as NCS have become more accessible with the advent of hand-held devices (which allow for a quick and relatively cheap test and computerised analysis to take place), its use in NHS clinics has increased. Whilst not supported by any change in any national guideline, an increase in use of investigations may represent a trend towards more risk-averse clinical practice, or indeed investigation results being used to ration access to CTR.

Joinpoint analysis of the use of surgery over time (Figure 3-8), suggests a significant increase between 1993 and 2007 (APC = 2.6), followed by a reducing trend between 2007 and the end of the study in 2013 (APC = -1.7). The initial increase in the apparent use of CTR may have been due to increased availability of the procedure, or have been an effect of the dissemination of the evidence generated by authors such as Gerritsen et al who, in 2002, published the results of a RCT showing CTR to be superior to splinting.[103]

Substantial changes to the structure of the NHS were taking place at the time of the 2007 joinpoint. Around 2007 to 2008, practice-based commissioning (PBC) was being introduced. This gave GP's notional budgets with which to purchase care for their patients. The aim behind this shift in funding streams was to align the clinical and financial responsibilities of primary care. The new commissioning consortia needed to find ways to reduce referrals and reduce costs of treatments. Referral management schemes were introduced and restrictions placed on procedures carried out in secondary care. Results showing a reduction in surgery rates would fit with restrictions being placed on the procedure (e.g. patients needing more serious symptoms for longer, having had tried injections and in some cases severe findings on nerve conduction studies). Such requirements may also explain the increase in the use of injections and nerve conduction studies being used as an alternative treatment and as a necessity prior to surgery, respectively.

CPRD is not directly set up to monitor sickness certification, however, by using Read codes, Figure 3-17 and Figure 3-18 are suggestive of an initial increase in sickness certification followed by a small but significant reduction in the proportion of patients having an episode of sickness certification between 2004 and 2013 (APC = -3.07). Reduction in sickness certification may represent either an improvement in care, meaning patients are able to return to work or stay at work or that patients were choosing to persevere at work rather than risk financial disincentives. It may also have been the case that the workplace had less of an effect on the incidence and severity of CTS. It seems more likely that with the development of electronic health records, sickness certification (or fit notes since 2010) are now embedded within the consultation and not necessarily coded as a separate entity.

3.8.3 Findings in relation to other studies

The increasing rate of CTR use has been recognised by other authors working in the NHS. Wildin et al's audit data from one tertiary hand centre, suggested that the rate of CTR procedures had increased over the earlier 10 year period between 1989-9 and 2000-1.[104] It would therefore be useful to observe the figures over these two periods and into more recent times to explore whether a trend truly exists and to hypothesise as to what the reasons behind this might be.

Possible reasons include: increased access to specialist services, perhaps via tier 3 community clinics; increased litigation leading to more definitive treatments being sought and increased patient expectations and demand. It may also be possible that fewer GP's were offering conservative management options, such as injections, and tended to refer patients into specialist care, where the operative rate was higher.

Latinovic et al found that in 2000, 31% of CTS patients in the GPRD population had surgery.[19] This is higher than the 25.54% described in this study. However, this study identified more individuals with a surgical code but used a different denominator, which partially explains the difference in reported rates of surgery. Latinovic et al used the incident population, whereas this study used the prevalent population as not all surgical episodes occurred in the same annual period as the incident episode (see below).

A further study carried out over a similar time-period using the nationwide patient registry of Sweden, observed that between 2001 and 2009, both the incidence of CTS diagnosed in secondary or tertiary care and first time CTR increased. Incidence increased from 216 to 243 per 100,000 person years in women and from 95 to 119 in men. The mean annual increase in first time CTR over the study period was 5.1% in women and 6.2% in men. Substantial differences in the percentage of patients having surgery were observed depending on region (53 to 91% in women and 51 to 77% in men).[105]

The effect of regional variation will be discussed further in Chapter 5, however it appears likely that the healthcare system in which the population is observed has a substantial impact on the reported

incidence of surgically treated CTS. The regional variation of CTR in the CPRD population over time is shown in Appendix B5.

Predicting what may happen to the rates of CTS and CTR in the future, Bebbington and Furniss observed for shifts in the presentation of and procedures for hand conditions within HES data. Linear regression was used to predict future trends in hand surgery. The authors suggest that whilst absolute numbers of CTS diagnoses and CTR procedures increased between 1998 and 2011, the pre-2008 increase in CTR was significantly steeper than the post-2008 slope ($p<0.001$).[106] This is suggestive of a decrease in the surgical management of CTS in terms of the proportion of patients with CTS having an operation, but not necessarily in the numbers of surgical episodes in absolute terms, which Bebbington and Furniss predict will have increased by 99% (95% CI 65 to 132) in 2030 compared to 2011.[106] The data from CPRD however, suggested a reduction in both real-term episodes of CTR as well as the proportion of the (increasing) prevalent population receiving surgical treatment. This difference may relate to the fact that linear regression modelling cannot account for the fact that services may be further rationalised or even decommissioned in the future. Whilst HES data will accurately identify CTR taking place in secondary care, it will not identify CTR taking place in the community.

3.9 Methodological considerations

Several limitations associated with the data used in this study exist. The quality of coding is a potential limitation of any research conducted using electronic healthcare data. This study relies on the clinician's initial diagnosis and further coding of CTS, being correct. The coding of the subsequent management, referral and treatment is also required to be as sensitive and specific as possible. Measures were taken to reduce the effect of inaccuracies in coding (e.g. by including surgery and injection codes in prevalence measures, if diagnostic codes had not been used). However, as discussed in 3.3.3, misclassification may lead to the results not being entirely representative of the true clinical picture.

Due to a lack of clarity in the accuracy of coding and the likelihood that associated clinical encounters following a CTR were coded using a surgical code, only the first surgical code could reliably be used to

indicate an episode of surgery. This is likely to have led to an underestimation of the frequency of true surgical episodes, as episodes on the contralateral hand will have been automatically excluded as they were indistinguishable from other clinical contacts using the same code. In fact, prevalence and incidence were also likely to have been underestimated as presentations in the contralateral hand are indistinguishable from repeat presentations for the ipsilateral hand. This is a possible reason as to why the proportion of patients having surgery is lower than that reported in some other studies (Tadjerbashi reported first ever CTR being as high as 81%).[105]

A further consideration, which may have led to errors in the estimation of prevalence and incidence with regard to time period, was the fact that treatment codes were also used to evidence a diagnosis of CTS. As discussed in section 3.3.3, this was felt necessary in order to ensure that patients seeking and receiving care with symptoms of CTS were still included even if they had either received no code or a more generic code but still had a condition specific treatment. To not include such treatment codes may have led to a substantial underestimate of the population actively receiving care for their CTS symptoms.

However, whilst the annual prevalence would be correct with regard to the period that the patient received care in, it is possible that incident patients were recorded in an annual period later than their initial yet un-identifiable incident presentation. It also means that, given the fact that they had surgery, patients with more severe symptoms may have been more likely to have been identified than those with less severe and potentially vaguer symptoms. This would potentially lead to an overestimate of the proportion of prevalent patients who had surgery, as those with milder and vaguer symptoms remained un-coded or otherwise un-identifiable by Read code.

The coding frequencies for CSI were also apparently low, although these did increase over the study period. It is likely that, with the availability of MIC's, patients were referred to this clinic where the injection took place. The intervention would then have been recorded in hospital records and not necessarily coded in primary care records on receipt of the clinic letter.

3.10 Clinical relevance of the findings

This study has shown that as well as an increase in the number of patients consulting in primary care with CTS, a greater proportion of these patients are being referred out of primary care. Although this does not necessarily translate into an increased proportion of patients having surgery or indeed experiencing a better outcome, it does suggest an increase in the cost burden of the condition. If GP's are not necessarily referring for assessment for surgery in each case, it is possible that more patients could be treated with NS and / or CSI within primary care and only referred when such treatment has failed or symptoms are severe. Learning how to most effectively manage CTS in primary care whilst understanding which patients are likely to require surgery, is likely to benefit both patients and the healthcare economy.

3.11 Suggestions for further research

Whilst CPRD provides a large sample size representative of the UK population, which has substantial benefits when estimating epidemiological trends, it cannot directly measure patient outcome. Surgery can be perceived as a 'gold standard' treatment, but it does not necessarily signify cure. Further research observing the characteristics of patients presenting in primary care with CTS in greater detail, in order to estimate their eventual outcome, may provide useful guidance to clinicians when deciding how best to counsel, treat or refer their patients with CTS. This thesis will present two prognostic studies with the aim of predicting firstly, an episode of surgery using a cohort derived from this study in CPRD and secondly, patient reported outcome in a trial population set in primary care.

3.12 Conclusion

This study has demonstrated that the prevalence and incidence of carpal tunnel syndrome increased over the study period between 1993 and 2013. Rates of referral for CTS have also increased over the study period, however in the later years of the study, the proportion of patients receiving surgery was observed to decline. Possible reasons for these observations have been proposed and are likely to be

associated with changes in healthcare delivery. In chapter 4, a systematic review and narrative synthesis of the literature will be presented with the aim of defining the clinical course of CTS and examining patient level predictors of outcome.

4 The prognosis of carpal tunnel syndrome: The clinical course and prognosis of conservatively managed carpal tunnel syndrome - a systematic review and narrative synthesis of cohort studies

Summary

The study reported in chapter 3 used data from electronic health records to describe the trends in the epidemiology and management of carpal tunnel syndrome presenting in UK primary care. It was concluded that whilst the prevalence and incidence of CTS was observed to increase over time, factors including changes in healthcare delivery were likely to have impacted on how CTS was managed. This chapter presents the identification and synthesis of scientific literature evaluating the clinical course and prognosis of carpal tunnel syndrome. The studies included in the review incorporate multiple settings and hence give a broader overview of prognosis and its possible determinants, not limited to a single healthcare setting. The aims of this chapter are therefore to summarise available evidence regarding the clinical course of conservatively managed carpal tunnel syndrome and to identify predictors of its outcome.

The work in this chapter has now been published in a peer-reviewed journal under a Creative Commons License:

Burton C, Chesterton LS, Chen Y, Van der Windt D. Describing the clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: A systematic review. Archives of Physical Medicine and Rehabilitation. October 2015 97(5): 836-852.e1

4.1 Introduction

Summarising the evidence regarding the course of CTS and predictors of its outcome using studies from multiple healthcare settings will identify any gaps in the research evidence and / or provide a

summary against which observations from UK primary care patients can be compared. The principles of the type 1 and type 2 prognosis studies as outlined by the PROGRESS Framework introduced in 1.7 will now be described in further detail.

4.1.1 Overall prognosis research

Overall prognosis research generates estimates of the average or overall prognosis (likely future course or outcome) for a given population with a particular health problem. It is therefore of use to public health policy makers as it allows for the population burden of a condition to be ascertained and appropriate resources to be planned. Furthermore, understanding the likely future outcome of patients with a condition, in relation to current clinical practice (clinical course) or in the absence of care (natural history), allows the potential impact of new interventions to be more fully assessed.[71] Thus, the availability of information about overall prognosis makes for more robust informed shared decision making in clinical practice, by helping to answer questions such as 'what is likely to happen if I do nothing?'

Potential limitations of prognosis research do exist. Henderson et al discuss the hazards of providing predictions of the course of a condition due to the implicit variability between individuals or individual clusters, (e.g. within clinicians, health care providers and geographical regions).[107] It should therefore be emphasised that overall prognosis research is concerned with describing and understanding variations around the average course of a condition rather than that of the individual.[71]

The systematic review and subsequent narrative synthesis presented in this chapter focus on summarising the results of existing prognosis research, which has investigated the course of untreated and conservatively managed CTS. The 'startpoint' for observing prognosis is ideally as early in the course of CTS as each individual primary study allows. The 'endpoint' varies across studies but is usually a specified patient reported outcome after a set time point, or referral for or episode of surgical management, marking the end of conservative management. The synthesis therefore seeks to describe the course of CTS managed with no treatment or conservative (non-surgical) management options.

4.1.2 Prognostic factor research

A prognostic factor (or predictor) is;

> *"…any measure that, among people with a given health condition (startpoint), is associated with a subsequent clinical outcome (endpoint).*[72] *pg 1.*

Prognostic factor research seeks to identify the predictive value of such factors and can begin to describe and explain the variability in overall prognosis, due to baseline differences between individuals.

Research of individual prognostic factors may subsequently contribute to the development of prognostic models, whereby individual prognostic factors are combined in order to estimate the prognosis of an individual, based on their baseline characteristics. Prognostic factors may also represent potential predictors of treatment effect (treatment effect moderators), which may further contribute to a stratified care approach to a condition, i.e. whereby particular treatments are matched to patients based on their baseline characteristics. Prognostic factors may also represent modifiable targets for interventions and could lead to the development of new management strategies through an improved understanding of disease mechanisms.[72]

Again, limitations to prognostic factor research exist. Riley et al discuss the fact that prognostic factor research studies are often poorly designed, analysed and reported. Recommendations for the improvement of prognostic factor research to help mitigate these issues were proposed. In order to reduce the risk of reporting bias, all factors and outcomes should be reported transparently, including null results. When summarising the findings of multiple studies, the ideal would be to prospectively plan and perform meta-analyses of individual patient data.[72]

The second part of this systematic review and narrative synthesis seeks to identify predictors of outcome in patients with CTS being managed conservatively with treatments available in primary care. Whilst the rate and predictors of surgical outcome have been reported in the literature,[108, 109] at the

time of preparing this review few studies and no systematic reviews had summarised the evidence for prognosis and prognostic factors in conservatively managed CTS.

4.2 Methods

The following work was based on a search conducted in 2013 and has since been published.[110] The review and synthesis informed the design of the reported studies in subsequent chapters and as such has not been formally updated. However, section 9.2.2 describes any relevant updates in the literature and the potential impact they may have had on the findings of this review. The protocol for this review was registered on PROSPERO (CRD42013006608) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42013006608#.VYk_RflVhBc.

Results of studies identifying or testing predictors of treatment effect (potential moderators) have been described in the review of intervention studies (trials) presented in Chapter 7.

4.2.1 Eligibility criteria

To be eligible for inclusion in the review, studies were required to fulfil the following criteria as shown in Table 4-1 and Table 4-2.

Table 4-1 Summary of inclusion criteria

	Inclusion criteria
Population	Adult population aged 18 years or over Diagnosed with carpal tunnel syndrome (method of diagnosis to be documented)
Interventions or exposure	The observation of patients with a diagnosis of CTS receiving no treatment or usual care (limited to conservative or nonsurgical management approaches)
Outcomes	Outcome measures able to indicate change in symptoms and/or function including: global improvement measures; Boston Carpal Tunnel Questionnaire score or similar disease or region specific outcome measure; return to work and / or requirement of further treatment (likely to be carpal tunnel release surgery). Associations of potential prognostic factors (baseline patient or disease characteristics) with these outcomes were required for inclusion in the second part of the review
Setting	Any healthcare setting
Study design	Retrospective or prospective cohort studies

Table 4-2 Summary of exclusion criteria

	Exclusion criteria
Population	Cohorts specifically of pregnant women with CTS Studies reporting conditions other than CTS Studies reporting outcomes in specific populations such as occupational groups Studies with a follow up of less than six weeks Studies investigating secondary CTS (e.g. post-traumatic)
Interventions or exposure	Studies reporting risk factors for onset of CTS (aetiology) as opposed to predictors of outcome (prognosis) Studies reporting prevalence and incidence alone Studies reporting only on outcomes following specific types of allocated / randomised treatment (to be investigated in a later review)
Study design	Papers in languages other than English where no translation was available Designs other than those described in the inclusion criteria, e.g. case studies, cross-sectional studies, and clinical guidelines

4.2.2 Search strategy

The methods used to identify studies fulfilling the eligibility criteria will now be discussed.

4.2.2.1 Medical Literature Databases

Ten medical databases were searched for relevant articles, from their creation to December 2013. These databases are briefly described below using information relevant at the time of the search:

4.2.2.1.1 MEDLINE

MEDLINE (Medical Literature Analysis and Retrieval System Online) is the U.S. National Library of Medicine bibliographic database containing over 21 million references to journal articles with a focus on biomedicine. The records are indexed with National Library of Medicine (NLM) Subject Headings (MeSH). The database runs from 1946 to the present with some older material. Citations are sourced from over 5,600 worldwide journals and are created by the NLM, its partners and collaborating organisations.[111]

4.2.2.1.2 EMBASE

EMBASE (Excerpta Medical Database) is a biomedical and pharmacological database hosted by the publisher Elsevier. Embase contains over 22 million records from 1974 – present. The database utilises 'Emtree' which is thesaurus of search terms.[112]

4.2.2.1.3 AMED

AMED (The Allied and Complementary Medicine Database) provides an alternative medicine database. It includes articles regarding complementary medicine, physiotherapy, occupational therapy and rehabilitation therapy. AMED contains records from 1995 onward and is produced by the Health Care Information Service of the British Library.[113]

4.2.2.1.4 HMIC

HMIC (Health Management Information Consortium (HMIC) is a compilation of data from the Department of Health's Library and Information Services and King's Fund Information and Library

Service. HMIC therefore covers official publications, journal articles and grey literature on: health service policy, management and administration. Information is focused on the UK and covers 1979 to present.[114]

4.2.2.1.5 PsychINFO

The PsycINFO database provide international coverage on psychology and allied fields, to include research within clinical fields. It runs from 1806 to date.[114]

4.2.2.1.6 CINAHL

CINAHL (Cumulative Index to Nursing and Allied Health Literature) provides information from the field of nursing and allied health professionals. Journals from biomedicine, alternative therapies, health sciences and health promotion are scanned for relevant articles. CINAHL covers the period from 1981 to date and uses a thesaurus adapted from Medical Subject Headings (MeSH).[114]

4.2.2.1.7 Cochrane

The Cochrane Library contains seven databases that contain difference types of high quality, independent evidence to inform health-care decision making. The databases include: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and the Cochrane Methodology Register.[115]

4.2.2.1.8 TRIP

Trip is a clinical search engine designed to provide access to high quality clinical research. The database has been online since 1997.[116]

4.2.2.1.9 SCI-EXPANDED

SCI-EXPANDED (Science Citation Index Expanded™), is accessed via Web of Science™ and provides a bibliographic and citation index from 8500 of scientific and technical journals from 150 disciplines.[117]

4.2.2.1.10 CPCI-S

CPCI-S (Conference Proceedings Citation Index – Science) is accessed via Web of Science™ and holds research published from conferences, symposia, seminars, colloquia, workshops and conventions. By including conference proceedings, the resource aims to provide the user with research beyond that included in current journal literature. The resource has been on line since 1990.[118]

4.2.2.2 Design of searches

The electronic databases were searched using a combination of free-text, MeSH and database specific headings. The full search strategies can be found in Appendix C. These search strategies were developed with the input of experts in health informatics and used some pre-existing strategies available within the Primary Care Centre Versus Arthritis, already developed to identify particular types of study.

"Carpal tunnel syndrome" was searched for using MeSH (or database-specific equivalent) terms and in free text. MeSH headings were 'exploded' to broaden their definition. Terms such as 'entrapment neuropathies' were included to ensure the search remained sensitive. The searches were combined using the Boolean operator "OR."

4.2.2.3 Additional search methods

4.2.2.3.1 EthOS

EthOS (Electronic Thesis Online Service) was searched from 1990 to December 2013 to identify previous theses relevant to carpal tunnel prognosis.

4.2.2.3.2 Charity websites: Arthritis Research UK

The Arthritis Research UK website (now: *Versus Arthritis)* was searched for further references.

4.2.2.3.3 Contacting experts

Dr Graham Davenport, an Royal College of General Practitioners (RCGP) Musculoskeletal Champion and Prof Christina Jerosch-Herold, the Principal Investigator of a large cohort study investigating the prognosis of carpal tunnel syndrome, were approached and asked to search their personal literature collections for any further studies, not identified by the methods reported here.

4.2.2.3.4 Conference Abstracts

Conference abstracts from the Primary Care Rheumatology Society (now the Primary Care Rheumatology and Musculoskeletal Medicine Society – PCRMM) were searched from 2005 onwards. British Society of Surgery to the Hand / British Association of Hand Therapists combined scientific meeting abstracts were also searched.

4.2.2.3.5 Reference checking

References of all included full-text articles were hand-searched.

4.2.2.3.6 Google Scholar

The first 15 pages of Google scholar results for "carpal tunnel syndrome and prognosis" were searched to ensure all hits had been identified by the search.

4.2.3 Selection of eligible studies

The citations identified using the methods described above were downloaded using Ovid SP and then transferred to and stored in REFWORKS (Legacy version). Duplicates were removed. All titles were screened against the eligibility criteria by the author. Full text review was undertaken for any abstract that could not be confidently excluded and could potentially fulfil the inclusion criteria. Abstracts and full texts were assessed independently by a second author (Dr Linda Chesterton – LC) to determine agreement. Any disagreements or queries were arbitrated through discussion.

4.2.4 Assessing the risk of bias

Whilst 'assessment of study quality' has been used to describe the critical appraisal of studies, this term also implies the extent to which the research was conducted to the highest standard. The quality of a study does not necessarily influence the likelihood of the conclusion being correctly estimated. 'Risk of bias' is a preferred construct to consider when assessing the extent to which the results of a study can be believed. Bias is a systematic error in results or inferences, which lead to an over or under-estimation of the truth. Differences in the risk of bias can help explain observed variation (or heterogeneity) between studies. A more rigorous study with a lower risk of bias is more likely to provide estimates closer to the truth. False positive conclusions may be drawn if the study effect is overestimated or the erroneous rejection of a true conclusion made if bias leads the effect to be underestimated. It is therefore important to consider the risk of bias of each study and consider this risk when pooling or combining effects.[119]

In order to assess the risk of bias in prognosis studies, the Quality in Prognosis Studies (QUIPS) tool was used.[120] It was decided to use this tool as opposed to other tools designed to assess the quality of non-randomised studies, such as the Newcastle-Ottawa Scale,[121] as this review was particularly focused on investigating predictors of outcome (i.e. prognosis and prognostic factors). QUIPS was developed specifically for this purpose, using a modified Delphi approach and nominal group technique, to define items which assess risk of bias in the six identified domains: 1. study participation; 2. study attrition; 3. prognostic factor measurement; 4. outcome measurement; 5. study confounding and 6. statistical analysis and reporting. Where studies investigated overall prognosis of untreated CTS and did not report on prognostic factors, bias domain 3 was not scored, as it was irrelevant. Bias domain 5 (study confounding) was scored in these studies, to judge if outcome could indeed be attributed to untreated CTS or whether or not confounding by treatment may have been present.

4.2.4.1 Using the QUIPS Tool

For each of the six domains, the tool provides a number of cues as summarised in Table 4-3. In order to inform the judgement of the risk of bias within each study, supporting information and comments based on these cues were required from the publications. The author and LC made judgements and any disagreements were then brought to discussion, after which 100% agreement was achieved.

Each cue and then each domain was graded as having a high, moderate or low risk of bias. To judge the overall risk of bias, studies were attributed a label of 'a low risk of bias' if all or most domains were described as low risk and at high risk of bias if all or most of the domains were judged as high risk. Studies were judged as being of moderate risk if all or most of the domains were of moderate risk.[120]

Table 4-3 Bias domains and cues provided by the QUIPS tool

Bias domains and associated cues
1. Study participation Source of target population, method used to identify population, recruitment period, place of recruitment, inclusion and exclusion criteria
2. Study Attrition Proportion of baseline sample available for analysis, attempts to collect information on participants who dropped out, reasons and potential impact of subjects lost to follow-up, outcome and prognostic factor on those lost to follow up
3. Prognostic Factor Measurement Definition of prognostic factor, valid and reliable measurement of prognostic factor, method and setting of prognostic factor measurement, proportion of data on prognostic factor available for analysis, method used for missing data
4. Outcome Measurement Definition of outcome, valid and reliable measurement of outcome, method and setting of outcome measurement
5. Study confounding Important confounders measured, definition of the confounding factor, valid and reliable measurement of confounders, method and setting of confounding measurement, method used for missing data, appropriate accounting for confounding
6. Statistical Analysis and Reporting Presentation of analytical strategy, model development strategy, reporting of results

Online resource from: Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013 Feb 19;158(4):280-6.

4.2.5 Data Extraction

Data were extracted by CB and checked by LC using a pre-defined data extraction form, which had been piloted and edited to ensure the required and correct information was captured.

4.2.5.1 Data extraction from prognosis studies

Data extraction included: details of the study setting; population demographics; diagnostic criteria of CTS used; management approaches used; prognostic factors (type of variable and how they were measured); outcome measures applied (definition and instrument used); sample size; rate of attrition and length of follow up. Concerning disease course, the proportion of patients with a poor outcome following conservative treatment or no treatment were recorded. All reported prognostic factors were listed and measures of association with their significance levels recorded.

4.2.6 Analysis

Pooling of results was deemed not possible due to heterogeneity with regard to study setting, the case definition of CTS applied, widely varying follow-up periods, the prognostic factors tested and measures of outcome used. Results regarding the course of symptoms in patients with untreated and conservatively managed CTS were therefore summarised narratively. Findings for the reported prognostic factors were synthesised by taking into account the number of studies evaluating each factor, the risk of bias of these studies and the consistency of available evidence (defined as significant association in the same direction of effect). A level of evidence was attributed to each prognostic factor, based on Sackett et al[122] and Ariens et al[123] and adapted for use with the QUIPS tool as shown in Table 4-4.

Table 4-4 Levels of evidence for prognostic factors

Level of evidence	
Strong	Consistent findings (≥ 75%) in at least 2 cohorts with a low risk of bias
Moderate	Consistent findings (≥ 75%) in one cohort with a low risk of bias and at least one cohort with a moderate/high risk of bias
Weak	Findings of one cohort with a low risk of bias or consistent findings (≥ 75%) in at least 3 or more cohorts with a moderate / high risk of bias
Inconclusive	Inconsistent findings irrespective of study quality, or less than 3 cohorts with a moderate / high risk of bias
No evidence	No data presented

Table based on Sackett et al[122] and Ariens et al[123]

4.3 Results

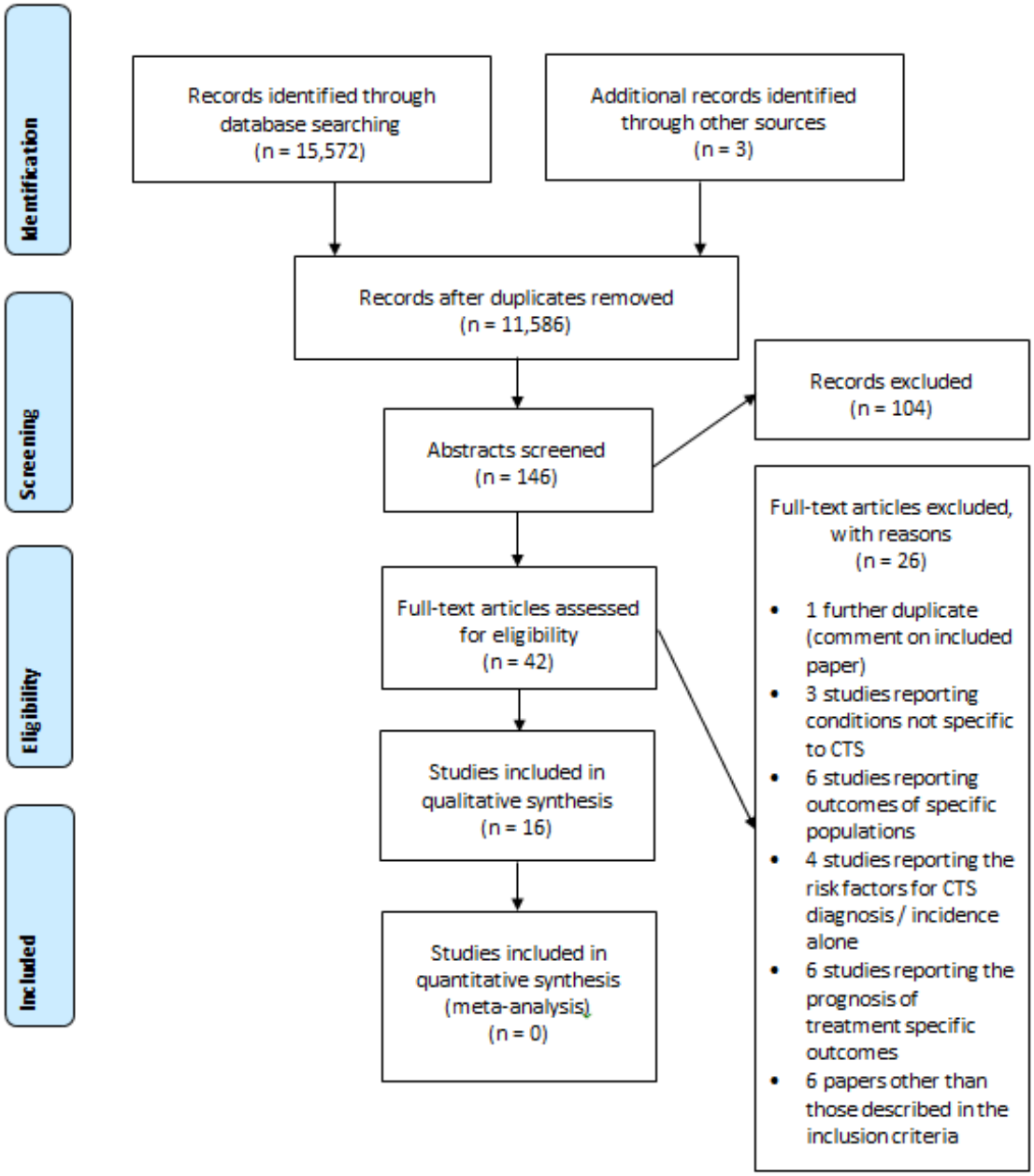
4.3.1 Summary of search results

15,572 citations were identified by the search. The number of citations from each source are shown in Table 4-5. As summarised in Figure 4-1, there were 11,586 citations after duplicates were removed, 146 following title screening and 42 following abstract screening. There were 16 studies included following full text screening.

Table 4-5 Summary of search results

Source	Number of citations
CINAHL	707
AMED	197
PsychInfo	92
HMIC	19
EMBASE	6445
Medline	6987
TRIP	0
Cochrane	755
SCI-EXPANDED + CPCI-S	370
Total	**15,572**

Figure 4-1 PRISMA flow diagram



4.3.2 Study characteristics

Table 4-6 summarises the characteristics of the studies including the QUIPS score, study design and setting, study population, interventions used in the study, the primary outcome measure including the definition of a poor outcome, and duration of follow-up. The table also presents the percentage of the cohort experiencing a poor outcome (e.g. proceeding to surgery) of conservative or no management.

One study was a retrospective follow-up study of CTS cases identified in the Marshfield Epidemiologic Study Area, a population-based cohort in the USA.[124] All other studies were based in secondary or tertiary care, of which six were surgical clinics and eight EMG laboratories. No studies were conducted in a primary care setting.

The case definitions used to identify CTS differed between studies: six studies utilised clinical features only, whilst the remaining ten studies required an accompanying electrophysiological abnormality to be present. The combination of clinical characteristics used and the electrophysiological classification criteria also varied between studies. The interventions and combinations of interventions used in the conservative management of CTS in the studies included; wrist splinting (seven studies), non-steroidal anti-inflammatories (NSAIDS) (three studies), other analgesia (two studies), oral steroids (three studies), local steroid injections (six studies) and paraffin wax heat treatment (one study). Three studies provided conservative management without specifying which interventions were used. In four studies, the natural course of CTS was observed.[69, 125-127] In some studies, parts of the cohort were treated surgically after initial conservative management. Surgical outcomes for these patients were not included in the review and surgery became the endpoint of observation. A range of outcome measures were applied: three studies used a surgical episode as a proxy for a poor outcome; one study used the *Quick*dash score;[128] five used measures of global improvement; two used a change in symptom and function severity scores; one used the Historic and Objective Scale (Hi-OB)[129]; one used work absence; two observed electrophysiological changes and one used absence of clinical contact as an indicator of recovery. The follow-up periods ranged from 12 weeks to 10 years.

Table 4-6 Summary of study characteristics and results regarding the course of symptoms of prognostic cohort studies in carpal tunnel syndrome

Author, year of publication and country	Risk of bias (QUIPS score)	Study population	Interventions provided to entire cohort	Primary outcome measure / duration follow - up	Measure of poor outcome of conservative management	Proportion of patients treated conservatively experiencing a poor outcome
Treated populations: prospective cohort studies						
Boyd et al. 2005 **Canada**	High	Setting: tertiary hand and upper limb centre CTS diagnosis: clinical findings and electrophysiological abnormality 68% female Mean age: 49.3 years N=25 patients (47 wrists) Drop-out = 17%	Splint: all wrists Surgery: 27 (57%) wrists	No surgery versus surgery by six months 12 weeks, with an option to continue follow-up >six months	Progression to surgery	57% of wrists
Duckworth et al. 2013 **Scotland**	Moderate	Setting: hand clinic CTS diagnosis: clinical findings and electrophysiological abnormality 67% female Mean age: males 57 (s.d. 14) years; females 54 (s.d. 14) years N=275 patients	Splint: all patients Injection: 150 (55%) (of whom 38 had surgery) Surgery: 122 (44%) patients No further treatment: 3 (1%) patients	*Quick*DASH Score 1 year	Progression to surgery	58% of patients

		Drop-out = 28%				
Goodwill. **1965** **England**	High	Setting: EMG laboratory CTS diagnosis: paraesthesia and pain with electrophysiological abnormality 93% female Age bands: 30-39: 7 40-49: 19 50-59: 39 60-69: 18 70+: 13 patients N=96 patients (155 wrists) Drop-out = 0%	Splint: 98 (63%) wrists Injection: 58 (37%) wrists Surgery: 55 (35%) wrists	Judgement made at follow-up: cured, temporary relief or no relief 1 - 3 years (average 14 months)	Evidence of symptoms	Following corticosteroid injection: 88% of patients Following splinting: 89% of patients Following surgery: 5% of patients
Kaplan, Glickel & Eaton. **1990** **USA**	High	Setting: hand clinic CTS diagnosis: presence of pain or paraesthesia and clinical findings (thenar atrophy, altered sensation or Phalen's sign) 75% female Mean age 55 years N = 229 patients (331 wrists) Drop-out = 12%	Splint: 'most patients' Non-steroidal anti-inflammatory: 149 (65.2%) patients Oral steroid: 61 (26.8%) patients Steroid injection: 38 (16.4%) patients	Success of therapy as defined by absence of symptoms for > six months Minimum of six months or until had surgical release (average 15.4 months)	Evidence of symptoms after six months Progression to surgery	82% of wrists 66% of wrists

Katz et al. 1998 a **USA**	Moderate	Setting: surgical clinics CTS diagnosis: paraesthesia involving at least 2 digits (thumb or index, middle or ring fingers) and symptom duration of at least 1 month 74% female Surgical cohort: >55yr mean age 68.0 years (sd 9.1); <55yr compensation non recipient 42.0 years (sd 7.3); compensation recipient mean age 39.0 years (sd 8.1). Non-surgical cohort >55yr mean age 64.0 years (sd 7.0); compensation non-recipient mean age 41.0 (sd 8.9); compensation recipient mean age 37.0 years (sd 8.8) N = 297 patients Drop-out = 31%	Non-surgical cohort: 34 patients received surgery at less than 3 months and were not included in analyses By 30 months: Splint: 76 (94%) patients Injection: 36 (44%) patients Physical or occupational therapist: all	Change in status in symptom severity, functional limitations and health status were recorded over time. Associations were measured for patients crossing between non-surgical to surgical cohorts after > 3 months. Follow up took place at 6, 18 and 30 months	Would not be happy to live the rest of their lives with symptoms	60% of patients
Kiylioglu et al. 2009 **Turkey**	Moderate	Setting: EMG laboratory CTS diagnosis: clinical findings,	Treatment methods not controlled or standardised	Symptom severity score and functional status (Boston questionnaire	Percentage improvement in symptom severity scale	Rehabilitation 82% Surgery 77% Untreated 25%

		supported by electrophysiological abnormality. 90% female Diabetic rehabilitation group mean age 59.3 years (sd 7.4); diabetic untreated group mean age 54.6 (sd 11.1); idiopathic rehabilitation group mean age 47.8 years (sd 9.9); idiopathic surgery group mean age 49.2 (sd 9.8) N = 42 patients (80 wrists) Drop-out = 0 (assumed)	'Rehabilitation': patients treated with splints, paraffin treatments and / or oral non-steroidal anti-inflammatories	translated into Turkish) Patients were followed up in the early follow-up period (3-5 months) and late follow up period (6-12 months)	Percentage improvement in function severity scale	Rehabilitation 73% Surgery 85% Untreated 17%
Treated populations: retrospective cohort studies						
Kouyoumdjian et al. 2003 **Brazil**	High	Setting: EMG laboratory CTS diagnosis: symptoms including hand paraesthesia, numbness and pain mainly at night. 95.8% female Surgical cure group mean age 46 years	Surgery: 147 (66%) wrists Non-surgical (splint, local injection, medication and others): 75 (34%) wrists	General patient satisfaction: complete relief; improved "much better"; improved "little"; unchanged; worsened Poorly recorded. Between 5-10 years,	Symptoms unchanged or worse	23.7% of wrists

		(range 24 – 70); unchanged / worse group 44 years (range 39 – 58); non-surgical cure group mean age 61 years (range 48 – 79); worse group 50 years (range 30 – 83) N = 165 patients (222 wrists) Drop-out = 69%		(mean 5.9 years following surgery)		
Lian, Urkunde & Verma. **2006** **Singapore**	High	Setting: EMG laboratory CTS diagnosis: clinical history and examination, confirmed using AAEM criteria and additional testing if this was normal 81.3% female Mean age 53.6 years N = 115 Drop-out 14%	Conservative management: 88 (77%) patients Surgery: 27 (23%) patients	Clinician review of medical records and decision made as to category: resolved; improved; same; worse Follow up took place at 3 and six months (limited data available)	Symptoms unchanged or worse	68.5% of patients
Miranda, Asaad & Cerovac. **2013** **UK**	High	Setting: plastic surgery clinic CTS diagnosis: based on clinical symptoms	Injection: 66 (49%) patients Surgery: 68 (51%) patients	Symptom relief and / or surgery 22.5 +/- 0.5 months	Progression to surgery	62% of patients

		Gender not reported Mean age 56 years (sd 3) N = 134 Drop-out 10%				
Muhlau, Both & Kunath. **1984** **Germany**	Moderate	Setting: EMG laboratory CTS diagnosis: distal motor latency was >4.7ms Gender and age not reported N = 157 (214 wrists) Drop-out 38%	Conservative management: 72 (48%) wrists Surgery: 112 (52%) wrists	An overall categorisation was made at follow up: cured; clear improvement; slight improvement; unchanged findings; further deterioration. These were then dichotomised so that groups 1 and 2 = cured and 3,4 and 5 = not cured. Follow up was at least 2 years and defined as when the patient had reached a 'steady state'	No evidence of cure	68% of patients
Treated populations: Retrospective follow-up study of a population-based case series						
DeStefano, Nordstrom & Vierkant. **1997** **USA**	Moderate	Setting: patients identified from the Marshfield Epidemiologic Study Area CTS diagnosis: ICD-9-CM code 354.0 and evidence of a	Analgesia: 143 (34%) patients Non-steroidal anti-inflammatories: 132 (31%) patients	No surgery versus surgery and resolution of symptoms Median follow- up 1979 - 1983: 12.0 years (5 and 95th	Evidence of symptoms	1 month: 75% of patients 2 years: 40% 8 years: 22%

		clinical and / or electrophysiological abnormality in the records. 62% female Mean age 62 years N= 425 Drop-out 0%	Injection: 6 (1%) patients Splint: 295 (69%) patients Surgery: 198 (47%) patients	percentiles:10.0 and 14.8 respectively). 184-1988: 7.3 years (5.0-9.8)		
Treated populations: Secondary analysis of Katz et al.1998 a						
Katz et al 1998 b **USA**	Moderate	Setting: surgical clinics CTS diagnosis: paraesthesia involving at least 2 digits (thumb or index, middle or ring fingers) and symptom duration of at least 1 month 72% female Mean age 43 years (sd 11) N= 253 patients Drop-out = 20%	Surgery: 179 (71%) patients	Out of work at 18 months Questionnaires were completed at 6, 18 and 30m	Work absence at 18 months, due to CTS	23% of patients
Untreated populations: prospective cohort studies						
OrtizCorredor et al. 2008 **Columbia**	High	Setting: EMG laboratory CTS diagnosis: as per Rempel et al	The course of untreated CTS was observed	The Historic and Objective Scale (HiOb) was used as the clinical	Deterioration in the Historic and Objective Scale	23.4% of patients

		81.1% female Mean age 48.8 years (sd 10.2) N = 132 patients Not possible to determine drop-out		classification. The electrophysiological classification was according to Padua 1997 (mild; moderate A; moderate B; Severe; Extreme) 24.2 months (sd 4.2)		
Padua et al. 1998 **Italy**	Moderate	Setting: EMG laboratory CTS diagnosis: based on neurophysiological evaluation graded: negative, minimal, mild, moderate, severe and extreme (Padua et al). 78.8% female Mean age 48.8 years (sd 10.2) N = 80 Drop-out 84%	The course of untreated CTS was observed	Patient reported global improvement scale: stable, worse, improved Neurophysiological classification: negative, minimal, mild, moderate, severe, extreme 11.six months (range 5-23)	Clinical outcome: unchanged Clinical outcome: worse	Electrophysiological classification Negative 50% Minimal 38% Mild 15% Moderate 27.5% Severe 0% Extreme 50% Negative 50% Minimal 31% Mild 58% Moderate 45% Severe 20% Extreme 0%
Padua et al. 2001 **Italy**	Moderate	Setting: EMG laboratory CTS diagnosis: based on clinical diagnostic criteria proposed by the American Academy of Neurology and	The course of untreated CTS was observed	Electrophysiological changes, patient reported changes and clinical changes were used to describe if patients had: improved,	Neurophysiologic class Symptoms Function	Stationary 57% Worsening 16% Stationary 45% Worsening 21% Stationary 61% Worsening 16%

		the American Association of Electrodiagnostic Medicine 82% female Mean age 52.0 years (sd 13.4) N = 202 (267 wrists) with a further 62 (87 wrists) re-evaluated by phone Drop-out 34%		remained stationary or worsened. 10 - 15 months	Historic and objective scale Pain	Stationary 46% Worsening 32% Stationary 62% Worsening 12%
Untreated populations: retrospective cohort studies						
Resende et al. 2003 **Brazil**	High	Setting: EMG laboratory CTS diagnosis: clinical findings, supported by electrophysiological abnormality Patients in an EMG lab with a diagnosis of CTS based on. N=12 Drop-out not possible to determine	The course of untreated CTS was observed	Clinical and electrophysiological changes were observed. 4 – 9 years	Conduction studies	Marked improvement 25% (of which 100% had improvement in symptoms) Slight improvement 15% (of which 33% had worsening of clinical symptoms) No significant change 50% (of which 50% had worsening of clinical symptoms) Worsening 10% (of which 50% had worsening of clinical symptoms)

4.3.3 Risk of bias

The results of the assessment for the risk of bias are presented in Table 4-7. The percentage agreement with regard to judgement of the overall risk of bias was 75% and 100% following discussion. Further adjudication was therefore not required.

The prognostic factor domain was not assessed in the four studies investigating course of CTS symptoms only. Eight studies were judged to have a moderate risk of bias and eight to have a high risk of bias. The domains that carried a particularly high risk of bias across all studies were: study attrition (12 studies); study confounding (10 studies) and statistical analysis and reporting (nine studies). Study attrition tended to be at high risk of bias as the follow-up response rates in several studies were low and the reporting of attempts to collect information on participants who dropped out was often lacking. Reasons for loss to follow-up were seldom provided and differences between those lost to follow-up and those actively followed up were not frequently compared. A high risk of bias due to confounding was also a frequent finding, largely because not all potential confounders were appropriately accounted for and hence the observed associations of the candidate prognostic factors with outcome were likely to be at least partly explained by other (unmeasured) variables. This was particularly true in studies using retrospectively collected data. Statistical analysis and reporting was commonly identified as being of a high risk of bias as presentation of the data was frequently insufficient and in some studies selective reporting of results was evident.

Table 4-7 Results of the methodological assessment of prognostic cohort studies on CTS (Hayden et al., 2013)

Author (year)	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	Overall Risk of bias
Studies including an analysis of prognostic factors							
Boyd et al. 2005	High	High	Moderate	Moderate	Moderate	High	**High**
DeStefano, Nordstrom & Vierkant. 1997	Low	Moderate	Moderate	Moderate	Moderate	Moderate	**Moderate**
Duckworth et al. 2013	Moderate	High	Moderate	Moderate	High	Low	**Moderate**
Goodwill. 1965	High	High	High	High	High	High	**High**
Kaplan, Glickel & Eaton. 1990	High	High	High	High	High	High	**High**
Katz et al. 1998a	Low	Moderate	Moderate	Moderate	Low	High	**Moderate**
Katz et al 1998b	Low	High	Moderate	Low	High	Low	**Moderate**
Kiylioglu et al. 2009	Moderate	High	Moderate	Moderate	Moderate	High	**Moderate**
Kouyoumdjian et al. 2003	Moderate	High	Moderate	Moderate	High	High	**High**
Muhlau, Both & Kunath. 1984	Moderate	High	Low	Moderate	Moderate	Low	**Moderate**
Padua et al. 2001	Low	Moderate	Low	Moderate	Moderate	Moderate	**Moderate**
Studies observing the course of CTS only (with no analysis of prognostic factors)							
Lian, Urkunde & Verma. 2006	High	High	Not applicable	High	High	High	**High**
Miranda, Asaad & Cerovac. 2013	High	High	Not applicable	High	High	High	**High**
OrtizCorredor et al. 2008	Moderate	Moderate	Not applicable	Low	High	High	**High**
Padua et al. 1998	High	High	Not applicable	Low	High	Low	**Moderate**
Resende et al. 2003	High	High	Not applicable	High	High	Moderate	**High**

4.3.4 Course of carpal tunnel syndrome

For each included study, Table 4-8 describes the course of CTS in conservatively managed or untreated patients, by describing the proportion of patients who experienced a poor or unsatisfactory outcome, the definition of which varied between studies (i.e. persisting or worsening symptoms, progression to surgery, or work absence due to CTS). Table 4-8 also summarises results regarding the course of CTS in terms of the percentage of patients reporting a poor outcome for different follow-up time points in order for between study comparisons to be made.

Four studies examined the course of untreated CTS.[69, 125-127] OrizCorredor et al observed that of 132 patients with untreated CTS over a 2 year period, 23.5% showed a deterioration in the Historic and Objective Scale (HiOb) score but most patients did not show an electrophysiological deterioration (89 remained the same, 33 recovered and 10 deteriorated). Only one patient experienced both electrophysiological and clinical deterioration.[126] Padua 1998 et al reported whether the clinical outcome was unchanged or worse in groups of patients with different electrophysiological classifications. They found the clinical outcome was worse in 50% of patients with negative electrophysiology, 27.5% with moderate electrophysiological findings and 50% with extreme results.[125] Padua 2001 et al further observed the electrophysiological, symptomatic, functional, HiOb and pain changes in patients with CTS. They reported that between 12% and 32% of patients depending on their classification of electrophysiological severity worsened over time, whilst between 23% and 34 % of patients improved.[69] Resende et al presented the change in electrophysiological measures and accompanying change in symptoms over four to nine year periods. They reported that 25% of patients had a marked improvement in electrophysiological outcome (100% of whom had improvement in terms of symptoms); 15% showed slight improvement (of whom 33% had worsening of symptoms); 50% showed no significant change (of whom 50% had worsening in terms of symptoms) and 10% had a worsening of electrophysiological measurements (of whom 50% had a worsening of clinical symptoms).[127]

In summary, a range of 32 - 58% of participants receiving no treatment for CTS were reported to have a poor outcome at 12 months follow-up in two studies,[69, 125] both of which were of moderate risk of bias. The studies reporting outcomes at 3 and 10 years reported a poor outcome in 23.4% [126] and 50% [127] of participants respectively; both studies were at high risk of bias.

In the nine cohorts of patients receiving conservative treatment: 68.5% to 75% of patients were reported to have a poor outcome within three months follow-up; [130, 131] 82% within six months follow up [132]; 23 – 89% within a 3 year follow up [124, 133-136] and 22 – 24% within 10 years follow up.[133, 137] A wide variation in findings was noted according to risk of bias, with studies of a moderate risk of bias appearing to show lower percentages of patients with a poor outcome (e.g. 23 – 68% at 3 years [124, 133-135]), compared to studies considered to be at a high risk of bias (82% at six months) [132] and 89% at 3 years.[136] Four studies used a surgical episode as a marker of a poor outcome of conservative management [68, 132, 138, 139]. A range of 57% to 66% of patients were observed to receive surgery following conservative management over a period of between 1 and 3 years.[68, 132, 138, 139] The reported course of conservatively managed CTS was highly variable but on average symptoms improved over time in most study populations.

Table 4-8 Course of carpal tunnel syndrome in conservatively treated or untreated patients (percentages not cumulative)

Number of studies	Sample size range	% of cases reporting deterioration within 3 months	% of cases reporting deterioration within six months	% of cases reporting deterioration within 12 months	% of cases reporting deterioration within 3 years	% of cases reporting deterioration within 15 years
Untreated cases						
4 [69, 125-127]	12 – 344	NA	NA	32 - 58	23.4	50
Studies observing cases receiving surgery as a consequence of conservative management failure (% of patients receiving surgery NOT outcome of surgery)						
4 [68, 132, 138, 139]	47 - 331	NA	57	58	62 - 66	NA
Studies of conservatively managed patients reporting other definitions of negative outcome						
9 [124, 130-137]	80 - 425	68.5 - 75	82	*% improvement of up to 82% **	23 - 89	22 - 23.7
The percentages shown are not cumulative as it cannot be assumed that patients reporting a change in symptoms at six months would not have reported something different at an earlier or later date if the study had provided them with such opportunity Abbreviation: NA, not applicable *% change provided in a positive direction [131]						

Table 4-9 presents candidate prognostic factors tested in the studies and the reported associations with outcome. Not all studies presented estimates of association with confidence intervals. Some presented *P* values only; some simply reported a finding as non-significant. Therefore, the number of studies investigating each candidate prognostic factor, the number of studies at moderate or high risk of bias (none were of low risk) and the number showing an association (direction and significance) are summarised.

In total 39 candidate prognostic factors were identified from the studies. All of these were found to have inconclusive levels of evidence of an association with poor outcome. This was due to inconsistencies between study findings, non-significant results, low numbers of studies investigating each factor and the moderate to high risk of bias of the studies included.

Table 4-9 Prognostic factors and strength of association for an unfavourable outcome of carpal tunnel syndrome in patients who are conservatively treated or untreated

Prognostic factor	Direction of association and significance	Risk of bias (number of studies)	Number and % of studies demonstrating predictive association with a poor outcome *(statistically significant)*	Level of evidence
Demographic characteristics				
Female gender	+* [139] + [124] 0 [133,135,134] 0[132]	Moderate (5) High (1)	2/6: 33% *(1/6: 17 %)*	Inconclusive
Increasing age (group not otherwise specified or >50 years)	+* [69,134] 0 [135, 133] -*[139, 131, 124] +* [132] -*[138] -[137]	Moderate (7) High (3)	3/10: 30 % *(3/10: 30 %)*	Inconclusive
Obesity	+ [124] -* [131]	Moderate (2)	1/2: 50% *(0/2: 0%)*	Inconclusive
Litigation	+* [134] 0 [135, 133]	Moderate (3)	1/3: 33% *(1/3: 33%)*	Inconclusive
Deprivation quintile	- [139]	Moderate (1)	0/1: 0 %	Inconclusive
Vibration tool use	- [139]	Moderate (1)	0/1: 0 %	Inconclusive
Occupation status	+*[134]	Moderate (1)	*(1/1: 100)%*	Inconclusive
Smoking	+[139]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Comorbidities				
Diabetes	+* [131]	Moderate (1)	*(1/1: 100%)*	Inconclusive
Diabetes *or* hypothyroid	+[124]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Pregnancy *or injury associated CTS*	- [124]	Moderate (1)	0/1: 0 %	Inconclusive
Arthritis	+[124]	Moderate (1)	1/1: 100%	Inconclusive

			(0/1: 0%)	
Previous fracture or sprain	0[132]	High (1)	0/1: 0 %	Inconclusive
Stenosing flexor tenosynovitis	+*[132]	High (1)	*(1/1: 100%)*	Inconclusive
Mental health status	+*[134]	Moderate (1)	*(1/1: 100%)*	Inconclusive
Disease characteristics				
Tinnel's sign positive	+ [139]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Phalen's sign positive	+*[69] + [139] +*[132]	Moderate (2) High (1)	3/3: 100 % *(2/3: 67%)*	Inconclusive
Thenar wasting	+* [133] +[139] +*[132]	Moderate (2) High (1)	3/3: 100 % *(2/3: 67%)*	Inconclusive
Paraesthesia	+*[132]	High (1)	*(1/1: 100%)*	Inconclusive
Abnormal two-point discrimination	0[135] +*[132]	Moderate (1) High (1)	1/2: 50% *(1/2: 50%)*	Inconclusive
Semmes Weinstein monofilament testing	0[135]	Moderate	0/1: 0 %	Inconclusive
Electrophysiological severity	+[139] 0[131] -*[69] +[136] -[137]	Moderate (3) High (2)	2/5: 40% *(0/5: 0%)*	Inconclusive
Symptom severity	-*[131] -*[69] +*[138]	Moderate (2) High (1)	1/3: 33% *(1/3: 33%)*	Inconclusive
Functional severity	+*[134] -*[131, 69] 0[138]	Moderate (3) High (1)	1/4: 25% *(1/4: 25%)*	Inconclusive
CTS category of severity[124]	+*[124]	Moderate (1)	*(1/1: 100%)*	Inconclusive
Sensory SF-MPQ	+[139]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Affective SF-MPQ	+[139]	Moderate 1	1/1: 100%	Inconclusive

			(0/1: 0%)	
SF-36	0[138]	High (1)	0/1: 0 %	Inconclusive
DASH	0[138]	High (1)	0/1: 0 %	
Hi-Ob	-*[69]	Moderate (1)	0/1: 0 %	Inconclusive
Visual analog scale	+[139]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Laterality: left only	-[124]	Moderate (1)	0/1: 0 %	Inconclusive
Laterality: right only	-*[124]	Moderate (1)	0/1: 0 %	Inconclusive
Laterality: left > right	-[124]	Moderate (1)	0/1: 0 %	Inconclusive
Laterality: right > left	-[124]	Moderate (1)	0/1: 0 %	Inconclusive
Bilateral	+*[69] +[139] 0[132]	Moderate (2) High (1)	2/3: 67% *(1/3: 33%)*	Inconclusive
Grip strength	0[135] m -[139] m	Moderate (2)	0/2: 0%	Inconclusive
Hand stress	-*[69]	Moderate (1)	0/1: 0 %	Inconclusive
Increasing symptom duration	+*[133], [69] +[131] +*[132] +[137]	Moderate (3) High (2)	5/5: 100% *(3/5: 60%)*	Inconclusive

0 = not significant and direction not provided + = predictive of a negative outcome - = not predictive of a negative outcome * = statistically significant	CTS - carpal tunnel syndrome SF-MPQ – Short-Form McGill pain questionnaire SF-36 **–** Short-Form 36 DASH – Disabilities of the arm, shoulder and hand questionnaire Hi-Ob – Historical objective scale

4.4 Discussion

4.4.1 Summary of main findings

Four studies observed the course of untreated CTS,[69, 125-127] which is helpful when considering the need for, or potential impact of treatment. Two studies suggest that a proportion, ranging between 32% - 58%, of yet to be identified patients will recover or remain stable in the absence of treatment in the initial 12-month period following diagnosis.

Because of inconsistencies between study findings and the lack of studies with a low risk of bias, it was not possible to identify conclusive evidence for any of the factors reported by individual studies as predictors of a poor (or unsatisfactory) outcome of conservative management.

There was however 100% agreement in at least three or more cohorts with a medium or high risk of bias that: symptom duration; a positive Phalen's test; and thenar wasting were associated with a negative outcome of conservative management over variable time periods, however not all results were statistically significant and hence the overall judgement remained inconclusive.

4.4.2 Interpretation of results

A certain period of 'watchful waiting' may be sensibly and safely considered when discussing treatment options with patients. The results also indicate however, that up to 70% of patients deteriorate and are likely therefore to require further intervention, whether that be a further injection, an alternative approach to conservative management or surgery. When considering potential mechanisms for recovery without further treatment Padua et al 1998 suggest that certain undefined CTS cases are self-limiting due to a process of neural adaption, whereby the functional relationship between the nerve and the carpal tunnel adapts over time.[125]

Because of outcomes being measured at discrete time points by each study, it was not possible to provide a cumulative proportion of patients recovering in each period, which may have provided more

clear information about what happens to patients with CTS over time. The data does however show that a proportion of patients can be observed to have deteriorated from baseline at any point between 3 months and 10 years, suggesting that the course of CTS is likely to be widely variable. It is possible that the studies with longer follow up periods may also represent patients who improve and relapse over time, but as none of the studies were designed to observe the longitudinal course of CTS (i.e. at a week-to-week or month-to-month level), such a symptom course could not be illustrated by this review.

With regard to symptom relapse, only one study[136] specifically addressed this issue. Goodwill et al reported that 85% of patients initially responding to conservative treatment approaches relapsed within one to four years.[136] The possibility of future relapse therefore questions the validity of observations of studies conducted over a shorter time frame and may to some extent explain the variability in findings in terms of response to specific treatments.

The observed between-study variability may be explained by differences in study setting, study design, case definitions, interventions (the effectiveness of which cannot be compared between studies), and outcomes used but possibly also by differences in patient or disease factors (potential prognostic factors) between studies.

Due to a lack of robust design and conduct of most of the included studies, the overall body of evidence identified was judged to be of moderate or high risk of bias. This limited whether the synthesised evidence could be considered to be conclusive and as such, evidence regarding the predictors of outcome of untreated and conservatively treated CTS was considered to be weak.

None of the included studies were set in primary care. Apart from one study where data was collected from a general population sample, the further 15 studies were set in secondary care (including EMG laboratories). One could assume that by the time patients were reviewed in these settings and recruited to the study, time from symptom onset would have passed and recall bias affected the patients' report of baseline factors, or baseline factors were collected at a much later point in the

disease course. In order to mitigate this issue and to capture the first point of clinical presentation of CTS and its earliest management, it would be beneficial to set a prognostic cohort study in primary care, where it is likely most patients present with their symptoms and commence initial treatment.

4.4.3 Predictors of outcome following specified modalities of conservative management: studies not included in the review

This review included patients who had been treated using a 'usual care approach.' This means that studies in which all participants were treated according to a standardised treatment protocol (e.g. corticosteroid injection), were not included. Although such studies often aim to investigate response to a specific treatment, predictors of treatment effect (or treatment effect moderators or modifiers) are best identified through adequately powered randomised trials (see chapters 7 and 8). There were however a number of non-randomised studies or observational studies of a single arm of an RCT which aimed to identify predictors of response to a particular treatment modality that may be relevant to report here. These studies are identified below, and any potentially important information is highlighted.

Gerritsen et al analysed the data of patients who were randomised to the splinting arm of a trial and reported that symptom duration ≤ 1 year and severity of paraesthesia at night ≤ 6 predicted success of splinting (predicted success 62 % versus actual success 67%).[140]

Three further studies were identified which specifically observed the course of carpal tunnel syndrome following treatment with splinting and/or injection.

Graham et al performed a prospective study assessing the outcome of corticosteroid injections combined with wrist splinting in 73 patients (99 wrists). They reported that at 1 year, 10 affected hands (10.2%) remained asymptomatic and had not required surgery. This group had a significantly shorter duration of symptoms pre-treatment (2.9 months versus 8.35 months; *P* = 0.039, Mann-Whitney test)

and had significantly less sensory change at baseline (40 % versus 72 %; *P* = 0.048, Fisher's exact test), when compared to the group that required surgical intervention.[141]

In a five-year follow-up study of 824 patients who received a corticosteroid injection as treatment for CTS, Jenkins et al reported the overall 5-year rate of surgery was 15% at 1 year and 33% at 5 years. A multivariable Cox regression model showed that progression to surgery was independently associated with female gender (OR 2.06, 95% CI 1.50 - 2.83, *P* < 0.001), diabetes mellitus (OR 1.58, 95% CI 1.05 - 2.39, *P* = 0.029) and the presence of positive nerve conduction results (OR 7.62, 95% CI 2.43 to 23.9, *P* = 0.001).[142].

Meys et al also observed the course of CTS in patients treated with a local corticosteroid injection. Of the 113 patients treated with an injection, 67.4% required surgery by 12 months (much higher than observed by Jenkins et al). Multiple logistic regression showed that best performing model predicting a successful outcome of CSI included: a lower median nerve ultrasonographic cross-sectional area (CSA) at the pisiform bone (OR 0.76, 95% CI 0.61 – 0.95, *P* = 0.014); increasing age in years (OR 1.04, 95% CI 1.00 – 1.08, *P* = 0.041) and a decreasing symptom severity score (OR 0.44, 95% CI 0.23 – 0.87, *P* = 0.018).[143] Symptom duration was not significantly associated with the need for surgery, and there were no observations made for results of nerve condition studies or co-morbidities to compare with the results of Jenkins et al.

4.4.4 Methodological considerations

A range of electronic databases considered to be important and relevant to the topic at the time, were searched following advice from experts in health informatics. Titles were screened by the author only due to the large number and the pressures of time. It remains possible that studies not included in databases and not identified through reference checking, Google Scholar and expert advice may have been overlooked, for example unpublished cohort studies. As the review did not find strong evidence for any of the prognostic factors tested, it is felt unlikely that further unpublished material would have strongly influenced the review's conclusions.

Results of studies presenting only descriptive results and *P*-values were included in the prognosis review, without any risk estimates. All the potential evidence that was found was therefore included. It is possible that the lack of statistical significance in some studies was due to small sample sizes. This would contribute to a lack of stronger evidence for some of the included prognostic factors, rather than a genuine absence of association. Future prognosis research in the area of CTS should therefore ensure that estimates of associations with outcome are adequately reported and that the study population is of adequate sample size to investigate the hypothesised associations with outcome.

The unit of analysis differed between studies, i.e. some studies analysed outcomes at patient level (not necessarily taking into account the laterality of the condition); whilst others analysed outcomes at wrist level (patients with bilateral symptoms would be included as 2 episodes, not taking dependence of outcomes within individuals into account). Issues relating to the statistical analysis of bilateral CTS have been discussed at length by Page et al.[144] A unit-of-analysis error, which may give rise to overly narrow confidence intervals and small *P* values, may occur when data is analysed on the basis of the number of wrists without adjustment for non-independence.[144] Such an error may occur in prognosis research, including the reviewed studies, and be a further source of bias. Future prognostic studies should, where possible, consider this risk of bias in their design and analysis plan.

4.4.5 Clinical relevance of the findings

Patients presenting with CTS can be informed that there is evidence that some patients recover with no treatment or conservative treatment only. However, the proportion of patients who recover and the factors which may predict the likelihood of falling into this group have not been robustly determined. This is due to the fact that many of the studies have been based in secondary care, when one can assume patients' symptoms are selectively more severe and more likely to require surgery. Likewise, high attrition rates may lead to surgical rates being overestimated, if it is assumed most patients lost to follow up recovered.

Longer symptom duration, a positive Phalen's test and the presence of thenar atrophy are likely to predict poor outcome of conservatively managed CTS but need confirmation in further well-designed prognostic studies. Clinically, both a positive Phalen's test and thenar atrophy are diagnostic indicators of CTS, so their role as predictors may also collide with the fact that a case is more likely to represent CTS rather than an alternative diagnosis. Thenar atrophy particularly indicates denervation of the muscle and its presence is an accepted feature of severity and indicates the need for (urgent) carpal tunnel decompression.

The criteria and processes set by the review did not specifically identify electrophysiological severity as a significant predictor of a poor outcome of conservative management. This may have implications for services which ration surgery to patients with more severe results and suggest other factors should be taken into consideration alongside laboratory investigations.

4.4.6 Suggestions for further research

In order to improve future research, key recommendations would include to identify patients with CTS at baseline using an agreed case definition. Patients should be followed up for a prolonged period, if relapse of symptoms is of interest (over 3 years); preferably at a number of time points using a clinically meaningful, valid and reliable outcome measure. This would allow a longitudinal picture of CTS to be mapped. Attempts could be made to reduce attrition or better describe the risk of attrition bias by collecting information from non-responders and to provide a description and reason for any loss to follow up. Ideally, all potential prognostic factors should be included and measured at baseline using valid and reliable measures.[120]

4.5 Conclusion

The systematic review of available literature has demonstrated that the course of untreated and conservatively treated CTS is likely to be variable and currently unpredictable. No consistent evidence

was found regarding prognostic factors that may help predict which patients respond less well to the conservative treatments that can be offered in primary care.

The review highlights a number of gaps in the evidence with regard to the course, prognosis and conservative management of CTS in primary care and the need for further research in this area. The following chapter presents an analysis of data from primary care with the aim of developing a prognostic model that predicts an episode of surgery in patients presenting with CTS.

5 The prognosis of carpal tunnel syndrome: Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care – a cohort study set in the Clinical Practice Research Datalink

Summary

Following the systematic review and narrative synthesis of studies detailing the course and prognosis of conservatively managed carpal tunnel syndrome presented in chapter 4, this chapter presents a prognostic cohort study of patients from a primary care population. The aim of this (type 3 prognostic) study was to develop a prognostic model based on candidate prognostic factors, derived from the literature and expert opinion and available in primary care consultation data, to predict the risk of poor outcome in CTS, as defined by (the first occurrence of) carpal tunnel release surgery.

The work in this chapter has now been published in a peer-reviewed journal under a Creative Commons License:

Burton C, Chen Y, Chesterton LS, Van der Windt D. Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care. *Clinical Epidemiology*. 2018;10:739-748. doi:10.2147/CLEP.S154409.

5.1 Introduction

The development of two (type 3) prognostic models are presented in this chapter and the next. Each model predicts a different outcome or 'end-point.' The study presented in this chapter evaluates time to an episode of CTR, which is assumed to represent an inadequate outcome of the conservative management of CTS. The prognostic model developed in chapter 6 predicts patient reported outcome following the conservative management of CTS. The setting of each development dataset varies

between the prognostic models. The study in this chapter uses the electronic health data from a historical cohort of patients observed over time. The Clinical Practice Research Datalink and the use of consultation data in research has been introduced and discussed in chapter 3. Chapter 6 will use data from a prospectively designed randomised trial, where it was possible to add to the information requested from participants at baseline, and further analyse the results as a prospective cohort.

Firstly, the concept of type 3 prognosis studies will be introduced. Then, the way in which candidate prognostic factors were identified will be presented. Next, the methods applied for the prognostic model study in CPRD will be described, guided by the criteria provided by TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis),[145] and the results presented and discussed.

5.1.1 Prognostic model research

Other names for prognostic models include clinical prediction rules or tools and can be defined as:

> *"…a formal combination of multiple predictors from which risks of a specific endpoint can be calculated for individual patients."* [73] *pg 1*

A prognostic model translates the combination of multiple predictor (or prognostic factor) values of a particular individual with a given startpoint, into an absolute risk of that individual experiencing a particular endpoint (or outcome). Prognostic models are being used with increasing frequency in clinical practice, with the aim of enhancing informed decision making by providing estimates of likely outcomes for individual patients.[73]

Key steps in building a prognostic model include: its development; its validation and its impact evaluation in a clinical practice setting. The development of a prognostic model involves the identification of a startpoint, endpoint (outcome) and prognostic factors to be included in the regression analysis. The predictive performance of a model is likely to be optimistic when tested in development data, especially when sample size is limited. It is possible to adjust for this optimism using

statistical techniques and subsequently provide adjusted measures of the model's performance. It is preferable, before recommending a model for clinical use, to test its performance in different settings or datasets (external validation). Finally, the clinical and cost-effectiveness of a model should ideally be tested, in order to ensure that its application does indeed improve outcomes without causing harm and is economically viable to use in a particular clinical setting.[73]

In order to reduce the risk of optimism or spurious findings the candidate prognostic factors to be included in a model should be clinically reasonable. The next section describes the processes applied to identify the prognostic factors used in the development of the prognostic models described in this chapter and in chapter 6.

5.2 Identifying candidate prognostic factors

A separate piece of work was conducted by the author before the start of this PhD, during the development of the INSTINCTS trial. The aim of this work was to identify from the literature and expert opinion, a limited number of candidate prognostic factors and predictors of treatment effect that could be collected in the participant questionnaires and clinical report forms. This information would also be used to identify candidate prognostic factors to collect from CPRD. Four approaches were used to identify candidate predictors of outcome and treatment effect. These approaches will now be summarised and will also apply to the candidate predictors tested in chapters 6 and 8.

5.2.1 Rapid review of the literature

Firstly, a rapid review of the literature was carried out. This was not intended to be a full systematic review but rather a scoping exercise to identify potential predictors of outcome in carpal tunnel syndrome and its conservative management. This preceded the formal reviews presented in chapters 4 and 7. Medline, Embase, PsychINFO and CINAHL were searched for prognostic studies of carpal tunnel syndrome. In total, 5549 citations were retrieved and 2039 duplicates extracted. A title search reduced the number to 235 citations of which 59 were utilised after the abstracts or full papers were

read as required. 63 candidate predictors were identified from the 59 studies and are included in the summary table shown in Appendix D2 .

5.2.2 Clinical think-tank

General Practitioners, General Practitioners with a Specialist Interest in Musculoskeletal Medicine, Extended Scope Physiotherapists and Rheumatologists were invited from the Primary Care Centre Versus Arthritis at Keele University, to attend a think-tank at a time when the initial aims and objectives of this thesis were being identified. The specific aims of the think-tank were to:

a. Identify routine practice and clinical challenges experienced by practicing primary care clinicians in the diagnosis, investigation and management of carpal tunnel syndrome

b. Receive feedback on the proposed research questions in terms of clinical utility

Specific to the area of generating candidate prognostic factors, the group were asked:

- What patient features particularly worry you in terms of treatment outcome and prognosis and do you alter your management strategy based on these features?

Seven GP's and one Extended Scope Practitioner attended the think tank where semi-structured questions were asked to facilitate discussion. The results from these discussions are included in more detail in Appendix D2.

5.2.3 Survey of General Practitioners

Further to the clinical think-tank and as part of the development of the INSTINCTS trial questionnaires, a brief survey was designed and sent out by email to 30 GP collaborators of the INSTINCTS trial, requesting them to identify predictors of CTS outcome and its different treatments. The aim was to identify factors that may not be extracted from the literature due to their inherently clinical nature or absence of evidence for their prognostic value.

The trial collaborators were asked to list the factors they identified from 1 to 4 (weakest to strongest association) to allow subsequent ranking to take place, as a means of reducing the list of potential prognostic factors down to a number that was appropriate to include in the statistical analysis in chapter 6. The scores have been displayed as the sum of all the responses. Seven GP's (23%) responded after one reminder email. The table presenting the outcome of this survey can be found in appendix D1.

5.2.4 PRO-GRES study

Finally, candidate prognostic factors were identified from a previously conducted study,[146] which investigated the hypothesis that generic indicators can be used by GPs to assess the prognosis of older people with musculoskeletal pain. Methods including a GP survey and a systematic review of prognostic indicators for musculoskeletal pain in primary care had been used to develop a brief prognostic tool for use during the consultation.

The brief prognostic tool includes the following domains: higher pain intensity, longer duration, multiple site / widespread pain, higher disability, higher levels of anxiety and depression, older age, poorer physical health, manual occupation, higher BMI, coping strategies, social support. Items included in this prognostic assessment tool were considered as candidate predictors for the design of the prognostic models developed in this thesis.

5.2.5 Combining the candidate predictors from different sources

A total of 95 variables were identified as being candidate prognostic factors of the outcome of CTS and / or predictors of treatment effect. At this stage variables representing the same concept but indicating different directions (e.g. unilateral versus bilateral CTS) had not yet been merged. The factors identified by the four different methods of data collection were combined and grouped into themes: comorbidities, clinical characteristics and demographics, for use at the different stages of the thesis as summarised in appendix D2.

5.3 Methods

5.3.1 Developing the risk prediction model: participants (setting)

The study setting was the Clinical Practice Research Datalink, which has been described previously in section 3.3.1. The Independent Scientific Advisory Committee (ISAC) protocol for this study (14_167) was approved on 16th September 2014 and can be found in appendix A.

5.3.1.1 Inclusion criteria

The study population was derived from the incident cases identified in section 3.3.3, with a diagnostic Read code for CTS (Read code F340); as opposed to a treatment code (Carpal Tunnel Release or Carpal Tunnel Injection). This was in order to capture patients at their 'start-point,' i.e. as they first presented in primary care. A treatment code, whilst possibly being the first code used to denote a prevalent or incident episode, would suggest that this was not the patient's initial presentation in primary care. All incident patients, identified between 1991 and 2013 were required to have at least two years up to standard research quality data, preceding the date of diagnosis. This cut off was previously decided upon in order to identify a new episode of CTS for the epidemiology studies described in chapter 3. In this study the two-year period was also required in order allow opportunity for the baseline candidate prognostic factors to be recorded and reduce the risk of bias due to variable observation periods between patients. Patients were aged 18 years and older at diagnosis.

5.3.1.2 Exclusion criteria

Patients with an incident episode associated with a surgical code were excluded, as it was not possible to identify when the patient was likely to have first presented in primary care.

5.3.2 Developing the risk prediction model: selecting candidate predictors

The candidate predictors of CTS outcome identified in section 5.2 were subsequently assessed as to whether they could be identified in consultation data (i.e. by Read code or available linked data). Table

5-1 presents the initial list of candidate prognostic factors and the time between the code and index CTS consultation. Codes for candidate predictors recorded beyond 2 years preceding the CTS code could not be included as there would be no consistency in record availability beyond this time point (see inclusion / exclusion criteria).

Table 5-1 Initial candidate prognostic factors considered and their source in CPRD

Demographic characteristics

1. Age at diagnosis
2. Gender
3. GP Practice
4. Obesity (Read code)*
5. Excess alcohol consumption (Read code)*
6. Current or ex-smoker (Read code)*
7. Pregnancy status (Read code)**
8. Perimenopausal women (define by age band)

Comorbidities

9. Affective disorders (anxiety or depression) (Read code)*
10. Dyssomnia (Read code)*
11. Hypothyroidism (Read code)*
12. Diabetes (Read code)*
13. Inflammatory conditions (Read code)*
14. Other neck or upper limb disorders (Read code)*
15. Multi-site pain including osteoarthritis (Read code)*
16. Tendonitis / epicondylitis (Read code)*
17. Previous wrist trauma (Read code)*

Disease characteristics

18. Laterality of symptoms (free text)***
19. Phalen's sign (Read code / free text)***
20. Tinnel's sign (Read code / free text)***
21. Weakness of thenar wasting (free text / Read code)***
22. Outcome of nerve conduction studies (Read code / free text)***
23. Symptom severity (free text)***
24. Time between first consultation and start of treatment (Free text)
25. Unemployed / receiving benefits / work role functioning to be measured by sickness certification and free text

*Read code within 2 years prior to incident CTS consultation

**Read code within 1 year prior to incident CTS consultation

***Read code at time of consultation +/- 1 month

The candidate prognostic factors presented in Table 5-1 were tested in the CiPCA pilot study and further changes made following reflection on this exercise. 'Perimenopause' was dropped, as it is an indistinct term with no universally accepted classification and would be defined by age band and gender, which were already being included in the model development. Dysomnia was dropped as it was felt to be a consequence of CTS rather than a predictor. This change was also made knowing that poor sleep related to CTS symptoms could be included later in the prognostic model study based on INSTINCTS data (chapter 6). Neck and upper limb problems were limited to neck problems as the possible code list was extensive and overlapped with a number of other prognostic factors. There was also a substantial risk that codes relating to upper limb could represent poorly coded CTS rather than a distinct other problem. The pilot study demonstrated almost zero coding of Tinnel's and Phalen's test results. Sickness certification was also not included in the CPRD analysis as there was no accepted means of identifying sickness certification in CPRD (it was attempted in the epidemiology study based on Read code but results were considered to be unreliably low). Sickness certification is also not a baseline measure, rather a later consequence of the condition. Due to the national coverage of CPRD, region was included as a potential confounder due to known variabilities in the service provision of CTS services.[64] Deprivation was included as it was available through linkage and felt to be potentially important as a both a predictor in its own right and as a proxy for occupation. The final list of candidate prognostic factors tested in CPRD and the source of the Read code lists are presented below in Table 5-2.

Table 5-2 Final list of candidate prognostic factors

Prognostic factor	Method of measurement	Time period to be applied	Source of Read code list (where applicable)
Age at diagnosis	Routinely recorded data	At time of index date	
Gender	Routinely recorded data	At time of index date	
GP Practice	Routinely recorded data	At time of index date	
Region	Routinely recorded data	At time of index date	
Deprivation score	Routinely recorded data for practices which provide Index of Multiple Deprivation scores	2010 quintile score	
Obesity	Read code or from the Test table	The closest recorded value preceding the index date	
Alcohol status	Read code or from the Test table	The closest recorded value preceding the index date	
Smoking status	Read code or from the Test table	The closest recorded value preceding the index date	
Pregnancy	Read code	Read code within a 1 year period prior to the index date	Code list developed for purpose of this study using the Clinical Terminology Browser
Affective disorders	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies. through clinical consensus
Hypothyroidism	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies
Diabetes	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies [147]
Inflammatory conditions	Read code	Read code within a 2 year period prior to the index date	Code list developed for purpose of this study
Neck conditions	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Versus Arthritis Primary Care Centre
Multi-site pain (including osteoarthritis)	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Versus Arthritis Primary Care Centre
Tendonitis / epicondylitis	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Versus Arthritis Primary Care Centre and developed for purpose of this study

Previous wrist trauma	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Versus Arthritis Primary Care Centre and developed for purpose of this study

The incidence of CTS and the use of surgery was shown by the CPRD analyses in chapter 3 to have changed over time in a non-linear fashion. The year of diagnosis was therefore included in the unadjusted univariable analysis, but it was not included in the development of the multivariable model. Including the year of diagnosis would limit the external validity of the model by applying the epidemiology and healthcare practice at one time point to the observations in another time period. Ideally, in order to keep them contemporaneous, prognostic models should be updated regularly. Whilst not ideal, in that the model is based in historical data, the model therefore presents average treatment observations over time.

CTS associated with pregnancy is a well-recognised phenomenon and is likely to have a defined pathophysiological mechanism associated with hormonal changes. As such, its symptom course is likely to be different from non-pregnancy associated CTS. For this reason, univariable analysis was carried out but pregnancy associated CTS was not included in the multivariable model.

Obesity was identified as a candidate prognostic factor. It is usually advised to use a continuous outcome in prognostic models where possible rather than apply cut-points, so as not to lose information. However, in this situation the closest BMI data preceding the index date was taken and dichotomised as being < or ≥ 30 rather than tested as a continuous variable. This is because Read codes for obesity were also being used and it can be argued that there is a clinical reason for using a BMI ≥ 30 cutpoint, in that it is the definition of a discrete entity. Smoking and alcohol consumption were also more frequently observed as a categorical variable in CPRD (yes / no / unknown outcome to 'smoker' and 'alcohol drinker'), than as 'cigarettes per day' or 'alcohol units per week' which were populated infrequently. These variables were therefore presented as categorical rather than continuous outcomes, as this resulted in fewer missing data and was considered to be more clinically meaningful.

5.3.3 Developing the risk prediction model: outcome

The 'end-point' of the observation was a coded episode of carpal tunnel release surgery (CTR). The maximum length of follow up was set to three years. Surgery occurring more than three years after a baseline diagnosis was felt, following discussion with a GP musculoskeletal expert (GD), unlikely to be related to the index episode. Three years was chosen to include the 2-year presumed time period during which an episode was considered to be ongoing, plus one further year for referrals, investigations and surgery to take place. The Read codes used to define an episode of CTR (not including re-do procedures) are shown in Table 5-3

Table 5-3 Table of Read codes used to define a surgical outcome

Read Code	**Term**
70560	Carpal tunnel release
70564	Endoscopic carpal tunnel release
7056011	Carpal tunnel decompression

5.3.4 Statistical methods

5.3.4.1 Sample size

After the above iterative process, 17 candidate prognostic factors were identified that would be available in CPRD, to be included in the development of the prognostic model. It has been proposed that there should be at least 10 events per variable in a study using regression analysis to develop a prognostic model.[148] The issue of sample size will be further discussed in Chapter 6 where it is a more pertinent issue, since the CPRD cohort was very large and the parameter per variable rate was not a concern.

5.3.4.2 Statistical analysis

Time-to-event or survival modelling is used when: the timing of the outcome of interest is important; patients drop out over time and not all patients are followed until a particular time point. Survival

modelling allows for all patients who are eligible at baseline to be included (therefore reducing bias) until their last point of follow up; a process called censoring.

Cox proportional hazards modelling, a form of survival modelling, was used to determine the association between candidate prognostic factors and time to surgical intervention. It is acknowledged that patients may have required further surgery for revision or treatment of the contralateral hand, but for the purposes of this study the initial episode of CTS and subsequent primary CTS surgery was the sole focus.

Cox regression modelling allows for the association of variables (in this case candidate prognostic factors) with time to 'failure,' to be estimated.[149] Length of follow up is taken into account by the hazard rate derived by the model; the hazard rate being the probability of an event (surgery) occurring in the next instant of time, given it has not already occurred.[150] This type of analysis was useful in the scenario of this study, as the time of surgery (end-point) could be determined and patients could potentially be lost to follow-up out over time (were recorded as deceased, left the practice or their practice no longer contributed to CPRD). The hazard of having an episode of surgery is therefore estimated by a cumulative hazard function (H(t)), providing an average risk over the observed period, taking into account censored patients and the fact that the hazard rate may change over time.

Assumptions are made when applying a Cox proportional hazards model in that hazard functions should be proportional across different levels of a prognostic factor over time.[150] The assumptions of the proportional hazards assumption were checked in this study using Schoenfield residual testing.[151] If the assumption is not met, it is then possible to add covariate-time interactions to the model to overcome the issue.[152] Since for the reasons detailed above, year was not included in the model, time-varying covariates were not introduced. The model therefore presents the hazard of surgery averaged over the observed period.

Univariable (unadjusted) analysis was initially performed to identify the crude association of each prognostic factor with outcome. In order to be inclusive and reduce the risk of missing important

(combinations of) predictors, a backward selection procedure was applied to determine the prognostic factors in the final multivariable model. Prognostic factors with a *P* value > 0.1 were omitted at each step. 0.1 was chosen as the cut off rather than the more traditionally used 0.05, to reduce the risk of missing prognostic factors that had clinical importance.[153] Prognostic factors eliminated were re-entered in the final multivariable model with adjustment for the remaining prognostic factors to ensure that no omitted variable would be significant when other variables were not included in the model.

The performance (discrimination) of the final multivariable model was assessed using concordance statistics (C-statistics), which is analogous to the receiver operating characteristics (ROC) curve for binary data.[154] A C-statistic can be interpreted as the probability that the model correctly predicts an episode of surgery in a patient presenting in primary care with CTS, compared to those who do not have surgery. Flipping a coin (chance) would produce a C-statistic of 0.5. Given that the model performed poorly, further measures of model performance and validation were not carried out given it would not have clinical utility and further work, as presented in chapter 6 was planned.

5.3.4.3 Missing data

Missing data was judged to be 'missing not at random' (MNAR) (i.e. a patient with obesity was more likely to have a BMI recorded that someone who was not obese). Imputing data that is MNAR increases the risk of bias and Sterne et al suggest therefore that such missing data can only be addressed through sensitivity analyses examining the effect of different assumptions about the missing data.[155] The management of missing data will be discussed further in chapter 6.

Deprivation data was missing for patients whose practice did not contribute to 'linked' CPRD data. Data was also missing in a proportion of patients for some lifestyle variables including BMI, alcohol consumption and smoking. A sensitivity analysis using complete cases only was therefore carried out.

5.4 Results

5.4.1 Describing the cohort

91,412 patients were included in the cohort from 685 practices contributing to the CPRD. 18,500 (20.2%) had surgery in the three-year period following the index presentation (absolute CPRD population rate: 1.52 episodes of surgery per 100 person years). The median time to surgery was 221 days (interquartile range, IQR: 111, 409).

2967 patients had a preceding incident episode denoted by a surgical code. 253 patients had a diagnostic code attributed on the same day as a carpal tunnel release code and eight patients were diagnosed on their 'end date' so had no follow up data to observe. These patients were excluded from the cohort, as it was not possible to observe the course between diagnosis and any treatment.

Table 5-4 describes the demographic and clinical characteristics of the 91,412 patients included at baseline (the attribution of an incident CTS diagnosis code) and those without any missing data in collected prognostic factors (n = 44,522).

Table 5-4 Description of the entire cohort and cohort with complete data

	All Patients		Patients with complete data
Participants	91,412		44,522
Patients with a coded episode of surgery n (%)	18,500 (20.24)		8,971 (20.15)
GP practice	685 practices contributed		383 practices contributed
Year of baseline diagnosis, median (IQR)	2006 (2002 – 2010)		2007 (2003 – 2010)
Year of surgery, median (IQR)	2007 (2004 – 2011)		2008 (2004 – 2011)
Time to surgery in days, median (IQR) [b]	221 (111 – 409)		249 (118 – 559)
Follow up time in days, median (IQR) [b]	1095.75 (385 – 1096)		1095.75 (370 – 1096)
Demographics			
Age at diagnosis, median (IQR)	53 (42 – 66)		53.96 (43.20 – 66.31)
Age group, *n* (%)			
18 – 29	4,713 (5.16)		1,810 (4.07)
30 – 39	13,741 (15.03)		6,504 (14.61)
40 – 49	19,366 (21.18)		9,504 (21.35)
50 – 59	21,597 (23.63)		10,825 (24.31)
60 – 69	13,964 (15.28)		6,9333 (15.57)
>70	18,032 (19.73)		8,946 (20.09)
Female, (n)%	63,194 (69.13)		32,030 (71.94)
Geographical region, n (%)			
North East	1,460 (1.6)		929 (2.09)
North West	9,637 (19.59)		5,928 (13.31)
Yorkshire & The Humber	3,984 (10.54)		2,248 (5.05)
East Midlands	3,583 (3.92)		1,613 (3.62)
West Midlands	8,281 (9.06)		5,193 (11.66)
East of England	10,191 (11.15)		6,230 (13.99)
South West	8,841 (11.15)		5,931 (13.32)
South Central	10,832 (11.85)		5,876 (13.20)
London	8,270 (9.05)		5,232 (11.75)
South East Coast	9,483 (10.37)		5,342 (12.00)
Northern Ireland	2,371 (2.59)		-
Scotland	6,366 (6.96)		-
Wales	8,113 (8.88)		-
Deprivation score		¶	
1 (least)	13,878 (15.18)	23.82	10,631 (23.88)
2	14,041 (15.36)	24.10	10,507 (23.60)
3	11,800 (12.91)	20.25	8,981 (20.17)
4	10,594 (11.59)	18.18	8,241 (18.51)
5 (most)	7,950 (8.70)	13.65	6,1362 (13.84)
Unknown [c]	33,149 (36.26)	-na	-na
Lifestyle			
Body mass index*, median (IQR)	27.2 (23.9 – 31.2)	¶	27.1 (24 – 31.2)
< 30	54,209 (59.30)	67.24	30,480 (68.46)
≥ 30	26,410 (28.89)	32.76	14,042 (31.54)
Unknown	10,793 (11.81)	-	-
Alcohol drinking, n (%)		¶	
Non drinker	10,968 (12.00)	13.94	6,034 (13.55)
Ever drinker	67,736 (74.10)	86.06	38,488 (86.45)
Unknown	12,708 (13.90)	-	-
Smoking status, *n* (%)		¶	
Non smoker	50,924 (55.71)	62.95	28,432 (63.86)
Ever smoker	29,967 (32.78)	37.05	16,090 (36.14)

Unknown	10,521 (11.51)	-	-
Pregnancy (in female patients)**, *n* (%)	3,869 (4.23)		1,908 (5.96)
Comorbidities			
Affective disorder***, *n* (%)	4,576 (5.01)		2,244 (5.04)
Hypothyroidsim***, *n* (%)	1,904 (2.08)		951 (2.14)
Diabetes***, *n* (%)	1,795 (1.96)		1,012 (2.27)
Inflammatory condition***, *n* (%)	851 (0.93)		426 (0.96)
Neck condition***, *n* (%)	2,371 (2.59)		1,113 (2.50)
Multi-site pain (including osteoarthritis) ***, *n* (%)	7,799 (8.53)		3,854 (8.66)
Tendonitis / epicondylitis***, *n* (%)	850 (0.93)		421 (0.95)
Wrist trauma***, *n* (%)	615 (0.67)		294 (0.66)

IQR, interquartile range; na, not applicable

* closest recorded value preceding the baseline diagnosis

** identified between 1 year prior to baseline and baseline

*** identified between 2 years prior to baseline and baseline

[a] censored at episode of surgery

[b] maximum follow-up 3 years

[c] applies at a practice level (not all practices contribute deprivation data)

[¶] Percentage of patients, excluding the 'unknown' category

5.4.2 Unadjusted univariable analysis

Table 5-5 shows the unadjusted univariable association of each candidate prognostic factor with time to surgery.

Table 5-5 Unadjusted univariable analysis

	Hazard ratio	*P* value*	95% Confidence Interval
Age at diagnosis	1.01	<0.001	1.01 to 1.02
Age group			
18 – 29	1 (referent)		
30 – 39	1.72	<0.001	1.59 to 1.92
40 – 49	2.28	<0.001	2.05 to 2.52
50 – 59	2.67	<0.001	2.41 to 2.95
60 – 69	2.70	<0.001	2.43 to 3.00
>70	3.33	<0.001	3.00 to 3.68
Gender (female)	0.97	0.10	0.94 to 1.00
Year of diagnosis	1.02	<0.001	1.01 to 1.02
Geographical region			
London	1		
North East	1.20	0.006	1.05 to 1.36
North West	1.30	<0.001	1.21 to 1.39
Yorkshire & The Humber	1.23	<0.001	1.13 to 1.35
East Midlands	1.62	<0.001	1.48 to 1.76
West Midlands	1.11	<0.001	1.34 to 1.53
East of England	1.21	0.004	1.04 to 1.19
South West	1.31	<0.001	1.12 to 1.29
South Central	1.23	<0.001	1.15 to 0.32
South East Coast	1.11	<0.001	1.00 to 1.24
Northern Ireland	1.69	0.06	1.57 to 1.82
Scotland	1.28	<0.001	1.19 to 1.37
Wales	1.20	<0.001	1.05 to 1.36
Deprivation score			
1 (least)	1		
2	0.96	0.14	0.912 to 1.01
3	0.99	0.82	0.94 to 1.05
4	0.92	0.01	0.87 to 0.98
5 (most)	0.96	0.18	0.90 to 1.02
Not known	1.00	0.94	0.96 to 1.04
Body mass index			
< 30	1		
≥ 30	1.21	<0.001	1.17 to 1.25
Not known	0.87	<0.001	0.83 to 0.91
Alcohol drinker			
No	1		
Yes	1.06	0.012	1.01 to 1.11
Not known	0.94	0.03	0.88 to 0.99
Smoker			
No	1		
Yes	0.97	0.12	0.94 to 1.01
Not known	0.99	0.55	0.94 to 1.03
Pregnancy (if gender = female)	0.24	<0.001	0.21 to 0.28
Affective disorder	0.96	0.30`	0.90 to 1.03
Hypothyroidism	1.06	0.23	0.96 to 1.17
Diabetes	1.26	<0.001	1.14 to 1.39
Inflammatory condition	1.26	0.001	1.10 to 1.45
Neck condition	1.15	0.001	1.06 to 1.25
Multi-site pain (including osteoarthritis)	1.22	<0.001	1.58 to 1.27
Tendonitis / epicondylitis	1.02	0.80	0.88 to 1.18
Wrist trauma	1.04	0.65	0.87 – 1.24

* *P* value obtained from each group compared to the referent group

5.4.3 Final multivariable model

Following the manual process of removing prognostic factors with a P value >0.1 and sequentially adding them back in; the final multivariable model was derived, as shown in Table 5-6.

Table 5-6 Final multivariable model of all patient data

	Hazard ratio	*P* value*	95% Confidence interval
Age at event	1.02	<0.001	1.01 to 1.02
Geographical region			
London	1 (referent)		
North West	1.30	<0.001	1.22 to 1.40
Yorkshire & The Humber	1.26	<0.001	1.15 to 1.38
East Midlands	1.65	<0.001	1.52 to 1.80
West Midlands	1.43	<0.001	1.33 to 1.53
East of England	1.09	0.013	1.02 to 1.18
South West	1.16	<0.001	1.08 to 1.25
South Central	1.31	<0.001	1.22 to 1.40
South East Coast	1.20	<0.001	1.12 to 1.29
Northern Ireland	1.18	0.004	1.06 to 1.33
Scotland	1.78	<0.001	1.65 to 1.93
Wales	1.32	<0.001	1.22 to 1.43
North East	1.20	0.006	1.05 to 1.36
Obesity			
Not obese	1		
Obese	1.23	<0.001	1.19 to 1.27
Unknown	0.89	<0.001	0.84 to 0.94
Deprivation			
1 (least deprived)	1		
2	0.96	0.137	0.91 to 1.01
3	1.00	0.998	0.95 to 1.06
4	0.94	0.053	0.89 to 1.00
5 (most deprived)	0.98	0.486	0.92 to 1.04
Unknown	0.92	0.001	0.87 to 0.96
Alcohol use			
No	1		
Yes	1.05	0.034	1.00 to 1.10
Not known	1.08	0.051	1.01 to 1.15
Smoking status			
No	1		
Yes	1.06	<0.001	1.03 to 1.10
Not known	1.01	0.563	0.97 to 1.07
Inflammatory condition	1.13	0.085	0.98 to 1.29
Neck condition	1.13	0.006	1.03 to 1.23
Multi-site pain	1.10	<0.001	1.05 to 1.15

* *P* value obtained from each group compared to the referent group

All variables except age, region and deprivation met the Cox proportional hazards assumption. For these variables the model therefore considers the average effect on the hazard of surgery, over the three-year observed period. The Harrell's C concordance statistic for this model was 0.588 (95% CI

0.584 to 0.592), meaning the model discriminated 59% of the time between patients who had an episode of CTR and those who did not (slightly better than chance).

5.4.4 Sensitivity analysis using complete patient data only

The process of building a multivariable model using a manual backward step approach, was then repeated in the data of patients who had complete data (i.e. entries for deprivation, BMI, smoking and alcohol status). The result of this process is shown in Table 5-7. The Harrell's C concordance statistic for this model was 0.587 (95% CI 0.581 to 0.593). The HR's for each prognostic factor in the multivariable models are compared in Table 5-8 showing in the complete case analysis; deprivation, smoking, alcohol and a history of neck problems do not remain in the final model. The hazard rates for age, obesity and a history of an inflammatory condition and multisite pain were similar in the two models.

Table 5-7 Final multivariable model of complete case data

	Hazard Ratio	***P* value**	**95% Confidence interval**
Age at diagnosis	1.02	<0.001	1.01 to 1.02
Region			
London	1 (as referent)		
North East	1.39	<0.001	1.27 to 1.52
North West	1.19	<0.001	1.06 to 1.34
Yorkshire & The Humber	1.80	<0.001	1.60 to 2.03
East Midlands	1.45	<0.001	1.32 to 1.58
West Midlands	1.21	<0.001	1.11 to 1.32
East of England	1.25	<0.001	1.14 to 1.36
South West	1.35	<0.001	1.24 to 1.48
South Central	1.30	<0.001	1.19 to 1.42
South East Coast	1.28	<0.001	1.09 to 1.50
Obese	1.21	<0.001	1.16 to 1.26
Inflammatory condition	1.37	<0.001	1.14 to 1.64
Multisite pain	1.08	0.04	1.00 to 1.15

* *P* value obtained from each group compared to the referent group

Table 5-8 Comparison of multivariable models derived from all versus complete patient data

	All Patients (Hazard ratio)	Complete Case (Hazard ratio)
Age at event	1.02	1.02
Region		
London	1 (as referent)	1
North East	1.20	1.39
North West	1.30	1.19
Yorkshire & The Humber	1.26	1.80
East Midlands	1.65	1.45
West Midlands	1.43	1.21
East of England	1.09	1.25
South West	1.16	1.35
South Central	1.31	1.30
South East Coast	1.20	1.28
Northern Ireland	1.18	na
Scotland	1.78	na
Wales	1.32	na
Obesity		
Obese	1.23	1.21
Unknown	0.90	na
Deprivation		
1 (least deprived)	1	na
2	0.96	na
3	1	na
4	0.94	na
5 (most deprived)	0.98	na
Unknown	0.92	na
Alcohol use		
No	1	na
Yes	1.05	
Not known	1.08	na
Smoking status		
No	1	na
Yes	1.06	-
Not known	1.01	na
Inflammatory condition	1.13	1.37
Neck condition	1.13	-
Multi-site pain	1.1	1.08

5.5 Discussion

5.5.1 Summary of main findings

17 candidate prognostic factors, derived from the literature and expert opinion, were identified and tested as prognostic factors of surgery in a cohort of 91,412 patients with physician diagnosed CTS, as recorded in the CPRD. 20.2% of the cohort had a recorded episode of CTR. The median time to surgery was 221 days (IQR 111 - 409). The final multivariable cox regression model performed poorly but confirmed the likely predictive value of prognostic factors including age, region, deprivation, obesity, being an alcohol drinker or smoker and having other pain, neck condition or inflammatory condition. Univariable analysis indicated that pregnancy in the preceding year was observed to reduce the risk of future surgery significantly.

5.5.2 Interpretation of results

5.5.2.1 Prognosis of carpal tunnel syndrome

20% of the cohort (patients with physician recorded diagnosis of CTS presenting in primary care) required surgery in the three-year period following their incident consultation, over the course of the study period. This figure underestimates the CPRD population who required surgery (27% over the study period), as there was a need, in order to conduct the 'time to' analysis, to exclude patients without a diagnostic code at baseline.

An episode of surgery is likely to indicate that the patient's symptoms or functional deficit due to the index episode of CTS had not been managed effectively using non-surgical approaches or had been severe enough at presentation to warrant expedited surgical consideration. These assumptions do not mean however, that the patients without a surgical episode were necessarily symptom free and functionally well at the end of follow up. Consultation data is unable to provide that level of patient orientated information.

The systematic review presented in chapter 4 concluded that the outcome of conservatively managed CTS was variable between studies and that this variability was likely to be due to the outcome measure applied and population observed. Four studies used a surgical episode as a marker of a poor or unsatisfactory outcome of conservative management. A range of 57% to 66% of patients were observed to receive surgery following conservative management over a period of between 1 and 3 years[68, 132, 138, 139]. This range is substantially higher than the figure reported in this cohort study. As well as the fact that some patients who had surgery were excluded, this could also suggest either that the occurrence of surgery in this cohort was underestimated by the methods applied or that the population studied was very different to those reported in the review. All four of the studies included in the review were set in secondary or tertiary hand clinics, where one could assume the patients had already been 'filtered' by severity and non-response to 'watchful waiting' or treatment in primary care or equivalent. This CPRD derived cohort is likely to be more representative of the UK general practice population; although as discussed below the approach to the analysis is likely to have underestimated the true number of surgical episodes.

5.5.2.2 Prognostic model determining risk of having a recorded episode of surgery

The results of univariable analysis suggested that increasing age, year of diagnosis, geographical region, obesity, a record of alcohol consumption, diabetes, inflammatory conditions, neck conditions, and multisite pain all increase the risk of having surgery. However, on multivariable analysis, diabetes, for example, did not retain significance (at a level of $P < 0.1$). The final model itself did not perform well. Although some previous studies have suggested a prognostic value of these candidate predictors, evidence regarding these prognostic factors from the systematic review was not consistent, which is in keeping with the results of this study.

Factors with the largest effect size in the final multivariable model included certain geographical regions (in particular Scotland and the East Midlands) and obesity. Region is likely to be a predictor of surgery due to the variability in local care pathways. It is important therefore that region, whilst it

cannot represent every different locally commissioned pathway, is included in the model to adjust for this potentially important confounder.

Obesity has been identified by a recent meta-analysis of 58 studies, to be a predictor of CTR (adjusted OR = 2.02, 95% CI 1.92 to 2.13) as well as an aetiological factor of disease onset. This is likely to be due to the shape of the wrist exerting increased amounts of pressure on the median nerve.[97] This study further suggests the role of obesity in predicting the need for surgery in patients presenting with CTS in primary care.

Table 5-5 suggests that on univariable analysis, in the female population, the prognostic factor with the largest and significant effect size was pregnancy (HR 0.24 95% CI 0.21 to 0.28). Pregnancy was defined as any ante-natal code in the 12-month period preceding the date of diagnosis. This was to allow a minimum of 3 months and maximum of 12 months for acute resolution of pregnancy related symptoms. A systematic review of studies observing the incidence and natural history of PRCTS suggested that the estimated incidence of CTS in pregnancy ranges from 0.8% to 70%. Symptoms persisted in more than 50% of patients after 1 year and in 30% at 3 years. The review concludes by suggesting that with high rates of resolution, surgery should be reserved for cases in which conservative management fails, where functional impairment is debilitating or in severe cases.[156] This cohort study, whilst unable to track resolution of symptoms post-delivery, suggests that recent pregnancy significantly reduces the risk of requiring surgery and that pregnant patients presenting with CTS may be reassured as such. Pregnancy was not included in the final model as, as well as having its own particular phenotype, it was felt that pregnancy would not be relevant to a large proportion of the population presenting with CTS in primary care with nearly 60% of the sample aged 50 or older, and 30% being male.

5.5.3 Methodological considerations

The predictive performance of the model was poor, as indicated by the C-statistic of 0.59. As will be discussed and applied in chapter 6, a prognostic model can be adjusted for the optimism automatically

introduced through using the development data set. Following estimation and internal validation, a model can then be externally validated in a new data set, before being recommended for testing in a healthcare setting. Processes of internal and external validation were not applied to this model, as it was clear from the initial results that the model did not perform sufficiently well enough to consider a potential clinical application. Optimism was also unlikely to be an issue in such a large data set that is already purported as being representative of the population.

The systematic review presented in chapter 4, although not conclusive, suggested that symptom duration, a positive Phalen's test and thenar atrophy were likely predictors of the failure of conservative management. Whilst Read codes do exist for Phalen's test and thenar atrophy, pilot work demonstrated they were seldom used and therefore unlikely to provide reliable data when extracted from CPRD. Likewise, CPRD data cannot provide a measure for patient preference nor practitioners' referral and management behaviour that may also confound which patients are referred for surgery and when in the time course of their CTS. Missing important predictors are a key reason a prognostic model may not perform well and give rise to a low C-statistic.

The existence of missing data is a substantial limitation when using consultation data. For example, in this dataset, 12% of the cohort had never had a BMI or smoking status recorded. As deprivation linkage was only available in practices in England and not the whole of the UK, this again limited the number of patients with complete data (to 46,890 patients, or 51 % of the original cohort). The complete case sensitivity analysis performed suggested deprivation, alcohol use and smoking history may not be significant predictors of surgery, as suggested by the full model.

It is possible that results based on complete case analysis are biased, given the assumption that at least some of the data were not missing not at random. The baseline characteristics of the complete case sample are different compared to the analysis sample (proportionally more smokers and more patients with obesity), potentially indicating poorer health/lifestyle behaviour. If it is this that was associated with the probability of requiring surgery, different associations between predictors and outcome in the complete case versus main analysis would be found.

The use of consultation data in research relies on patient information being complete and accurate. It is possible that the coding of some prognostic factors and indeed diagnosis of CTS, was inaccurate or absent. For example, a history of neck pain in a patient presenting with CTS may not have received a Read code and hence not have been identified by the study. Patients with chronic conditions such as diabetes, due to the regular structured follow-up they receive in primary care, may have been more likely to receive a code than a patient presenting with a pain related problem. Likewise, although attempts were made to ensure that code lists were comprehensive; it is possible that relevant Read codes were not included in the generated lists. The consequence of this would be that bias was introduced to the model due to variability in the accuracy and completeness of coding, depending on the candidate predictor.

The study was also reliant on a surgical episode being captured by clinical coding in the database. As procedures now take place outside of the secondary care environment, it was felt that Hospital Episode Statistics would in fact underestimate the episodes recorded in CPRD. Likewise, there remains a risk that administrative and coding processes did not identify every episode of CTR. If funding had allowed, it may have been possible to compare or combine the two approaches of i) relying on clinical administrative coding and ii) the use of data from Hospital Episode Statistics, but this was not feasible.

As discussed in Chapter 3, the population studied in CPRD is likely to be different to the population observed in most other existing studies which are set in specialist clinics, where patients with mild to moderate disease are more likely to have already been treated or have improved and hence not referred. Patients with a surgical code only and no preceding diagnostic code, were not included in the observed cohort as a baseline analysis of candidate prognostic factors was not possible to conduct, neither was a time to analysis. It is possible that by excluding such patients (who had been included in the prevalence / incidence calculations) a less severe population was selected leading to a model that did not perform well in predicting a surgical event.

5.5.4 Clinical relevance of the findings and suggestions for further research

The aim of this study was to use consultation data to predict the risk of an episode of surgery in patients presenting in primary care with CTS, by developing a prognostic model. In order for a model to have clinical utility, it should have good predictive performance, that is maintained when the model is tested (externally validated) in populations that share a similar range of predictor variables, be unambiguous in its definitions of predictors and outcomes in order for them to be reproducible in other settings, and be tested in impact studies. Impact studies allow the effect of using the model in clinical practice, to include the effect of physician and patient behaviour, to be estimated and the clinical and cost effectiveness of care using the model to be considered.[157] Whilst CPRD is accepted to be generalizable to the UK population,[82] given the disappointing predictive performance of model presented in this chapter, it would need further development to improve its predictive performance before it could be further validated and investigated for its potential impact in clinical practice. Ideally, data from a high-quality a-priori designed prospective cohort study or studies with sufficient information regarding prognostic factors would be required in order to do this.

5.5.5 Conclusion

The final model performs inadequately but suggests the likely combined predictive value of several prognostic factors including obesity, being an alcohol drinker and presence of other musculoskeletal pain on future risk of CTR. Neither the systematic review, nor this CPRD cohort study have been successful in providing strong evidence for predictors of outcome in non-pregnancy related CTS. This is potentially because prognostic factors of greater importance have not yet been effectively identified and / or measured. Further work would be required to investigate the predictive performance of these candidate prognostic factors and develop a prognostic model that might have clinical utility.

In the next chapter, a cohort will be constructed from participants of a randomised clinical trial and further analysed to develop an alternative prediction model for patients presenting with CTS in primary care. This study benefits from including prognostic factors purposively measured at baseline, including

symptom duration and severity, which could not be measured in CPRD. A well validated patient recorded outcome measure will also be available to more precisely measure change in symptoms and function over time. Using a patient reported outcome will also mitigate the confounding effect of local variation in access to CTR.

6 Describing the course of symptoms and predicting outcome in patients with carpal tunnel syndrome receiving conservative management as part of a randomised controlled trial (Injection versus Night Splints for Carpal Tunnel Syndrome)

Summary

The aim of this chapter is to further explore if the patient reported outcome of carpal tunnel syndrome (CTS), presenting in a primary care setting, can be predicted. The study presented in this chapter uses data from the Injection versus Night Splints for Carpal Tunnel Syndrome (INSTINCTS) trial. The trial was conducted independently of the work this thesis and whilst CB was a member of the Trial Management Group, did not conduct the trial independently. The trial protocol and publication can be found at:

Chesterton LS, Dziedzic KS, Van der Windt D, Davenport G, Myers HL, Rathod T, Blagojevic-Bucknall M, Jowet S, Burton C, Roddy E, Hay EM. The clinical and cost effectiveness of steroid injection compared with night splints for carpal tunnel syndrome: The INSTinCTS radmonised clinical trial study protocol. BMC Musculoskeletal Disorders BMC. 2016. 17:415

Chesterton LS, Blagojevic-Bucknall M, Burton C, Dziedzic KS, Davenport G, Jowett SM, Myers HL, R Oppong R, Rathod-Mistry T, Van der Windt DA, Hay EM, Roddy E. 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. *The Lancet*, Volume 392 , Issue 10156 , 1423 – 1433

6.1 Introduction

In Chapter 5, the Clinical Practice Research Datalink (CPRD) was used to develop a prognostic model to predict the likelihood of patients with physician diagnosed CTS having future carpal tunnel release (CTR) surgery. This information could have been used by clinicians to help guide decision-making around the use of conservative management options and follow up in a primary care setting, or

whether it was more appropriate to refer patients for consideration of surgery. However, the model performed poorly and was considered not to have clinical utility. This may have been due to several reasons including: the importance of factors other than clinical prognostic indicators (i.e. variation between local commissioning pathways) or that it was not possible to measure or measure well, potentially important prognostic factors such as symptom severity and symptom duration in CPRD. It was hoped that using data from the INSTINCTS trial, whilst the sample size was much smaller than that available from CPRD, would afford the advantage of measuring at baseline potentially important candidate predictors that were not available from electronic patient data. The use of a patient reported outcome measure would more directly reflect the course of CTS symptoms over time than a decision to refer for CTR, which may be influenced by other non-clinical factors.

The trial population, adjusting for intervention, was therefore prospectively observed as a prognostic cohort. The course of CTS was described using the Boston Carpal Tunnel Questionnaire (BCTQ) score. *A-priori* identified candidate prognostic factors were used to develop a prognostic model to predict patient-reported CTS at six months, following primary care management (corticosteroid injection or night splinting).

The trial methods and results will first be summarised, followed by a description of the methods applied for the prognostic study, using the reporting guidelines provided by TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis). [145] The development of the prognostic model will then be presented and discussed.

6.2 Source of data: The INSTINCTS trial

INSTINCTS is an open-label, parallel group, randomised control trial.[59] The trial had a pragmatic design, meaning that it was intended to recruit a sample representative of the population in primary care presenting with CTS, amenable to conservative management. The exclusion criteria were limited and were designed to not restrict the participants eligible to participate too stringently, in order to maximise the generalisability of the results.

Participants were randomly assigned (1:1) to either treatment group using permutated blocks of sizes two and four, pre-stratified by research site. Treatment allocation was concealed during analysis. Participants randomly received either 20mg Methylprednisolone injected into the carpal tunnel using an approach between the proximal and distal wrist crease or a resting night splint to be worn at night for six weeks. Self-report at six weeks was used to assess adherence to splinting.

Both trial interventions were treatment options commonly offered in primary care for CTS, and random allocation of the interventions avoided the risk of so-called treatment bias (or confounding by indication),[158] which may affect the results of prognosis studies in observational cohorts. Finally, since the trial showed only small, non-significant differences at six months between the two arms, treatment was considered unlikely to influence results.

6.2.1 Participants

Participants (≥ 18 years of age) with mild or moderate CTS were recruited from 25 primary and community musculoskeletal clinics and services. Eligible participants were required to have had a new episode of idiopathic CTS, as defined by criteria developed as part of a consensus survey of GPs from the PCRMM Society, for at least six weeks duration. Participants with bilateral disease were investigated based on the hand with the most severe symptoms. Exclusion criteria included: severe disease, previous surgery in the affected wrist, current or previous infection, pregnancy and lactation, treatment in the past six months and intercurrent illness. Written, informed consent was obtained from eligible patients.

6.2.2 Approvals and monitoring

The INSTINCTS trial was approved by the National Research Ethics Service Committee North West – Liverpool (UK: reference 13/NW/0280) and the Medicines and Healthcare products Regulatory Agency (European Clinical Trials Database, number 2013-001435-8). An external trial steering and data monitoring committee oversaw the conduct and analysis of the trial. The trial was prospectively

registered with ClinicalTrials.gov on 16/01/2014 (NCT0.038542) and registered with Current Controlled Trials on 1/05/2014 (ISRCTN09392969).

6.2.3 Outcome measures

Baseline data were collected using a self-completed questionnaire before randomisation. All outcome measures were collected at six weeks and all but adverse events were collected at six months. Further follow up took place at 12 and 24 months (data not available at the time of writing).

The primary outcome measure for the trial was the overall score for symptom severity and limitations in hand function as measured by the Boston Carpal Tunnel Questionnaire (BCTQ)[32] at six weeks. This is a condition-specific questionnaire referring to a typical 24-hour period in the previous 2 weeks. It has been shown to be highly reproducible, internally consistent, valid and responsive to clinical change.[159] The BCTQ comprises of two sub-scales: the symptom severity scale (SSS: 11 items) and function severity scale (FSS: 8 items). Both sections are scored on 1-5 scales, with final scores for each dimension calculated as a mean score between 1 and 5. Higher scores indicate more severe symptoms and greater functional impairment.

6.3 Describing the course of symptoms and predicting outcome in patients with carpal tunnel syndrome: Methods

6.3.1 Describing the course of CTS over a six-month period of time

Whilst INSTINCTS reported the BCTQ scores at six weeks and six months for each intervention arm of the trial, this study summarises the course of both the combined (BCTQ sum score) and separate scores for symptom severity (SSS) and functional outcome (FSS) for the entire trial cohort at each of these time points.

6.3.2 Developing the prognostic model: outcome

The outcome measure (and 'end-point') for the model, was the sum score for symptom severity and functional limitation on hand function using the Boston Carpal Tunnel Questionnaire (as per the main trial), at six-month follow-up. Six-month data was chosen as the time point of interest as the six-week outcome was felt to represent too short a timeframe and lacked clinical importance. Whilst longer-term outcome data may provide further clinical information, it was not feasible to wait for this data to become available and it was not expected that substantial differences in prognostic factor outcome associations at 12 or 24 months would be present, if they could not be detected at six months. Further (non-randomised) interventions such as repeat injections or episodes of surgery were more likely to have occurred at later time-points and as such may confound prognostic factor – outcome associations.

6.3.3 Developing the prognostic model: identifying and measuring candidate prognostic factors

The approaches used to identify candidate prognostic factors and predictors of treatment effect have been described in section 5.2. The identified candidate predictors were amalgamated and grouped into a list of 69 single items by category (comorbidities, clinical characteristics and patient demographics). The list was further reduced to 41 items using the following reasons for exclusion:

- Exclusion criteria for the trial (e.g. CTS during pregnancy, disease severity – including presence of thenar wasting)
- Rare characteristics that would not carry significance within the study (e.g. acromegaly)
- Information not available within the dataset (e.g. results of nerve conduction studies)
- Items not measurable within the study (e.g. accuracy of placement of the steroid injection)
- Items specific to surgical intervention (e.g. approach to surgery)

Of the 41 items, 21 were already included in pre-existing questions or items to be recorded in the case report forms (for example, symptom severity and demographic details respectively). When developing the additional questions, brevity was a major concern expressed by the Trial Management Group, in order to minimise patient burden. Validated single questions were used where possible, for example items from the Revised Illness Perception Questionnaire.[160] Where validated questions were not available, questions from previous questionnaires developed in the Centre were utilised or if necessary, designed through agreement with members of the Trial Management Group and reviewed for content and presentation by the Research User Group.

Two items (Phalen's test and presence of thenar wasting) were collected in the case report form, however were not further considered as there was strong overlap with eligibility for the trial, (i.e. patients were highly likely by definition to have a positive Phalen's sign and should not have had thenar wasting). As obesity was recognised as a candidate prognostic factor, this was added to the Confirmation of Eligibility and Randomisation case report form, to be recorded by the randomising clinician. Table 6-1 describes the candidate prognostic factors, type of question used and the source of the measure.

Table 6-1 Candidate prognostic factors measured at baseline

Variable	Outcome measure	Source of outcome measure
Gender		
Age		
Occupation		
Depression	Two items (yes/no)	Progress brief assessment tool [146]
Sleep quality	Revised 4 items (yes/no)	Jenkins Sleep questionnaire[161]
Functional disorders	Single item question (yes/no)	Progress brief assessment tool
Obesity	Body mass index	Height and weight entered into CRF
Absence / presence of any associated co-morbidity • Hypothyroidism • Diabetes • Neck and upper limb pain		
Laterality of symptoms	Single item question (yes/no)	
If affecting dominant hand	Single item question (yes/no)	
Recurrent symptoms	Single item question (yes/no)	
Baseline symptom severity	Boston Carpal Tunnel Questionnaire (whole scale)	Levine et al[32]
Baseline functional severity	Boston Carpal Tunnel Questionnaire (whole scale)	Levine et al
Baseline Boston Carpal Tunnel sum score	Boston Carpal Tunnel Questionnaire (whole scale)	Levine et al
Symptom duration / time to intervention	Single item question	Question developed for purpose of this study
Postural symptoms only	Single item question	Question developed for purpose of this study
Constancy of symptoms	Boston Carpal Tunnel Questionnaire (single item)	Levine et al
Symptoms limited to night-time	Boston Carpal Tunnel Questionnaire (single item)	Levine et al
Daytime symptoms	Boston Carpal Tunnel Questionnaire (single item)	Levine et al
Nature of onset	Single item question	Adapted from [162]
Multi-site pain	Single item question	Progress brief assessment tool *Full symptom checklist likely to be over-burdensome*
Phalen's sign	Checked at eligibility screening	
Previous response of CTS to wrist injection / splint and surgery	Multiple item question	BeBack [163]
Previous response to any treatment	Single item question	BeBack
Previous response to injection (any site)	Multiple item question	BeBack
Acceptability / preference of treatment	Single item question	Question developed for purpose of this study
Acceptability / expectation of treatment	Single item question	Question developed for purpose of this study
Quality of patient education regarding the use of splints	Single item question	Question developed for purpose of this study
Support of employer	Multiple item question	Adapted from Karasek questions [164]
Successful work role functioning	Single item question	Presenteeism scale
If symptoms are work related	Single item question	Adapted from Karasek

If unemployed / receiving social support	Single item question	Question developed for purpose of this study
Locus of control	Single item question	Illness Perception Questionnaire (taken from the multi-item subscales (dimensions) [160]
Treatment control	Single item question	Illness Perception Questionnaire (taken from the multi-item subscales (dimensions)
Adherence to treatment	Single item question	Question developed for purpose of this study
Peri-menopause	Female: age 45 – 55 years	
Perceived health scores	Whole scale	EQ 5D https://euroqol.org/eq-5d-instruments/
Excess alcohol use	Single item question	North Staffordshire Osteoarthritis Project (NorStOP)
Smoking	Single item question	NorStOP

This pool of candidate predictors was further considered for overlap or redundancy in order to reduce them to a more acceptable number, with the initial aim of achieving 10 events (parameters) per variable, as per the recommendation of Peduzzi et al.[148]

Continuous candidate predictors (age, BMI, BCTQ scores) were not categorised in order to preserve information and their potential non-linear trends were considered.[165]

6.3.3.1 Further reduction in the number of candidate prognostic factors and description of missing data

Following the process of defining variables, it was recognised that some of the candidate prognostic factors were not measured at baseline; only applicable to a subgroup of participants (e.g. employment related factors); or they collided with other variables (e.g. taken from scales that were also measured in full or were composite measures like 'peri-menopausal', which was derived from age and gender).

Table 6-2 shows the candidate prognostic factors that were removed and the reasons for their removal.

Table 6-2 Further reduction of candidate prognostic factors

Removed candidate prognostic factor	**Reason for removal**
Employment related factors	132 (56%) of the participants were in paid employment, hence the predictors apply to only a subgroup of patients. It may be possible in the future to investigate the role of employment on the outcome of trial participants, in the future
Individual items from the Boston Carpal Tunnel Questionnaire	Individual items derived from the BCTQ will collide with the overall score. However, the symptom severity score (SSS) and functional status scale (FSS) will be considered
"Particular position cause hand or wrist problems"	This item is a diagnostic feature as opposed to a prognostic factor and as such the majority of patients are likely to have a positive response and as such the variable will not discriminate well
Phalen's test	This item is a diagnostic feature screened for in the trial participants and used in the selection criteria and as such the majority of patients are likely to have a positive response
Satisfaction with education received as part of the intervention	This is not measured at baseline and hence cannot be included as a prognostic factor, which by definition are measured at baseline
Treatment adherence	This is not measured at baseline and hence cannot be included as a prognostic factor, which by definition are measured at baseline
Menopause	This collides with age and gender. However, it may need to be considered as a moderator as there may be a physiological reason why women with low levels of progesterone may respond to one treatment better than another

Functional disorders / multisite pain	Functional disorders and multisite pain were described by the same outcome, hence they were combined

6.3.3.2 Permissions for amending trial questionnaire

In order to permit a more complete description of the baseline characteristics of the participants, additional questions were added to the original INSTINCTS baseline questionnaire, following discussion with the Trial Management Group (which included PPIE members). The addition of these questions to the baseline questionnaire was approved on 03/07/13 by the National Research Ethics Service Committee North West – Liverpool, following a request for a substantial amendment. The Patient Information Leaflet for INSTINCTS included a paragraph explaining that anonymised data may be used for further research,

> *"The study information collected about you may be shared with other research teams to answer new research questions in the future. If this is the case, information will be anonymised. Your full name and contact details will not be disclosed."*

The Internal Request for data to be released by the trial data custodian was signed on 24/2/17 by the Principal Investigator and a further amendment to acquire six week data signed on 31/01/19, in accordance with the Keele University Health and Social Care Standard Operating Procedure Number 48. These requests can be found in appendix F.

6.3.4 Developing the prognostic model: statistical analysis

Firstly, descriptive statistics were used to describe characteristics of the study population and illustrate the course of the SSS and FSS and sum BCTQ between recruitment (start-point) and six week and six-month (end-point) time points.

6.3.4.1 Missing data

Missing data risks introducing bias into estimates and standard errors and should be examined and managed in order to reduce this risk.[166] It is firstly important to consider why data might be missing. Missing data can be considered: missing completely at random (MCAR); missing at random (MAR) or missing nor at random (MNAR). The difference between MAR and MCAR being that a systematic difference between missing and observed values exists in MAR data, whereas in the case of MCAR data, there is no systematic difference leading to data being missing. Typically, data is assumed to be MAR, however there are no ways to test for this assumption. Options for handling missing data include complete case analysis and single imputation, however both these techniques are inefficient and waste data and in doing so can bias parameter estimates. They also do not account for the uncertainty in imputing values.

If data is MAR (or MCAR), multiple imputation (MI) can be used to impute missing values '*M*' times rather than once. This technique incorporates uncertainty into its estimates and thereby maintains an unbiased model. It is also efficient in that data is not lost. MI involves developing multiple datasets (whereby the number of datasets is equal to the % with any missing, so for example, 50 data-sets if 50% of the original participants have some data missing) and performing the analysis in each of the datasets. The results of these analyses are then pooled to give an overall multiple imputed result. The outcome as well as the candidate predictors to be tested were included in the imputation model.[167]

The number of participants with missing outcome and candidate predictor data and the baseline characteristics of these participants was considered. As data was collected at baseline in a trial setting and each patient followed up using standardised methods (using reminders via postcard, text messaging and telephone calls), any missing data was assumed to be at least missing at random (MAR), if not missing completely at random (MCAR).

Multiple imputation using chain equations was therefore used to account for missing data and reduce the risk of bias. 37 imputations were used given the amount of missing data present (37%). As a

sensitivity analysis and in order to check whether the model developed using MI did result in a very different composition or performance of the prediction model, a complete case analysis was also presented.

6.3.4.2 Methods

As the outcome was a continuous variable, multivariable linear regression analysis was used to identify the combination of factors measured at baseline most strongly associated with symptoms and function limitation (BCTQ sum score) at six months.

A backward stepwise sequential approach was applied to the data, meaning that all candidate predictors were included in the (full) model. Variables were then removed in turn, with the least significant first, using $P < 0.1$ as the acceptable level of significance. Each variable to have been removed was re-tested at each stage to ensure it should not re-enter the model. The model was considered to be complete when no variables in the model met the criteria for exclusion and none of the variables to have been excluded, met the criteria for inclusion. Residual plots were used to test if the use of linear regression was appropriate, without the need for transformation of the variables. As per the recommendation of Groenwold et al, treatment was included as an additional variable (co-variate) during prognostic model development in order to adjust for any effect on the associations between prognostic factors and outcome.[168]

A small sample size increases the risk of optimism in a prognostic model, which means that the strength of associations between candidate predictors and outcome is likely to be over-estimated. This can be particularly important if variables are included by chance and / or the effects of predictors are inflated. Optimism in a model means that the observed outcome for a new individual will be less extreme than the outcome predicted by the model (which has been fitted to the original dataset). This is the underpinning principle of 'Stein's paradox,'[169] the result of which requires a model to be adjusted or penalised for optimism.[165]

Whilst it may have been preferable to adjust the model for optimism (internal validation) using a boot-strapping procedure, after consultation with a statistician with particular expertise in this field, it was decided to use heuristic shrinkage as a means of uniform linear shrinkage of the model. Data had already been subject to multiple imputation and the possible detrimental effects of imputation combined with bootstrapping in the same dataset is an area of ongoing research.

Boot-strapping is a process whereby participants are randomly selected from the original dataset (and replaced back into the original dataset), until a new dataset with an equal sample size is obtained. For internal validation of a prediction model, this process is often repeated 100 or 200 times, allowing for the developed model to be tested in a large number of samples, taking into account sampling variation.[165] Heuristic shrinkage, proposed by Van Houwelingen and le Cessie[170] is an example of uniform shrinkage. First the shrinkage factor is calculated based on the total degrees of freedom for the predictors in the model and the likelihood ratio statistic for testing the joint influence of all the predictors at the same time. This shrinkage factor is then applied to the Beta coefficients for all the variables in the model. The intercept of the equation is then calculated and the shrinkage factor applied, to give the final shrunken model equation.

The performance of the shrunken model was then described by providing a calibration plot. Calibration is a graphical representation of how values predicted by the model compare with the values observed in the dataset. Discrimination is not possible to determine given the use of a continuous outcome, as by definition, discrimination it is the ability of the model to differentiate between individuals who do and do not experience the outcome.

6.3.4.3 Sample size

INSTINCTS was designed to detect a 15% greater improvement in the combined BCTQ score from an expected baseline value of 2.9 points in the corticosteroid injection group compared with night splinting, with a pooled standard deviation of 1.0 and standardised mean difference of 0.45. Given 90% power, 5% two-tailed significance and assuming 15% loss to follow up, 240 patients (120 in each arm)

were required. The final number of participants recruited to INSTINCTS was 234. For development of the prognostic model, this sample size was a given. The final list of candidate prognostic factors equates to 25 variables and, consequently, a case per variable rate (EPV) of 9.3 but 27 parameters and an event per parameter rate (EPP) of 8.6.

A more precise post hoc sample size estimate was provided by using the Stata programme 'PMPSAMPSIZE.'[171] This package was developed using the sample size calculation criteria recommended by Riley et al.[172] The aim of a sample size calculation for developing a prediction model is to minimise the risk of overfitting and ensure the important parameters in the model are estimated precisely. This approach goes beyond the previous 'rule of thumb' (10 cases per variable) approach applied above. This more specific approach takes into account the anticipated R-squared of the model and the average value and standard deviation of outcomes in the model (in this case, the BCTQ at six months as presented in INSTINCTS).[172] This sample size calculation using the Stata package was presented post hoc as the package became available following the development of the study protocol and the results therefore offer additional information regarding how robust (precise) estimates regarding the model's performance might be.

6.4 Describing the course of symptoms and predicting outcome in patients with carpal tunnel syndrome: Results

6.4.1 The participants

INSTINCTS randomised 234 participants. 16 (6.8%) of participants did not have a complete BCTQ baseline score, and 48 (20.5%) of participants did not have a complete BCTQ score at six months. 57 (24.3%) participants did not have complete data for the baseline or six-month time-point. In total, 148 (63%) patients had complete data for all variables, BCTQ outcome as well as for candidate predictors. The distribution of features between all participants compared with complete cases are described in Table 6-3. Patients with complete data appear similar to the full cohort.

Table 6-3 Baseline description of participants

	All participants (n=234) n (%)	Complete cases (n=148) n (%)
DEMOGRAPHICS		
Sex		
Male	80 (34.2%)	50 (33.8%)
Female	154 (65.8%)	98 (66.2%)
Age		
Mean (SD)	52.4 (15.9)	54.5 (15.2)
Median (IQR)	52 (40 – 65)	55 (44 – 66)
CURRENT CTS EPISODE		
Bilateral symptoms		
Yes	116 (50.8%)	78 (52.7%)
No	112 (49.1%)	70 (47.3%)
Missing	6 (2.6%)	-
Dominant hand affected		
Yes (incl bilateral)	189 (83.3%)	123 (83.1%)
No	38 (16.7%)	25 (16.9%)
Missing	7 (3.0%)	-
Recurrent symptoms		
Yes	31 (13.5%)	16 (10.8%)
No	199 (86.5%)	132 (89.2%)
Missing	4 (1.7%)	-
Baseline symptom severity		
Mean (sd)	2.93 (0.63)	2.87 (0.63)
Missing	5 (2.1%)	-
Baseline functional severity		
Mean (sd)	2.28 (0.89)	2.23 (0.85)
Missing	14 (0.60)	-
Baseline Boston Carpal Tunnel sum score		
Mean (sd)	2.65 (0.67)	2.60 (0.65)
Missing	16 (6.8%)	-
Duration of hand or wrist problems		
<3 months	36 (15.8%)	25 (16.9%)
3-six months	70 (30.7%)	52 (35.1%)
6 – 12 months	49 (21.5%)	26 (17.6%)
>12 months	73 (32.0%)	45 (30.4%)
Missing	6 (2.6%)	-
Onset of symptoms		
Suddenly: symptoms developed quickly within a few days	50 (21.9%)	29 (19.6%)
Gradually: symptoms developed more slowly over weeks to months	178 (78.1%)	119 (80.4%)
Missing	6 (2.6%)	-
GENERAL HEALTH		
Anxiety and / or depression (both screening questions answered 'yes')		
Yes	64 (27.8%)	41 (27.7%)
No	166 (72.2%)	107 (72.3%)
Missing	4 (1.7%)	-
Poor sleep quality		
Yes	127 (55.2%)	83 (56.1%)

No	103 (44.8%)	65 (43.9%)
Missing	4 (1.7%)	-
Functional disorders / multisite pain		
Yes	146 (63.5%)	95 (64.2%)
No	84 (36.5%)	53 (35.8%)
Missing	4 (1.7%)	-
Obesity		
BMI (sd)	30.4 (7.6)	30.3 (7.0)
Obese		
Yes	112 (49.8%)	73 (49.3%)
No	113 (50.2%)	75 (50.7%)
Missing	9 (3.8%)	-
Diagnosed with hypothyroidism		
Yes	14 (6.1%)	12 (8.1%)
No	215 (93.9%)	136 (91.9%)
Missing	5 (2.1%)	-
Diagnosed with diabetes		
Yes	21 (9.2%)	14 (9.5%)
No	90.8%)	134 (90.5%)
Missing	5 (2.1%)	-
Any other conditions affecting neck, shoulder or elbows		
Yes	73 (31.9%)	45 (30.4%)
No	156 (68.1%)	103 (69.6%)
Missing	5 (2.1%)	-
Perceived health scores		
Mean (sd)	0.77 (0.19)	0.77 (0.19)
Missing	8 items expressed as 1	-
Excess alcohol use		
Yes	22 (9.6%)	16 (10.8)
No	208 (90.4%)	132 (89.2)
Missing	4 (1.7%)	-
Current smoker		
Yes	32 (14%)	20 (13.5)
No	197 (86.0%)	128 (86.5)
Missing / ambiguous	5 (2.1%)	-
TREATMENT EXPECTATIONS		
Received preferred treatment		
Yes	69 (30.3%)	48 (32.4)
No or no preference	159 (69.7%)	100 (67.6)
Missing	6 (1.3%)	-
Expectation that treatment given will improve symptoms		
Yes	108 (49.1%)	75 (50.7%)
No or unsure	112 (50.1%)	73 (49.3%)
Missing	14 (6.0%)	-
PSYCHOLOGICAL MEASURES		
Locus of control		
There is a lot I can do to control my hand/wrist problems:		
Agree	66 (28.8%)	45 (30.4%)
Disagree	163 (71.2%)	103 (69.6%)
Missing	5 (2.1%)	-

What I do determines whether hand/wrist problems get better or not: Agree Disagree Missing	 124 (54.2%) 105 (45.9%) 5 (2.1%)	 79 (53.4%) 69 (46.6% -
Treatment control *Treatment can control my hand/wrist problem:* Agree Disagree Missing	 170 (74.6%) 58 (25.4%) 6 (2.6%)	 103 (69.6%) 45 (30.4%) -

6.4.1.1 Clinical course of carpal tunnel syndrome

Table 6-4 summarises the sum and component score of the BCTQ at baseline, six weeks and six months for the whole trial population, observed as a cohort. These values are represented graphically in Figure 6-1. The number of participants at each time point are also shown as this descriptive analysis was based only on cases with information on the outcome at either six weeks or six months.

Table 6-4 Scores of the Boston Carpal Tunnel Questionnaire over time

Outcome measure	**Mean score at baseline**	**Mean score at six weeks**	**Mean score at six months**
BCTQ sum score	2.63 218 observations	2.14 212 observations	2.08 186 observations
Symptom severity score	2.93 228 observations	2.27 215 observations	2.24 189 observations
Function status score	2.28 220 observations	1.98 214 observations	1.88 188 observations

Figure 6-1 Graphical representation of the BCTQ and its component score over the course of the six month follow-up period

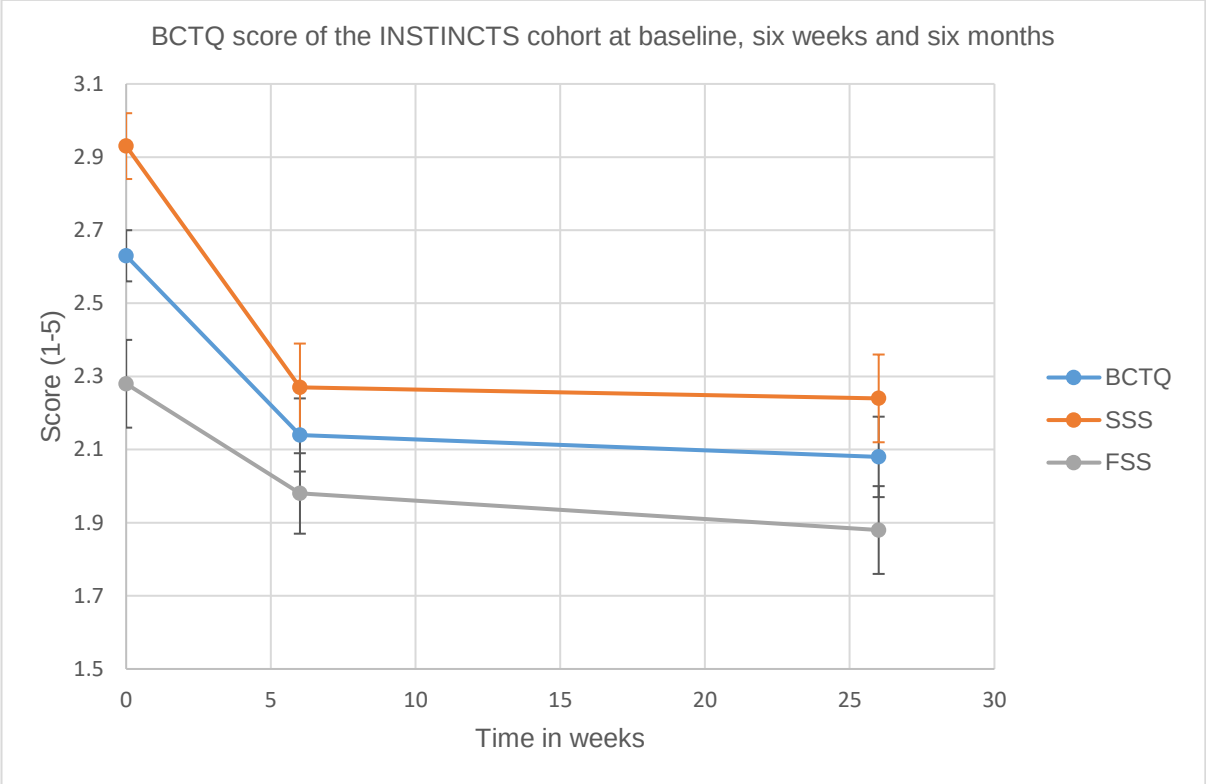


Figure 6-1 shows a rapid improvement in symptoms and function between the start-point of the study and six weeks follow-up. These trajectories then slow, with a more gradual improvement over the following 4.5 months.

6.4.2 Model development

6.4.2.1 Univariable and multivariable linear regression analysis of candidate predictors and BCTQ at six months, using multiple imputed data

Table 6-5 shows the results of the univariable analysis of associations between candidate predictors and BCTQ at six months in the 37 multiple imputed dataset. Univariable (unadjusted) analysis demonstrated that at a significance level of 0.1, a more severe BCTQ sum score at six months was associated with bilateral symptoms, the dominant hand being affected, a more severe BCTQ SSS and FSS score at baseline, depression, poor sleep and a lower perceived health score. Table 6-6 then shows the final multivariable model developed in imputed data and in the complete case dataset. Following the backward stepwise variable selection using a significance level of 0.1, the model using multiple

imputed data included a more severe baseline BCTQ sum score, a less severe baseline symptom severity score and the absence of other neck and upper limb symptoms as being associated with a more severe BCTQ sum score at six months (adjusted $R^2 = 0.31$). The model based on complete cases included a less severe baseline score being associated with a more severe sum BCTQ sum score at six months (adjusted $R^2 = 0.36$).

Table 6-5 Univariable associations with outcome using multiple imputed data

	Univariable analysis of association with BCTQ at six months using multiple imputed data	
	Regression coefficient (95% confidence interval)*	*P* value
DEMOGRAPHICS		
Female	0.12 (-0.10 to 0.35)	0.28
Age	-0.00 (-0.01 to – 0.00)	0.39
CURRENT CTS		
Bilateral symptoms	0.28 (0.05 to 0.50)	0.02
Dominant hand affected	0.25 (-0.05 to 0.55)	0.10
Recurrent symptoms	0.22 (-0.11 to 0.55)	0.20
Baseline BCTQ score	0.64 (0.49 to 0.78)	<0.01
Baseline symptom severity	0.54 (0.38 to 0.70)	<0.01
Baseline functional severity	0.47 (0.36 to 0.59)	<0.01
Duration of hand or wrist problems <3 months 3-six months 6 – 12 months >12 months	 1 (as referent) -0.02 (-0.38 to 0.33) 0.00 (-0.40 to 0.40) 0.08 (-0.26 to 0.41)	 0.90 1.00 0.65
Onset of symptoms *Suddenly*: symptoms developed quickly within a few days *Gradually*: symptoms developed more slowly over weeks to months	 1 0.09 (-0.20 to 0.37)	 0.55
GENERAL HEALTH		
Depression (both screening questions answered 'yes')	0.33 (0.08 to 0.58)	0.08
Poor sleep quality	0.23 (-0.00 to 0.45)	0.05
Functional disorders / multisite pain	0.11 (-0.12 to 0.34)	0.36
BMI	-0.00 (-0.02 to 0.01)	0.75
Diagnosed with hypothyroidism	0.08 (-0.36 to 0.53)	0.72
Diagnosed with diabetes	0.07 (-0.31 to 0.45)	0.72
Any other conditions affecting neck, shoulder or elbows	0.07 (-0.18 to 0.31)	0.59
Perceived health scores	-1.33 (-1.90 to -0.76)	<0.01
Excess alcohol use	-0.17 (-0.55 to 0.22)	0.40
Current smoker	0.06 (-0.27 to 0.38)	0.74
Received preferred treatment	-0.06 (-0.30 to 0.19)	0.66
Expectation that treatment given will improve symptoms	-0.09 (-0.33 to 0.14)	0.44
Locus of control		

There is a lot I can do to control my hand/wrist problems: Agree *What I do determines whether hand/wrist problems get better or not:* Agree	-0.05 (-0.30 to 0.19) 0.03 (-0.19 - 0.25)	0.67 0.78
Treatment control *Treatment can control my hand/wrist problem:* Agree	 -0.13 (-0.38 to 0.13)	 0.33
Injection (treatment)	0.09 (-0.14 to 0.31)	0.45

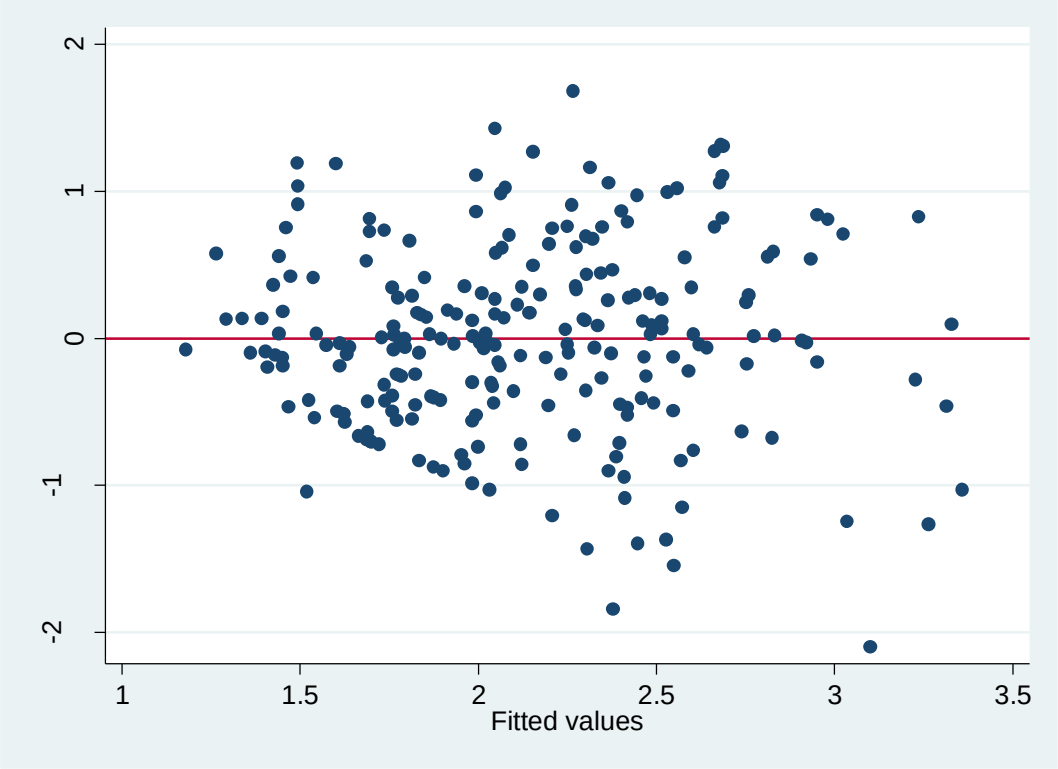
Table 6-6 Multivariable model using backward stepwise variable selection in imputed data and complete cases

	Multivariable analysis of association with BCTQ at six months **IMPUTED DATA**		**Multivariable analysis of association with BCTQ at six months** **COMPLETE CASES**	
	Regression coefficient (95% confidence interval)	P value	Regression coefficient (95% confidence interval)	P value
Baseline BCTQ	0.95 (0.60 to 1.30)	<0.01	-0.41 (-0.76 to -0.08)	0.02
Baseline symptom severity	-0.32 (-0.68 to 0.29)	0.07		
Any other condition affecting neck, shoulder or elbows	-0.21 (-0.43 to 0.02)	0.07		
	Adjusted R^2 = 0.31		Adjusted R^2 = 0.36	

6.4.2.2 Checking linear regression assumption

The residuals plotted on the y axis of Figure 6-2 represent the differences between the observed and predicted values ofsix- month BCTQ scores. The fact that the points are randomly dispersed around the horizontal axis, not clustered around lower digits of the y axis and that there are no clear patterns, suggest that linear regression is appropriate for this data and no further transformation of the variables is necessary.

Figure 6-2 residual plot of fitted values (of the BCTQ score)



6.4.3 Adjusting the final model for optimism and assessing performance

The multivariable model was then adjusted for optimism using heuristic shrinkage. The statistical process of heuristic shrinkage is shown in Figure 6-3.

Figure 6-3 Process of applying heuristic shrinkage to the model

1. Calculating heuristic shrinkage for the continuous outcome:

S = 1 - ((p-2)/LR)

Stata code LR = display -2*(e(ll_0)-e(ll))

S = shrinkage factor p = parameter LR = likelihood ratio

=0.73943638 (m==1)

=0.74086464 (m==2)

2. Imputed model with shrinkage factor applied to beta coefficients:

Original model

E(Y) = 0.61 + (0.9541716*cts_BL) - (0.3246921*sev_cts_BL) - (0.2108877*nul)

E(Y) = predicted mean

Shrunken model

E(Y) = ? + (0.70554919 *cts_BL) - (0.24008915*sev_cts_BL) - (0.15593804*nul)

3. Calculating the shrunken intercept: multiply each beta by the shrinkage factor, calculate the linear predictor minus the intercept using the shrunken betas.

gen LP_shrunk = (0.70554919 *cts_BL) - (0.24008915*sev_cts_BL)- (0.15593804*nul)

constraint define 1 LP_shrunk = 1

mi estimate: cnsreg cts_6M LP_shrunk, constraint(1) = 1.010474

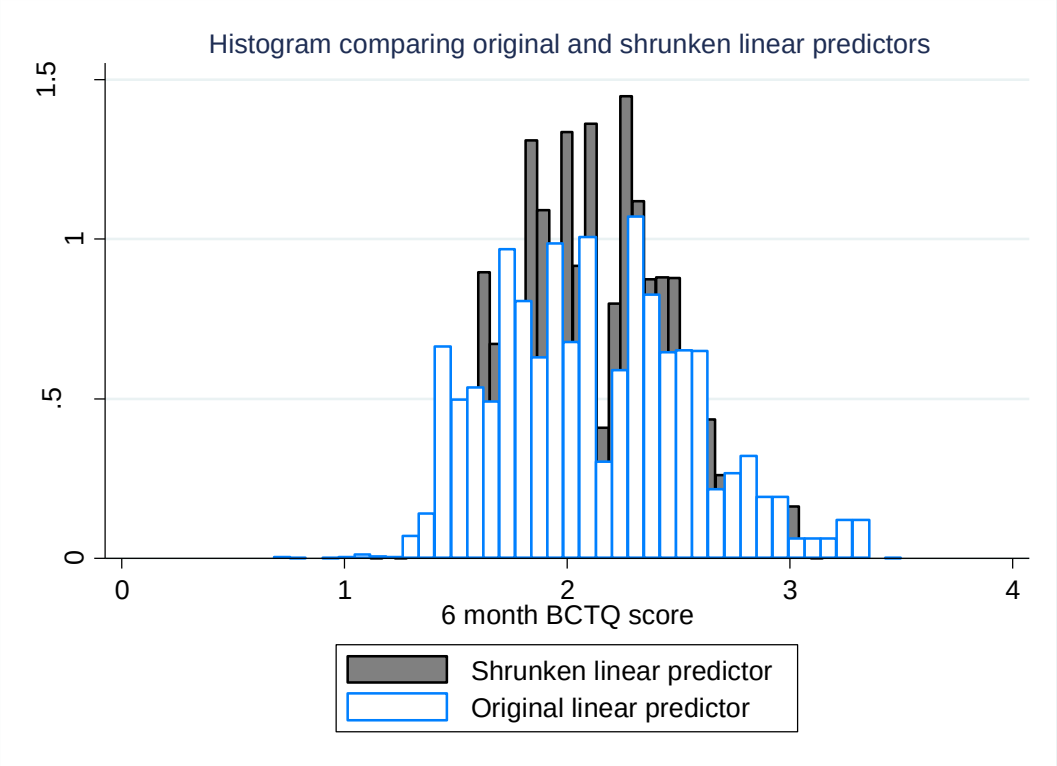
E(Y) = 1.010474 + (0.70554919 *cts_BL) - (0.24008915*sev_cts_BL) - (0.15593804*nul)

Summary of original and shrunken linear predictor (LP):

	Observations	**Mean linear predictor**	**Standard deviation**	**Minimum**	**Maximum**
Original LP m=1	234	2.125345	0.4367796	1.277017	3.351376
Heuristic LP m=1	234	2.130975	0.3229707	1.50369	3.037547
Original LP all data	8875	2.126608	0.4437389	0.6846382	3.500507
Heuristic LP all data	8875	2.131909	0.3281167	1.065664	3.14782

Figure 6-4 shows a histogram comparing the shrunken and original linear predictor, demonstrating how adjusting the model for optimism has reduced both the extremes of the distribution of the linear predictor and the mean of its distribution. This means that the predicted outcome for a new patient using the shrunken linear predictor would be less extreme than it would have been using the original.

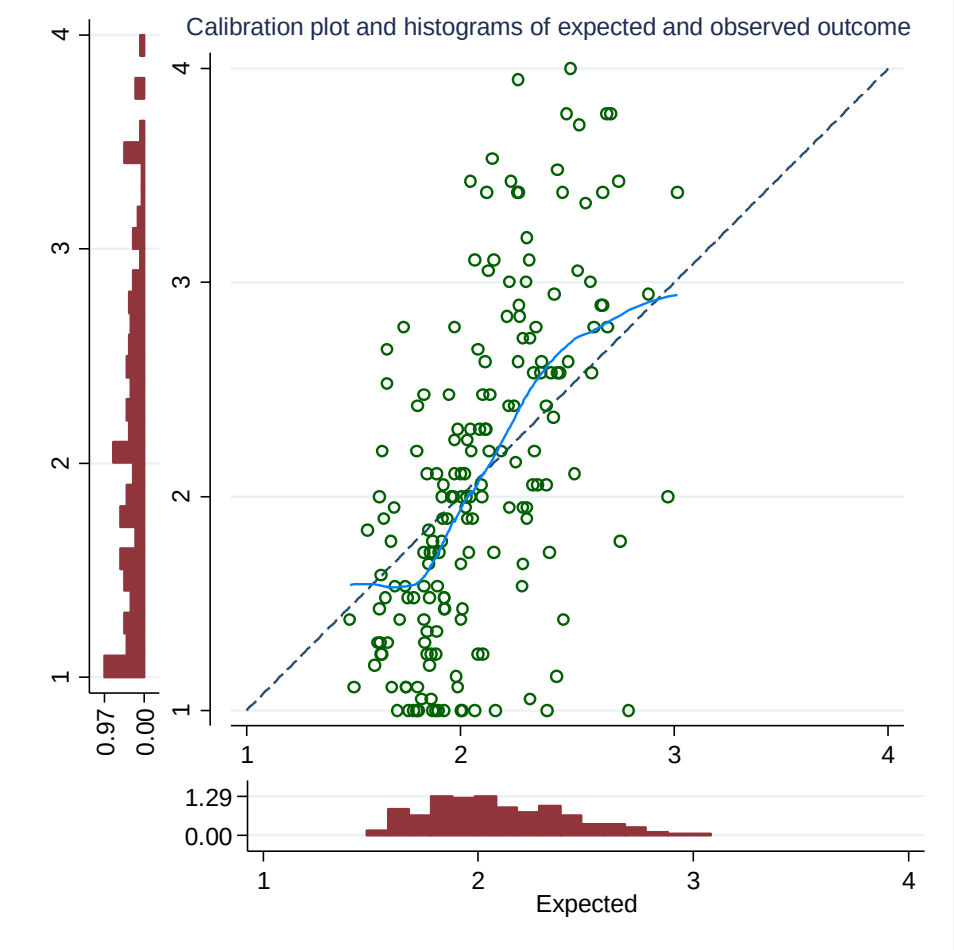
Figure 6-4 Histogram comparing the original and shrunken linear predictors



6.4.4 Calibration of the shrunken model

Figure 6-5 then plots the expected and observed outcomes against each other to demonstrate how well the model is calibrated. Of note there is no R^2 presented as the Betas in the model have already been shrunken so this information would not be meaningful.

Figure 6-5 Calibration plot of the shrunken model



The calibration plot of the shrunken model suggests that it does not perform well. Ideally, the points should align along the reference (dashed) line but instead they are in an almost vertical alignment. This suggests the model overestimates the severity of outcome in patients with less severe observed CTS and underestimates the severity of outcome in patients with more severe observed CTS. This also means the model does not discriminate very well between participants with different levels of BCTQ scores at six months; predicted BCTQ values appear to cluster around a score of 2. It is not possible to produce a discrimination statistic for the model given the use of a continuous outcome.

6.4.4.1 Post hoc sample size calculation

As described in 6.3.4.3, an alternative and more precise approach to assessing the number of participants required per variable, based on the R^2 of the model, the number of parameters to be

included, the intercept of the regression equation and the standard deviation of the linear predictor is to apply PMSAMPSIZE [171] to the dataset. Figure 6-6 below presents the process of in a posthoc sample size calculation.

Figure 6-6 Process using pmsampsize to calculate post hoc sample size

Process using the pmsampsize programme (Ensor et al):

pmsampsize, continuous rsquared(0.29) parameters(27) intercept(2.66) sd(0.67)
NB: Assuming 0.05 acceptable difference in apparent & adjusted R-squared
NB: Assuming MMOE<=1.1 in estimation of intercept & residual standard deviation
SPP - Subjects per Predictor Parameter
Minimum sample size required for new model development based on user inputs
= 650 participants

Worked in reverse: the number of parameters suited to this dataset:

pmsampsize, continuous rsquared(0.29) parameters(10) intercept(2.66) sd(0.67)
NB: Assuming 0.05 acceptable difference in apparent & adjusted R-squared
NB: Assuming MMOE<=1.1 in estimation of intercept & residual standard deviation
SPP - Subjects per Predictor Parameter
Minimum sample size required for new model development based on user inputs = 244
* 95% CI for intercept = (2.57, 2.75), for sample size n=244
* 95% CI for intercept = (2.61, 2.71), for sample size n=676

Based on the R^2, number of parameters, the intercept and standard deviation of the outcome, this sample size calculation suggests that a participant per variable rate of substantially more than 10 (24 variables) would be required to ensure the model is optimised to reduce the risk of overfitting. This is likely because the average change observed in the outcome measure over time was small.

6.5 Discussion

The methods and findings of this prognostic study will now be discussed. Reflections on the differences between the prediction model developed in the CPRD dataset and this model alongside related research will be discussed in chapter 9, in terms of the different populations, outcomes, candidate predictors and statistical approaches used.

6.5.1 Summary of main findings

A prognostic model was developed, using data from a randomised controlled trial, to predict patient reported outcome at six months following conservative management of mild to moderate CTS. The model, based in imputed data, included a small number of prognostic factors (BCTQ, SSS and neck and upper limb symptoms). The model was found to have poor predictive performance, likely due to the relatively small sample size and homogeneity within the cohort.

6.5.2 Methodological considerations

It was decided to model the outcome of CTS using this trial data-set as there were substantial limitations with the model developed in the CPRD data; particularly the inability to include potentially important prognostic factors reflecting patient and disease characteristics. Data from the INSTINCTS trial was available and there was an a-priori plan to measure certain features at baseline in order to investigate prognosis and explore potential predictors of treatment effect (chapter 8).

The trial had been designed pragmatically to represent patients presenting in a primary care setting with purposively few exclusions. The trial however was targeted at patients with mild to moderate CTS who would be amendable to primary care / conservative treatment options. Patients with features in their history or examination findings suggestive of severe CTS were excluded from the trial. Such patients should have been referred for consideration of surgery, perhaps with conservative treatment options used as an interim measure. This may have led to the trial population being relatively

homogenous and not necessarily representative of the entire CTS population presenting in primary care. A homogenous population with similar baseline features and outcomes would make a predictive model difficult to develop and demand a large sample size, as is illustrated above by the application of the PMPSAMPSIZE calculation in Figure 6-6. The performance (calibration) of the model and histogram of the shrunken linear predictor does suggest that firstly the model does not predict well and secondly, predictions are focused narrowly around the mean with little spread.

Whilst measured at baseline, many of the candidate predictors were based on self-report. Items such as symptom duration were at particular risk of misclassification due to incorrect recollection. The quality of the data and precision of the candidate variables can therefore not be substantiated other than by the fact that completion of the baseline questionnaire was checked by the investigator prior to randomisation. However, established and validated tools were applied where possible.

The pragmatic design of the trial was such that diagnosis of CTS was based on clinical opinion using a criteria developed to represent current practice. Some may argue that more objective measures of diagnosis including use of NCS should have been applied to the patients at inclusion, however clinical guidelines do support the trial's approach to diagnosis. Misclassification of patients as having CTS or additional diagnoses (e.g. 'double crush syndrome') cannot be ruled out. It is of interest that patients with symptoms in their neck or upper limb appeared to exhibit greater improvement (adjusting for BCTQ and SSS in the model) than those that did not. This seems counter-intuitive and at odds with the CPRD model but may be due to sample size (small number of participants with additional neck or upper limb symptoms), misclassification, or correlation between this candidate predictor and other variables in the model (e.g. baseline symptom severity).

Whilst not a survival analysis, events may have occurred in the cohort which altered the observed outcome, other than the initial set of candidate predictors and conservative intervention, and in effect acted as a competing benefit. The main trial reports that at six months, 30 (12.8%) of participants had had surgery.[59] If patients with a poorer response to treatment or who had more severe CTS at baseline received surgery and presumably therefore experienced a satisfactory outcome, this may have

influenced the association of baseline prognostic factors with outcome and partly explain the weak performance of the model.

The issue of laterality and the associated risk of a unit of analysis error will be discussed in Chapter 9. However, whilst bilateral CTS was included as a candidate predictor, attempting to distinguish between symptoms of each hand or wrist for research purposes, can be an issue for patients and affect the reporting in studies.[173]

6.5.3 Clinical relevance of the findings

A reflection on the similarities and differences between this model and the model developed in CPRD data will be fully discussed in Chapter 9 in the context of results from previous research. Due to the limitations as discussed, the model does not appear to have clinical utility and would not be proposed as a useful tool in the management of CTS. A well performing model would have been further internally and externally validated and proposed as a tool to help identify patients who were likely to do well with conservative management and those who should be more closely observed / referred for consideration of surgery.

6.5.4 Conclusion

The model presented in this Chapter was developed using the data of trial participants, being observed as a single cohort. The aim was to describe the clinical course of CTS in this population and predict patient reported outcome. Whilst patients did show improvement over time, the improvement was relatively small, and it would have required a much larger sample size than was available to test the already much reduced list of candidate predictors that had been developed. The post hoc application of PMPSAMPSIZE, highlighted the relative redundancy of a participant per parameter = 10 'rule of thumb.'

In Chapter 7, the focus will move from the general prognosis of CTS to its management and whether treatment options can be better targeted to patients, dependent on observations made at baseline, in order to improve the outcome of conservative management.

7 The management of carpal tunnel syndrome: matching patients to treatments in carpal tunnel syndrome - a systematic review and narrative synthesis of trial evidence

Summary

The aim of this chapter is to investigate candidate predictors of treatment effect (effect moderators) to common primary care treatments of carpal tunnel syndrome (CTS), specifically corticosteroid injection (CSI) and night splinting (NS). The available evidence regarding predictors of the effect of CSI and NS from randomised controlled trials will be summarised and any gaps in current knowledge identified. This will be achieved by conducting a systematic literature search and narrative synthesis of clinical trials that have performed subgroup analyses of their data and suggested likely predictors of treatment effect. Any identified or suggested moderators will then be considered for testing within INSTINCTS (Injection versus Splinting in Carpal Tunnel Syndrome) trial data in Chapter 8. Whilst non-confirmatory (given limited statistical power), results may suggest ways in which CSI and NS can be better targeted to patients, based on their baseline characteristics, with the future aim of improving patient outcomes and efficiency in healthcare.

7.1 The concept of stratified care and moderators of treatment effect

Stratified care can be defined as *"the targeting of treatments according to the biological or risk characteristics shared by subgroups of patients."*[74] Stratified care thus utilises information about an individual's likely response to treatment to inform management decisions. This approach moves from the more traditional notion of stepped care, whereby patients are managed incrementally according

to treatments tried previously, to stratified care, whereby patients are offered treatment informed by their individual baseline profile.

A stratified approach to management may be of benefit when treatment effect is inconsistent across patients due to at least one individual measure being associated with a change in treatment effect i.e. there is interaction between a patient-level variable and the effect of the treatment on the outcome. Such an interaction may represent a mechanism for the observed difference in treatment effect.[74]

Prognostic factors are measures associated with an outcome, even in the absence of a particular treatment. A prognostic factor may also be a predictor of differential treatment response (or effect moderator), when there is a causal or mechanistically relevant effect.[74] A moderator is therefore a characteristic, measured at baseline, which influences the relationship between an intervention and an outcome and hence predicts response to treatment.[174] Most prognostic factors however are not moderators when tested for their association with the effect of treatment, while only in some instances moderators are not associated with outcome in the absence of treatment (and hence are not also prognostic factors).

In terms of CTS, a stratified approach would mean suggesting to patients presenting with symptoms of CTS that they may do better with an injection compared to night splinting given that they or their wrist problem has certain characteristics. The outcome of this chapter is to begin to identify what these features (candidate moderators) in the case of treatment with either injection or splints might look like.

This chapter will present a systematic review of trials testing CSI and NS as treatments for CTS. Moderators tested by these trials will be identified and the evidence for them appraised. Randomised trials are required as a study method to demonstrate, through the use of tests for interaction, that one intervention is significantly more effective than another (control or active), in patients with certain baseline characteristics.[174, 175] This differs from the identification of prognostic factors, whereby, a

single treatment arm (or an observational cohort study) identifying general predictors, not necessarily unique to an intervention, are investigated.[174]

7.2 Conservative treatment options of CTS: corticosteroid injection and night splinting

7.2.1 Carpal tunnel syndrome

The pathophysiology of CTS is not fully understood, however theories exist as to how complex mechanisms interact and lead to the observed clinical syndrome. An increase in pressure in the carpal tunnel leads to disordered intraneural microcirculation, lesions in the myelin sheath and the axon and changes in the supporting connective tissue. Reduction in the endoneurial blood flow increases the permeability of the endoneurial vasculature resulting in the formation oedema. As well as further pressure changes from oedema, hypoxia occurs leading to axonal degeneration and median nerve neuritis. The upregulation of angiogenic factors (HIF-1 and VEGF) cause synovial hypertrophy, thus leading to further pressure changes and a positive feedback mechanism of neural damage.[176] These interacting pathophysiological processes gives rise to localising symptoms, which include pain, numbness, tingling, and in the more severe cases, weakness and associated impairment of function.

7.2.2 Corticosteroid injections and night splinting

The mainstay of treatment options deliverable in primary care are CSI and NS. A trial of such treatments is usually carried out and if unsuccessful, surgery may be considered to manually decompress the carpal tunnel. The mechanisms of action and evidence base for their use has been presented in 1.4, but will now be summarised:

The rationale for the use of CSI is based on the theory that the steroid reduces oedema in the carpal channel and hence reduces the pressure on the median nerve from the surrounding tissues[2] However, since the pathophysiology of CTS is complex and not fully understood,[176] it seems reasonable to conclude that neither is the pharmacological action of a corticosteroid injection.

A Cochrane review evaluating the effectiveness of CSI for CTS versus placebo injection or other non-surgical interventions concluded that CSI's do improve symptoms in the short term, compared to placebo, however symptom relief beyond this period has not been clearly demonstrated.[45] The more recent RCT by Atroshi et al provided some longer-term data suggestive that steroid injection may be clinically effective in reducing the symptoms of CTS and reducing the number of patients having surgery, but only at a dose of the steroid higher than what would perhaps ordinarily be used in clinical practice.[53] Further research is hence required to investigate whether steroid injections have the potential to improve symptoms and the need for surgery, in the longer term and at what dose.

The evidence base for the use of wrist splinting as a treatment for CTS is not as robust. A Cochrane review by O'Connor et al observed the effectiveness of multiple approaches to nonsurgical treatments of CTS, with the exception of CSI, to include wrist splinting. This review concluded that no significant evidence existed for the benefit of a nonsurgical treatment.[177] Page et al conducted a Cochrane review of randomised and quasi-randomised trials comparing splinting with no treatment (or placebo) or with other non-surgical interventions. The authors' conclusions suggest there is limited evidence that night splinting is more effective than no treatment in the short term (less than 3 months follow-up).[42] Splinting may be a treatment option for some patients but there is limited evidence regarding its effectiveness compared to no treatment or other conservative option.

Given that evidence for the use of CSI and NS in the average population of patients with CTS is limited, whether the treatments may benefit particular subgroups of patients will now be investigated. Firstly, the evidence for predictors of treatment effect investigated in existing trials will be summarised, and in Chapter 8, the most promising candidate predictors identified from the literature and expert opinion will be tested within trial data.

7.3 Methods

The aim of this systematic review and narrative synthesis was to summarise evidence regarding predictors of the effect of CSI and NS tested in previously published randomised controlled trials. The

following work was based on a search conducted in 2013 run at the same time as the search for the systematic review presented in chapter 4. The review and synthesis informed the design of the reported study in a subsequent chapter and as such has not been formally updated. However, section 9.2.3 describes any relevant updates in the literature and the potential impact they may have on the findings of this review. The protocol for this review was registered on PROSPERO (CRD42013006608) and can be accessed at

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42013006608#.VYk_RflVhBc.

7.3.1 Eligibility criteria

To be eligible for inclusion in the review, studies were required to fulfil the following criteria as described in Table 7-1 and Table 7-2.

Table 7-1 Summary of inclusion criteria

	Inclusion criteria
Population	General adult population (non-pregnant) aged 18 years or over Diagnosed with carpal tunnel syndrome (method of diagnosis to be documented)
Interventions or exposure	Patients receiving a steroid injection to the wrist or splints as a treatment for CTS
Comparisons	Where trials are being used to investigate moderators of treatment effect: placebo, surgery (carpal tunnel release) or alternative non-surgical treatments were used as a comparator.
Outcomes	Outcome measures able to indicate improvement in symptoms and/or function including: dichotomised global improvement measures; positive changes in the mean Boston Questionnaire score or similar disease or region specific self-reported outcome measure; return to work, and no need for further treatment (likely to be carpal tunnel decompression surgery).
Setting	Any healthcare setting
Study design	Randomised controlled trials with evidence of an investigation of moderators or subgroup analyses

Table 7-2 Summary of exclusion criteria

	Exclusion criteria
Population	Studies of pregnant women with CTS Studies reporting diseases other than CTS Studies reporting outcomes of specific populations (not the general population)
Interventions or exposure	Studies with a follow up of less than six weeks Studies investigating secondary CTS (e.g. post-traumatic)
Comparisons	Studies where the intervention or comparator is not a steroid injection or wrist splint Studies comparing methods of delivering treatments alone (e.g. injection technique)
Study design	Papers in languages other than English where no translation is available Papers other than those described in the inclusion criteria, e.g. case studies and clinical guidelines

7.3.2 Search strategy

The same databases and additional search methods were used and applied as described in 4.2.2. The electronic databases were searched using a combination of free-text, MeSH and database specific headings. The full search strategies can be found in appendix C. These search strategies were developed with the input of experts in health informatics and used some pre-existing strategies available within the Primary Care Centre, already developed to identify particular types of study.

"Carpal tunnel syndrome" was searched for using MeSH (or database-specific equivalent) terms and in free text. MeSH headings were 'exploded' to broaden their definition. Terms such as 'entrapment neuropathies' were included to ensure the search remained sensitive. The searches were combined using the Boolean operator "OR."

This systematic review required randomised controlled trials to be identified by the search. Strategies used to identify trials were adapted from:

- The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (http://handbook.cochrane.org/chapter_6/6_4_11_1_the_cochrane_highly_sensitive_search

_strategies_for.htm) This strategy was adapted for use within the other E-Databases depending on their specific search terms

- Sign methodology filters (http://www.sign.ac.uk/methodology/filters.html#random) were used to search for trials within EMBASE

7.3.3 Selection of eligible studies

The citations identified using the methods described above were downloaded using OVID SP and then transferred to and stored in REFWORKS (Legacy version). Duplicates were removed. All titles were screened against the eligibility criteria by the author. Full text review was undertaken for any abstract that could not be confidently excluded and could potentially fulfil the inclusion criteria. Abstracts and full texts were assessed independently by LC to determine agreement. Disagreements and queries were managed through discussion.

7.3.4 Data Extraction

Data were extracted by CB and checked by LC using a pre-defined data extraction form, which had been piloted and edited to ensure the correct information was captured.

Data extraction included details of the aims and objectives of the study, inclusion and exclusion criteria, recruitment and blinding procedures, intervention and setting, outcome and analysis and sub-group analyses reported. The sub-groups were then specifically described, the type of analysis presented and outcomes presented narratively.

7.3.5 Assessing the risk of bias

In order to appraise the risk of bias and methodological quality of the included trials, it was decided to use two approaches. Firstly, the Cochrane Collaboration's 'Risk of Bias Tool'[119] was used to judge the overall risk of bias for each trial included in the review. Secondly, the 'Methodological Criteria for the Assessment of Moderators in Systematic Reviews of Randomised Control Trials' by Pincus et al, were used to more specifically score quality of the moderation analysis.[178]

7.3.5.1 Using the Cochrane Risk of Bias Tool

Bias can be defined as a *"systematic error, or deviation from the truth, in results or inferences*."[119] Bias can therefore lead to an overestimation or underestimation of the true intervention effect. Errors in the design, conduct and analysis of trials may lead to bias, however this is not a certainty, therefore the term 'risk of bias' is used. Considering the risk of bias in each study to be included in a systematic review was important to explain any observed variation in the study results and to alert to the possibility of erroneously making a false positive or false negative conclusion.[119]

The Cochrane Risk of Bias tool is a domain based evaluation of six possible sources of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias (for example, claims the study may be fraudulent). Each study was judged under each of the seven domain headings as being of 'low risk of bias,' 'high risk of bias,' or 'unclear risk of bias.' The tool provides criteria under each heading by which each study is reviewed. Supporting information and comments based on these criteria were required for each study, to inform the judgement of the risk of bias. Judgements were made by the author and LC and disagreements brought to discussion, after which 100% agreement was achieved.

7.3.5.2 Using the Criteria Developed by Pincus et al

Criteria to assess the quality of moderation analysis were developed by Pincus et al, following an identified need to extend contemporary advice about assessing the analysis of subgroups and focus specifically on the analysis of baseline factors that moderate treatment effect.[178]

In order to develop the agreed criteria, Pincus et al identified methodological manuscripts found using a snowballing technique and searches of electronic databases. The initial criteria comprised of 19 questions derived from this search are shown in Table 7-3. An international Delphi panel of 21 experts were then involved in a consensus exercise to agree the final criteria. The final criteria recommend whether moderation analysis from a trial can be considered to be either confirmatory or exploratory. Confirmatory analyses test a priori defined hypotheses and exploratory analyses inform future

(confirmatory) research or may inform clinical practice. Pincus et al proposed that for inclusion in a meta-analysis of moderators, three criteria should be met: baseline factors should be measured prior to randomisation, their measurement should be of sufficient reliability and validity and a specific test for interaction should be presented. In order to be considered confirmatory the analysis should also be planned a-priori and the factor selection based on either theory and / or evidence. These final criteria are summarised in Table 7-4.[178]

This systematic review did not identify RCT's in sufficient quantity or homogeneity to include in a meta-analysis. The Pincus criteria were therefore adapted slightly and used to describe whether the moderation analysis presented in each individual paper could be considered to be confirmatory, exploratory or indeed insufficient.

The authors suggest that the proposed criteria are less conservative than the guidance provided by the Consolidated Standards of Reporting Trials (CONSORT) statement (The Centre for Reviews and Dissemination and the Cochrane Handbook), in that the criteria allow for post-hoc subgroup comparisons and do not limit the number of sub-group analyses carried out at the meta-analytic stage. It is suggested that this prevents a too rigid set of criteria impeding the progress of research in the area of analysis of moderators and preventing the exploratory analysis of studies, which may go on to inform further research.

Table 7-3 Summary of the methodological criteria proposed by Pincus et al for the assessment of methodological quality of moderation analysis

Methodological criteria
Stage 1
Rationale
1a. Was the analysis a-priori (planned in protocol rather than post-hoc)?
1b. Was selection of factors for analysis theory / evidence driven?
Method
2a. Was there an equal distribution of moderators between groups at baseline?
2b. Were moderators measured prior to randomisation?
Power
3a. Do authors report a power analysis for moderator effect (a-priori or post hoc, but using an a-priori ES, not the observed one?
3b. Was sample size adequate for the moderator analysis (at least 4 fold the required sample size for main treatment effect in the lowest sub-group for the moderator effect)?
3c. If not, were there at least 20 people in the smallest sub-group of the moderator?
3d. Have authors employed analysis to compensate for insufficient power(i.e. boot-strapping techniques)
Correction for multiple comparisons
4a. Was the regression significant at P<0.006, or (if more than three comparisons) corrected or significance adjusted to P<0.01?
4b. Did the authors explore residual variances of interactions if carrying out multiple two-way interactions?
Measurement validity and measurement error. Was measurement of baseline and process factors reliable and valid (from published information) in the target population?
5a. Is there evidence that the measurement error of the instrument is likely to be sufficiently small to detect the differences between sub-groups that are likely to be important?
5b. Did the authors comment on measurement validity in reference to construct validity, face validity etc
Analysis
6a. Contains an explicit test of the interaction between moderator and treatment (eg regression)
6b. Was there adjustment for other baseline factors?
6c. Is there an explicit presentation of the differences in outcome between baseline sub-groups (eg standardised mean difference between groups, Cohen's d)
Stage 2
1. Difference between sub-groups should be clinically plausible
2. Reporting of sub-group analysis is only justified in cases where the magnitude of the difference is large enough to support different recommendations for different sub-groups
3. Within study comparisons are more reliable than between study comparisons
4. At least ten observations should be available for each characteristic explored in sub-group analysis (ie ten studies in a meta-analysis)

Adapted from [178]

Table 7-4 Criteria for considering moderation analysis to be confirmatory or exploratory

Criterion	Necessary for confirming moderator effect	Necessary for exploring moderator effect	Criteria for the judgement of yes	Exceptions
1. Was the analysis a-priori?	Yes	No	Mention of explicit hypothesis planned in protocol stating which sub-groups will be tested for which outcome	Criterion is not fulfilled in cases where the protocol includes a considerably large set of stated hypotheses or vague hypotheses (eg psychological factors will interact with treatment outcome)
2. Was selection of factors for analysis clinically plausible and either or both:	Yes	No	A description of theoretical background, or reference to other published evidence leading to the hypothesis	Is not fulfilled in cases where the meta-analyst considers the theory / evidence to be weak, but should not form reason for exclusion
i. Theory based?				
ii. Evidence based?				
3. Were moderators measured prior to randomisation?	Yes	Yes	Specific statement that baseline measurement occurred prior to randomisation	Not applicable for baseline factors that do not change over time, such as gender, or for cluster randomisation
4. Adequate quality of measurement of baseline factors	Yes	Yes	If there is published evidence to support good measurement properties of measurements for target population, according to meta-analysts protocol	Is not fulfilled where there is inadequate variability in baseline measure
5. Contains an explicit test of the interaction between moderator and treatment	Yes	Yes	Ideally, Report a pooled effect size with 95% confidence intervals. Other acceptable analysis includes regression etc	Not fulfilled when sub-groups are tested separately, or in excessive multiple testing

Adapted from [178]

The analyses of moderators from each trial were assessed by the author and LC - A 'yes' / 'no' / 'unsure' judgement and the reason for the decision were made by the author and LC and disagreements brought to discussion, after which 100% agreement was achieved.

7.3.6 Analysis

Substantial heterogeneity between the trials was found, related to trial inclusion criteria; interventions; outcomes and sub-groups included in the analysis. Therefore, the main findings and the outcome of the sub-group analyses were not pooled but discussed narratively, taking quality of the evidence (risk of bias and quality of moderator analysis) and the consistency of findings into account.

7.4 Results

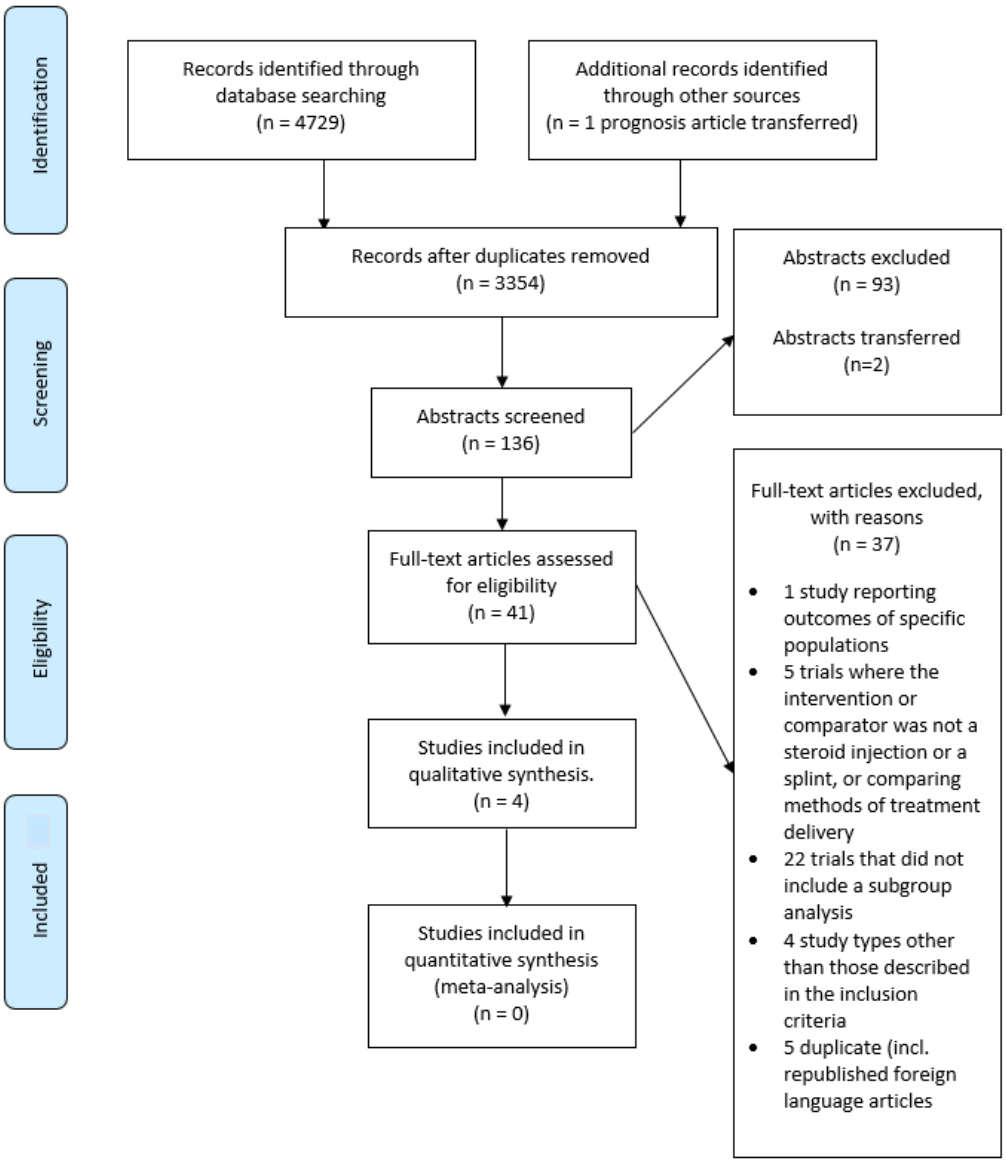
7.4.1 Summary of Search Results

4729 citations were identified by the search. The number of citations from each source are shown in Table 7-5. As summarised in Figure 7-1 , there were 3354 citations after duplicates were removed, 136 following title screening and 41 following abstract screening. There were four studies included following full text screening, which were not suitable for including in a meta-analysis.

Table 7-5 Summary of search results

Source	**Article titles**
CINAHL	417
AMED	86
PsychInfo	37
HMIC	3
EMBASE	2031
Medline	1021
TRIP	308
Cochrane	755
SCI-EXPANDED + CPCI-S	71
Total	**4729**

Figure 7-1 PRISMA flow diagram



7.4.1.1 Trial characteristics

A summary of the main characteristics of the four trials identified by the search, suitable for narrative synthesis can be found in appendix E. All four trials were set in secondary care, three trials required a clinical diagnosis and electrophysiological confirmation of CTS, one (Atroshi et al) only required a clinical diagnosis. The inclusion and exclusion criteria differed: two trials (Atroshi et al and Ly-Pen et al) required a previous treatment of splinting + / - non-steroidal anti-inflammatories (NSAID's) whereas Celiker et al and Gerritsen et al excluded patients with any previous treatment. Celiker et al had a more pragmatic exclusion criteria, and hence was more likely to be representative of the population presenting with symptoms in primary care, whereas the other trials excluded patients with co-morbidities such as diabetes and hypothyroidism.

In order to identify predictors of treatment effect, the systematic review required patients within the identified trials to receive either injection or splinting as one of the trial interventions. Atroshi et al compared two different doses of Methylprednisolone with placebo. Celiker et al compared Methylprednisolone with wrist splinting and NSAID's. Gerritsen et al compared surgery with splinting whilst Ly-Pen et al compared surgery with injection. Follow-up ranged from 8 weeks to 18 months and no trial used the same outcome measure.

Atroshi et al demonstrated Methylprednisolone was more beneficial than placebo and Ly-Pen reported that at 3 months a greater improvement was observed in the Methylprednisolone group, compared with the surgery group. Gerritsen et al observed a higher success rate in the surgery group compared to splinting but Celiker et al did not note a significant difference between splinting and injection. Due to the variation in the trial settings, populations, interventions, follow-up periods and outcome measures, the extent to which the trial outcomes can be compared was limited, and hence, meta-analysis was not suitable.

7.4.1.2 Risk of bias

As illustrated by Table 7-6, of the four included trials, two (Atroshi et al and Gerritsen et al) were considered to be of low risk of bias in six out of seven and seven out of seven of the Cochrane Risk of Bias domains, respectively. Celiker et al was felt to be at high risk of bias in two criteria, of unclear risk of bias in four criteria and low risk of bias in one criterion. This was largely because the reporting of the methods was unclear with respect to the generation of the randomised sequences and any blinding that may or may not have taken place. Ly-Pen et al was considered to be at high risk of bias in three criteria, unclear risk of bias in three criteria and low risk of bias in one criterion. This was due to the incomplete reporting of the methods regarding the handling of envelopes and blinding of participants and staff. There was a risk of attrition bias with missing outcome data, likely to be related to the true outcome with associated imbalance across the intervention groups. The trials by Atroshi et al and Gerritsen et al could therefore be considered to be of overall low risk of bias whilst the trials by Celiker et al and Ly-Pen et al could be considered to be of unclear risk of bias.

With respect to the judgement of the methodological criteria for the assessment of moderators, Table 7-7 shows that, given there was an a priori defined analysis of candidate moderators that had been selected based on theory, only Ly-Pen et al provided a moderation analysis, which could be considered confirmatory. Atroshi et al, Celiker et al and Gerritsen et al presented apparently ad hoc exploratory sub-group analyses.

In summary, two trials (Atrohsi et al and Gerritsen et al) were considered to be at low risk of bias for overall trial conduct, and one of the trials (Ly-pen et al, which had an unclear risk of bias) can be considered to have provided an adequate level of quality of moderation analysis to be considered confirmatory. Due to the limited number of trials investigating different candidate moderators with different outcomes, meta-analysis was not possible.

Table 7-6 Agreed risk of bias of each included trial

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other sources of bias
Atroshi et al, 2013 [53]							
Celiker et al, 2002 [48]							
Gerritsen et al, 2002[103]							
Lypen et al, 2012 [179]							

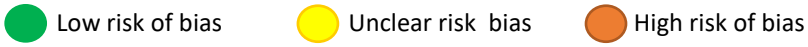


Table 7-7 Methodological assessment of moderation analysis (as per Pincus et al.)

	Was the analysis *a-priori*	Was selection of factors for analysis clinically plausible and either or both…			Were moderators measured prior to randomisation?	Adequate quality of measurement of baseline factors	Contains an explicit test of the interaction between moderator and treatment	Conclusion
		Theory based	*Evidence based*					
Atroshi et al, 2013[53]	Yes		Unsure	Unsure	Yes	No	Yes	Insufficient
Celiker et al, 2002 [48]	No		No	No	Yes	Yes	No	Insufficient
Gerritsen et al, 2002 [103]	No		No	No	Yes	Unsure	No	Insufficient
Ly-pen et al, 2012 [179]	Yes		Yes	No	Yes	Yes	Yes	Confirmatory
Yes Unsure No								

7.4.2 Predictors of treatment effect

The sub-group analyses presented in each included trial are summarised in Table 7-8. Attempting to compare the trial results was unlikely to be helpful due to the significant heterogeneity in methods, interventions and outcomes. With regard to the sub-group analyses, only Atroshi et al and Ly-Pen et al present a formalised model with interaction terms. The two remaining studies elude to the fact narratively that subgroup analyses were carried out. Gerritsen et al did write a further paper on the prognostic outcome of patients who received splinting but as this was not a moderation analysis and has been summarised separately in chapter 4.

7.4.2.1 Symptom duration

Both Atroshi et al and Celiker et al identified symptom duration as a possible predictor of treatment effect with cut offs at > 1 year vs. ≤ 1 year and > 9 months vs. ≤ 9 months, respectively. Atroshi et al reported that symptom duration did not moderate the response to Methylprednisolone injection compared to placebo. The difference in score change at 10 weeks was -0.81 (-1.20 to -0.43) in patients with a symptom duration of > 1 year, compared to -0.41 (-1.51 to 0.69) in those with a symptom duration ≤ 1 year. The test for interaction between symptom duration and treatment was reported as $P = 0.47$. Celiker et al reported narratively that *"patients with symptom duration more than 9 months did not respond well to treatment in either group" (*splinting or Methylprednisolone injection).

7.4.2.2 Symptom and nerve conduction severity

Atroshi et al also reported that the effect of Methylprednisolone injection on the 10 week post treatment symptom severity score, compared to placebo, was significantly larger in patients with higher baseline nerve conduction abnormalities (-0.87, -1.20 to -0.48 versus -0.26, -1.26 to 0.75; test for interaction $P < 0.001$) and more severe symptom scores at baseline (-1.02, -1.54 to -0.51 versus -0.38, -0.82 to 0.05; test for interaction $P < 0.001$).

7.4.2.3 Patient preference

Gerritsen et al investigated whether patient preference would affect response to treatment (methods and data were note reported) and reported that:

> *"subgroup analysis showed that treatment effects did not depend on the patients' preference prior to randomisation."*[140]

No further detail was provided making further analysis difficult.

7.4.2.4 Bilateral carpal tunnel syndrome

Ly-Pen et al performed a sub-group analysis to test the robustness of their trial conclusion, concerned that patients with bilateral CTS (included at the wrist level) may respond to surgery or splinting differentially than those patients with unilateral disease. They did not find a significant subgroup effect, reporting a *P* value of 0.5 and hence discarded the hypothesis that "*bilateral CTS responds differently" [to unilateral disease].*[180] Whilst the trial overall was not of low risk of bias, the moderation analysis was judged to be of such a quality as to provide confirmatory evidence. It can therefore be concluded that there is no evidence from this trial that bilateral or unilateral CTS responds differentially to either splinting or surgery.

Table 7-8 Summary of moderation analyses within included trials

Author (Year)	Candidate moderators	Intervention	Outcome	Statistical test	Results
Atroshi et al 2013	Duration of symptoms: >1y vs. ≤ 1y Nerve conduction study result: Moderately or severely abnormal vs. normal or mildly abnormal Baseline symptom severity score: ≥ 3.0 vs. < 3.0	Methylprednisolone (doses combined) (n=74) vs. placebo (n=37)	Difference in symptom severity score change at 10 weeks	Mixed models with interaction terms (treatment by subgroup)	Symptom duration >1y- (difference in change score between combined doses vs. placebo) 0.81 (-1.2 to -0.43) vs. Symptom duration <1yr- 0.41 (-1.51 to 0.69) *P value for interaction =* 0.47 **NCS moderate or severe-** **0.87 (-1.25 to -0.48)** **vs.** **NCS normal or mildly abnormal** **-0.26 (-1.26 to 0.75)** *P value for interaction <0.001* **Baseline CTS SSS >3.0** **-1.02 (-1.54 to -0.51)** **vs.** **Baseline CTS SSS <3.0** **-0.38 (-0.82 to 0.05)** *P value for interaction <0.001* *"…the effect of Methylprednisolone on symptom severity score was larger in patients with*

					higher nerve conduction abnormality and baseline symptom severity scores."
Celiker et al 2002	Duration of symptoms: >9m vs. ≤ 9m	Wrist splints at night with acemetacine 120mg/day (NSAID) (16 wrists, 11 patients) vs 40mg local Methylprednisolone (21 wrists, 12 patients)	Median nerve motor and sensory distal nerve latencies at 8 weeks	Not reported	*"patients with* ***symptom duration more than 9 months did not respond well to treatment in either group****"*
Gerritsen et al 2002	Patient preference	Wrist splinting at night vs. open carpal tunnel release	General improvement	Not reported	*"subgroup analysis showed that treatment effects did not depend on the patients' preference prior to randomisation" (data not shown)*
Ly-Pen et al 2005 Spain	Unilateral CTS vs. the most symptomatic wrist of bilateral CTS	Local steroid injection vs. carpal tunnel release	Percentage of wrists that reached ≥ 20% response for nocturnal paraesthesia at 3 months	Hierarchical linear models with 3 levels	*Random effect of having bilateral CTS P* > 0.5 Discards…*"the hypothesis that bilateral CTS responds differently"* [to unilateral disease]

7.5 Discussion

7.5.1 Summary of main findings

In summary, few (four) randomised trials testing the effectiveness of corticosteroid injections or splinting and included a sub-group analysis, were identified. The trials were heterogeneous and moderation analysis was not always presented. Evidence from one trial suggests that participants with a higher symptom and electrophysiological severity scores exhibit a greater response to CSI compared to placebo, when compared to participants with lower severity scores.

7.5.2 Interpretation of results

Subgroup analyses are performed in intervention studies in order to assess whether treatment effects vary across sub-populations. Outcomes between treatment groups are compared within subsets of patients, defined by their individual characteristics. The aim of a subgroup analysis is therefore to show if treatment effect varies depending on baseline patient characteristics. [181]

Whilst this can be a useful methodology to answer specific questions regarding the most effective application of a study intervention, such approaches have potential hazards.[182-187] The criteria as described by Pincus et al represent a consensus of expert opinion about what should be included in a study testing moderators and recommend qualities that determine whether a study provides exploratory or confirmatory evidence for a candidate moderator.[178]

None of the trials presented in this review were powered to perform moderation analysis. It is recommended that randomisation is stratified by potential moderators to ensure the subgroups of interest are sufficiently represented and that the trial is powered to detect any moderation effect.[181] Not having sufficient power can thus lead to false negative findings and hence a type II error.[74] This is likely to apply to all trials included in this review as none were specifically powered for moderation analyses.

A statistical test of interaction is recommended in any model used to detect moderation [178, 181] but was only clearly presented in two trials.[53, 180] The remaining trials appeared to present their sub-group findings on an ad-hoc basis with little information on the techniques employed to draw their conclusions given. No evidence of multiple statistical testing or data dredging was observed (which carries the risk of false positive results and hence type I errors).[74] Symptom duration was the only candidate moderator to be explored by more than one trial and in each situation an apparently arbitrary cut-off (9 months and 12 months) was used. The categorisation of variables and outcome measures can also lead to false positive findings.[74] Celiker et al report that patients with a longer symptom duration do worse than those with a shorter symptom duration overall (not quantified). Whilst Atroshi et al report no interaction between symptom duration and treatment effect, patients with a symptom duration > one year showed greater improvement over 10 weeks after methylprednisolone compared with placebo (difference in change score -0.81, 95% CI -1.20 to -0.43) compared to those with a symptom duration of less than 1 year (-0.41, -1.51 to 0.69). The lack of significant interaction may be due to sample size so the results of this trial are suggestive that patients with a longer symptom duration may respond better to CSI than no treatment.

Symptom duration was identified as a candidate predictor of poor outcome in the review of observational prognostic studies. However, there was no high-quality consistent evidence of this across studies and this review of trial evidence does not confirm that patients with a longer duration symptoms may respond more or less well to steroid injection or splinting. It is unlikely that symptom duration necessarily equates to symptom severity and / or electrophysiological outcomes. Padua 1998 et al describe how over time no clear trend in electrophysiological findings based on severity at presentation was observed.[125] In their later study, Padua et al investigated the correlation between symptom severity and neurophysiological results and report that discordance between neurophysiologic evolution and symptom evolution occurred in 9% of patients.[69] Thus, symptom duration is unlikely to be strongly associated with either clinical or electrophysiological severity but may still play a pathophysiological role which affects the likelihood of a spontaneous recovery or satisfactory response to treatment.

Atroshi et al's results suggest that patients with higher baseline nerve conduction abnormalities and symptom severity scores show a greater response to injection than to placebo. If 'no treatment' or 'watchful waiting' can be considered to be a valid treatment, one could argue that patients with CTS of higher severity should be considered for injection, over watchful waiting. It would be helpful to investigate for a differential treatment response between injection and a more active treatment such as splinting or surgery (which Atroshi does not present).

Gerritsen et al and Ly-Pen et al appear to have been using sub-group analyses as a means of exploring the robustness of their main trial findings rather than investigating predictors that may be used to develop a stratified approach to care. This is likely to be the reason that methods and results of the analysis was not presented. Patient preference was identified as a potential moderator in Gerritsen's trial comparing NS with CTR. Whilst not clearly expressed in the paper, one could assume that patients randomised to splinting may have felt less likely to receive benefit from their treatment, compared to those who had an operation. The evidence however did not substantiate this.

Page et al have described how, by analysing outcome data based on the number of wrists, without adjusting for non-independence of bilateral observations, a unit-of-analysis error may occur. This could subsequently lead to overly narrow confidence intervals and small *P* values, hence increasing the risk of type I errors.[144] By performing a sub-group analysis stratifying patients with bilateral and unilateral CTS and identifying no significant difference of treatment effect, Ly-Pen et al suggest that no such bias has been introduced into the study and that patients with unilateral versus bilateral disease do not respond to treatment any differently.

No predictors of a differential treatment response were definitively identified, highlighting the need for further investigation in this area. Such investigation would ideally include a trial or number of trials which fulfil the requirements of Pincus et al in that the study method: is designed *a-priori* to test sub-groups for pre-specified outcomes; that the selection of factors is clinically based on theory and / or evidence; moderators should be assessed prior to randomisation and measured adequately and that the statistical analysis includes a specific test of interaction.[178]

The number of trials available was limited due to the fact few had attempted or reported a sub-group analysis. The synthesis of available information was conducted at a study level and used published data only. Obtaining patient level data would have been a further possibility but as the trials were not designed to perform sub-group analyses and were so heterogeneous in their design, this approach was unlikely to obtain data that could be pooled and included in a meta-analysis.

7.5.3 Methodological considerations

Electronic databases considered to be important and relevant to the topic were searched. Titles were screened by one person therefore human error may have led to some titles being erroneously excluded. Studies not included in databases and not identified through reference checking, Google Scholar and expert advice may have been overlooked, such as unpublished studies. As the review did not find strong evidence for there being predictors of treatment effect, it is unlikely that further unpublished material would have strongly influenced the conclusions made.

7.5.4 Conclusion

This systematic review of trial data did not generate information that could be implemented clinically. In three of the four trials, the moderation analysis was of poor quality. None of the trials were powered to detect a moderation effect and apart from symptom duration, data for each of the candidate predictors came from one study only. Evidence exists suggesting that whether CTS is bilateral or unilateral does not differentially alter response to splinting or surgery. There is exploratory evidence that severity in terms of NCS results and patient reported symptoms do interact with the effect of CSI compared to placebo in that patients with more severe CTS show a greater improvement at 10 weeks following CSI than those with less severe CTS. This may mean that patients with more severe CTS should be offered treated at presentation rather than adopting a 'watch and wait' approach. Data from the INSTINCTS trial will now be used to further explore predictors of a differential treatment response to CSI versus NS in mild to moderate CTS.

8 Testing predictors of the effect of treatments for carpal tunnel syndrome in primary care – An exploratory analysis of data from the INSTINCTS (Injection versus Night Splints in Carpal Tunnel Syndrome) trial

Summary

Following the systematic review and narrative synthesis of predictors of treatment effect presented in chapter 7, this chapter identifies selected candidate predictors of treatment effect highlighted by the systematic review and suggested by a clinical advisory group, and tests them in data from the INSTINCTS trial, which specifically compares CSI versus NS in a primary care population. Whilst exploratory, results may suggest ways in which CSI and NS can be better targeted at patients, based on their baseline characteristics, with the future aim of improving patient outcomes and efficiency in healthcare use.

8.1 The INSTINCTS trial

The INSTINCTS trial was an open-label, parallel group, randomised control trial.[59] The methodology has been discussed in 6.2. The trial was designed to detect a 15% greater improvement in the combined BCTQ score,[32] from an expected baseline value of 2.9 points, with a pooled SD of 1.0 and standardised mean difference of 0.45. Given 90% power, 5% two-tailed significance and assuming 15% loss to follow up, 240 patients (120 in each arm) were required to be randomised. The trial was not powered to detect a moderation effect and the analysis presented in this chapter is entirely exploratory.

8.1.1 Overall trial results

234 patients were randomised (118 to the night splint group and 116 to the corticosteroid group), 217 returned their six-week questionnaire and 193 returned their six-month questionnaire. At six weeks, a significantly greater improvement in the overall BCTQ score was observed in the CSI group (mean score 2.02 [SD 0.81]) than the NS group (2.29 [0.75]); adjusted mean difference -0.32 (95% CI -0.48 to -0.16; *P*=0.0001). At six months the NS group showed further improvement, whilst the corticosteroid injection group sustained their six-week level of improvement, however there was no statistically significant or relevant difference observed between the groups (0.06; 95% CI -0.11 to 0.23; p=0.499). No serious or unexpected events were reported.[59]

Subgroup analyses based on participants with unilateral and bilateral symptoms and on those who received their preferred treatment allocation, were planned a-priori.[58] There was no statistically significant difference in the comparative effect estimate of CSI versus NS between those with unilateral and bilateral CTS (-0.14, 95% CI -0.47 to 0.19). The adjusted mean difference for CSI versus NS was -0.25 (95% CI -0.47 to -0.02) for patients with unilateral symptoms at six weeks and -0.15 (95% CI -0.48 to 0.19) at six months. The adjusted mean difference for those with bilateral symptoms was -0.39 (95% CI -0.62 to -0.15) at six weeks and -0.01 (95% CI -0.25 to 0.23) at six months.

Differences in BCTQ scores were observed in participants allocated their preferred treatment (n=42 adjusted mean difference -0.52, 95% CI -0.93 to -0.12) compared with those who were not allocated the treatment of their preference (n=52, -0.12, 95% CI -0.50 to 0.26). Individuals who preferred and received CSI showed a greater effect than those who preferred and received a night splint (CSI: n=58, -0.60, -0.97 to -0.23 versus preferred NS: n=52, -0.22, -0.60 to 0.16). Those with no preference also showed less improvement (n=128, -0.24, -0.44 to -0.05). The trial concluded that for each subgroup analysed, any effect modification was not statistically significant.[59]

8.2 Exploratory subgroup analysis: Methods

For the purpose of this thesis, further moderation analyses were carried out in order to explore whether predictors of treatment effect could be identified based on findings of the systematic review and clinical advisory group, also taking into consideration the prognostic factors included in the model developed in chapter 6. The intention was not to duplicate work conducted during the trial analysis but to develop methodological skills and test a small number of further plausible candidate moderators.

In order to reduce the risk of 'data dredging' potentially leading to false-positive (type 1 errors), treatment-predictor interactions to be tested should fulfil proposed criteria as described in chapter 7; they should be based on plausible hypotheses based on theory or evidence.

8.2.1 Selection of candidate predictors of treatment effect

8.2.1.1 Systematic review

The systematic review presented in chapter 7 identified five potential predictors of treatment effect that had been tested in the subgroup analyses of previous trials, which had included CSI or NS as one of their interventions: symptom duration, NCS severity scores, baseline symptom severity scores, patient preference, and laterality. All but the NCS severity outcomes could be identified within INSTINCTS data. By the fact that they were tested in previous trials, rationale exists that these variables may be predictors of treatment effect and given the risk of a type 2 error in underpowered trials, it was considered worthwhile to replicate testing in INSTINCTS data. INSTINCTS would also allow symptom severity to be tested as a predictor of a differential response to CSI compared to NS (rather than placebo).

8.2.1.2 Survey of General Practitioners

In chapter 5, a survey of seven GP trial co-investigators was presented. These practicing clinicians were asked to identify potential predictors of outcome of CTS presenting in primary care. They were also

asked what factors they felt may predict a differential response to CSI and NS. The survey was conducted during the design of the trial in order to inform the development of the baseline questionnaire, with a view to performing future subgroup analyses. Table 8-1 presents the list of features reported by the clinicians, which may either increase or decrease the likelihood of a favourable response to each of the treatment modalities being tested. In order to allow subsequent ranking to take place, the clinicians were asked to rate the features they identified from 1 (least likely to predict a differential response to treatment) to 4 (most likely to predict a differential response to treatment). The scores have been displayed as a sum score. The variables have been highlighted according to whether they:

i. could be extracted from INSTINCTS data and hence tested as candidate moderator (could be included in the analysis);

ii. substantially overlapped with the exclusion criteria of the trial (exclusion);

iii. did not represent a baseline characteristic (exclusion) or

iv. would only apply to a small subgroup of the trial population (and as such could not be included as the sample size would be further reduced) (exclusion).

Table 8-1 Candidate predictors of treatment effect generated by GP survey

NIGHT SPLINTING			
Likely to predict benefit	**Rank sum score**	**Likely to predict failure**	**Rank sum score**
Patients willing to try (for 2 weeks) / Good compliance / Motivation	9	Previous failure of splint to other wrist	9
Previous benefit from splint (to other wrist)	8	Thenar muscle weakness or wasting	6
Early morning pain and numbness predominate	7	Splinting at night is not acceptable / not willing to try	6
Pregnant	6	Long symptom duration	6
Nocturnal or wakening symptoms only	5	History of anxiety / depression	4
Short symptom duration	5	Continuous numbness	4
No thenar muscle weakness or wasting	4	Patients find splints uncomfortable	4
Work ethic	3	Daytime symptoms	4
Postural symptoms only	3	Poor compliance	4
Patient asks for splint	3	Unemployed / On sickness benefit	3
Good patient education	3	Poor education	3
Symptoms not related to work	2	Symptoms related to work	2
Symptoms not present at time of examination (may be evident on provocation)	2	Previous surgery on the effected side	2
Unilateral symptoms	2	Poor sleep because of CTS	2
Intermittent night symptoms	2	Long time interval before commencing treatment	1
Mild symptoms	2	Patients who normally fail to improve no matter what you offer them	1
No previous anxiety / depression	1		
CORTIICOSTEROID INJECTION			
Likely to predict benefit	**Rank sum score**	**Likely to predict failure**	**Rank sum score**
Previous benefit from injection (to other wrist)	11	Previous failure of injection (to other wrist)	15
Severe symptoms with defined distribution of symptoms	6	Continuous numbness / symptoms	8
No thenar muscle weakness or wasting	5	Thenar muscle weakness or wasting	5
Inflammatory arthritis causing CTS	5	Underlying OA	4
Nocturnal or wakening symptoms only	4	Diagnostic uncertainty	4
Short duration of symptoms	4	Previous failure of injection to another joint	3
Good education	4	Muscle wasting	3
Previous benefit from injection to another joint	3	Recurrent symptoms	3
Postural symptoms only	3	Needle phobia	3
Accurate placement of injection	3	Co-existing WRULD or radiculopathy	3
Intermittent symptoms / mild to moderate symptoms	3	Unemployed / On sickness benefit	2
Good post injection advice	3	Previous surgery on the effected side	2
Patient requests	3	Slow progression of symptoms over long period of time	2
Self-limiting history like pregnancy	3	Severe symptoms	2

Good work ethic	2	Symptoms related to work	1
Symptoms not present at time of examination (may be evident on provocation)	2		
Patients flexible to ideas of management	2		
Symptoms not related to work	1		
Positive provocation tests	1		
First attendance	1		
Abnormality in wrist like a previous fracture	1		
No co-morbidity	1		
No thenar muscle weakness or wasting	1		
Correct diagnosis	1		

KEY	
	Able to extract from INSTinCTS data
	INSTinCTS exclusion criterion or present in all patients
	Not measured or not a baseline characteristic
	Present in a small subpopulation of trial participants

8.2.1.1 Potential predictors of treatment effect and theories generated by a think tank

Further to the GP survey, 7 GP's and an extended scope practitioner took part in a think tank, set up to identify routine practice and clinical challenges experienced by practicing primary care clinicians in the diagnosis, investigation and management of carpal tunnel syndrome. The group were asked if they were able to identify factors at baseline that may change their pattern of treatment and for any reasoning behind their answer.

It was commented that adherence to splinting would be an important factor determining whether it would be of benefit or not. Whilst the likelihood of future adherence could not be assessed at baseline, it was suggested that patients with an internal locus of control may be more likely to adhere to splinting and hence experience benefit, whereas patients with a more external locus of control may benefit more from a CSI. A further observation was that splints may not benefit patients who were 'over a certain weight.'

8.2.2 Final selection of candidate moderators to be tested

As described in chapter 7, the pathophysiology of CTS is not fully understood. The therapeutic mechanisms of NS and CSI are therefore not entirely clear. Splinting maintains a neutral angle of the wrist, therefore preventing the increase of pressure within the carpal tunnel caused by flexion and extension. This may reduce the positive feedback mechanism of oedema, inflammation and

subsequent neural ischemia and damage. CSI's likely suppress any inflammatory response to nerve damage. Without clear evidence of benefit from these treatments and a lack of clarity as to their mechanisms of action, it remains difficult to fulfil the requirement that factors to be tested as moderators should have a clear biological hypothesis behind their selection. Therefore candidate predictors were selected based on clinicians' observations and experience, which can be used to aid selection and reduce the risk of 'data dredging.' Using the information available, a suggested mechanism of action has been provided for each potential moderator in Table 8-2.

Table 8-2 also represents a consolidated list of candidate predictors of treatment effect, put forward by the clinicians in the survey, which can be identified within the main INSTINCTS trial data. The only variable generated by the systematic review, which does not appear in the list suggested by clinicians but is already reported in the main paper, was treatment preference. A high baseline symptom severity as a predictor of outcome of CSI was found only in the systematic review, whereas a low symptom severity score was listed by the clinicians as a potential predictor of benefit from night splinting. The think tank also purported locus of control and BMI as a candidate predictors of treatment effect with some background reasoning to their suggestion.

Table 8-2 Candidate predictors of treatment effect and potential hypothesis

Potential predictors of benefit from night splints			Potential predictors of benefit from corticosteroid injections		
Potential moderator	**GP survey score / source**	**Hypothesis of action**	**Potential moderator**	**GP survey score / source**	**Hypothesis of action**
Nocturnal or symptoms on wakening only	9	Suggestive of mild symptoms. Symptoms exist during the time splints would be worn. Symptoms likely to be posture related	Intermittent symptoms	8	Suggestive of mild symptoms and potentially reversible neural damage.
Short duration of symptoms	6 + review	Early in the pathophysiological course. Early treatment may prevent the positive feedback of oedema and neural damage	Nocturnal or wakening symptoms only	4	Suggestive of mild symptoms.
No previous depression	5	General marker of a good prognosis in musculoskeletal conditions	Short duration of symptoms	4 + review (no evidence)	Early in the pathophysiological course. Possible that mechanism of action of CSI may be more effective in the early stages.
Intermittent symptoms	4	Suggestive of mild symptoms.	First episode	4	No chronic / longstanding nerve damage and therefore injection more likely to alleviate symptoms before more permanent neural damage occurs
Postural symptoms only	3	Suggestive of mild symptoms. Splints would prevent the trigger (postural change) of symptoms	Postural symptoms only	3	Suggestive of mild symptoms.
Unilateral symptoms	2 + review (no evidence)	Patient wouldn't need to wear 2 splints	Sudden onset of symptoms / not a gradual progression	2	No chronic / longstanding nerve damage
Low symptom severity	2	Early in the pathophysiological process where longstanding neural damage may not have taken place	Positive provocation tests	1	Diagnosis more likely, as opposed to other cause that may not respond to treatment with local corticosteroid
Sleep not affected by symptoms	2	Early in the pathophysiological process where	No co-morbidity	1	No other physiological cause for neuropathy so may be more likely to

		longstanding neural damage may not have taken place			respond to corticosteroid treatment
Patient preference	Review only (no evidence)	Assumption that patients will benefit from a placebo effect	High symptom severity	Review only (no evidence)	A more active inflammatory process may be more amenable to treatment with a corticosteroid
Internal locus of control	Think tank only	More likely to adhere to wearing splints and therefore benefit	External locus of control	Think tank only	Patients would not be required to adhere to a course of treatment due to the 'one off' nature of the treatment
High BMI (may NOT respond)	Think tank only	Splints may not be tolerated or as effective in patients with a larger wrist			

	Unique to the modality of treatment
	Appears as a candidate predictor of both modalities

The number of candidate moderators was reduced further by excluding those with a summed rank score of less than four, unless they were also found in the systematic review or think tank. The final list of candidate predictors of treatment effect to be tested in INSTiINCTS data is shown in Table 8-3:

Table 8-3 Final list of candidate predictors of treatment effect to be tested in INSTINCTS data

Potential predictors of a differential treatment response	**Score for potential benefit from night splints**	**Score for potential benefit from corticosteroid injection**
Nocturnal or symptoms on wakening only	9	4
Short duration of symptoms	6 + review	4 + review
No previous depression	5	
Intermittent symptoms	4	8
Unilateral symptoms	2 + review	-
New episode	-	4

The final list of predictors of treatment effect to be tested was kept to a reasonable minimum (6 candidate predictors). Since most randomised trials are not powered to detect interactions, false-negative or type 2 errors may result. The sample size required to detect a treatment-predictor

interaction will often need to be at least four times greater than that required to detect the overall treatment effect.[184] It is therefore acknowledged that any apparently statistically significant result would be considered exploratory and not confirmatory. Likewise, an absence of a statistically significant interaction may also be due to sample size and not a true null result.

8.2.3 Statistical analysis

As per the main trial, analysis was performed on an intention to treat basis. Since the data was considered to be missing at random, as per the prognosis study, multiple imputation using chain equations was used to manage missing data. In order to avoid losing further power when testing for interactions, each analysis was set in an imputed data-set developed to include the interaction term in the chain equations.[166] Injection (comparator) * moderator 'yes' (comparator) interactions with a *P* value of <0.1 would be suggestive of a significant interaction.

Given the continuous outcome and categorical potential moderators variables, interaction terms were generated using the following categories (splint*moderator'no'; splint*moderator'yes'; injection*moderator'no'; injection*moderator'yes'). The number of participants in each category for each treatment were described.

First, the crude treatment effect on the overall sum BCTQ outcome was presented. Secondly, an unadjusted test for interaction between the candidate predictor and treatment with the BCTQ outcome score was conducted. Thirdly, this model was adjusted for the variables included in the prognostic model developed in chapter 7 (baseline BCTQ score, baseline symptom severity and presence of associated neck and upper limb symptoms), which are considered to be potential confounders in this analysis. A stratified analysis was then carried out in each of the subgroups.

Analysis was carried out using six-week and six-month outcome data. At the time of writing, 12 and 24 months data were not available. Even if interactions did not appear to be statistically significant, exploratory sub-group analyses would be carried out with the acknowledgement that they would be under-powered but based on theoretical or clinical hypotheses.

Any positive findings would remain exploratory and would require external validation in a pre-stratified and adequately powered randomised controlled trial or in a future meta-analysis using Individual Patient Data -analysis (if appropriate trials were available to include in such an analysis).[75]

8.3 Exploratory subgroup analysis: Results

Table 8-4 shows the frequency distribution of candidate predictors with treatment at baseline, in an imputed dataset (n=234).

Table 8-4 Distribution of candidate predictors between treatment groups at baseline

	Nocturnal or symptoms on wakening only (n, %)	**Short duration of symptoms (≤ 3 months) (n, %)**	**No depression (n, %)**	**Constant symptoms (n, %)**	**Unilateral symptoms (n, %)**	**First episode (n, %)**
Splint & predictor 'no'	112 (47.86%)	100 (42.74%)	28 (11.97%)	94 (40.17%)	59 (25.21%)	15 (6.41%)
Splint & predictor 'yes'	7 (2.99%)	19 (8.12%)	90 (38.46%)	24 (10.26%)	59 (25.21%)	103 (44.02%)
Injection & predictor 'no'	105 (44.87%)	96 (41.03%)	40 (17.09%)	86 (36.75%)	61 (26.07%)	16 (6.84%)
Injection & predictor 'yes'	10 (4.27%)	19 (8.12%)	76 (32.48%)	30 (12.82%)	55 (23.50%)	100 (42.74%)

Table 8-4 demonstrates that only laterality of symptoms (unilateral versus bilateral) was distributed equally between all groups (around half the trial participants had bilateral CTS) and randomisation appears to have split each sub-group equally between the interventions. Due to the initial sample size, the existence of some overlap between candidate predictors with trial inclusion criteria (e.g. patients had to have had symptoms for at least six weeks, leading to a narrow window of opportunity to have had symptoms less than three months) and no pre-stratification by candidate predictors, there were very small numbers of participants in some sub-groups (e.g. seven patients with nocturnal or waking symptoms only who receive a splint).

8.3.1 Interaction tests and subgroup analyses

Table 8-5 and Table 8-6 present for six week and six month outcomes respectively: i. the crude treatment effect in the dataset imputed to include the treatment*predictor interaction, ii. the value for the interaction term between treatment and candidate predictor (to include the treatment and moderator as independent terms) and iii. the value of the interaction term between treatment and predictor, adjusted for covariates. The table also includes the stratified analysis for the trial population based on the candidate predictor, which helps to interpret direction and magnitude of effects within subgroups.

Table 8-5 Six-week subgroup analysis

	Nocturnal or symptoms on wakening only	Short duration of symptoms (< 3 months)	No depression	Constant symptoms	Unilateral symptoms	First episode
Unadjusted linear regression analysis of six-week BCTQ outcome: Adjusted mean difference (95% confidence interval, *P* value)						
Treatment effect (injection versus night splinting)	-0.29 (-0.49 to -0.08, < 0.01)	-0.31 (-0.53 to -0.09, <0.01)	-0.30 (-0.51 to -0.09,<0.01)	-0.31 (-0.52 to -0.09,<0.01)	-0.31 (-0.52 to -0.09, <0.01)	-0.29 (-0.50 to -0.08,<0.01)
Effect of candidate predictor	-0.83 (-1.30 to 0.36, <0.01)	-0.22 (-0.51 to 0.07, 0.13)	-0.42 (-0.66 to -0.17, <0.01)	0.61 (0.37 to 0.86, <0.01)	-0.09 (-0.31 to 0.14, 0.43)	-0.12 (-0.43 to 0.19, 0.44)
Effect of treatment x predictor	-0.04 (-0.98 to 0.90, 0.93)	-0.13 (-0.71 to 0.46, 0.67)	0.16 (-0.30 to 0.61, 0.49)	-0.21 (-0.70 to 0.28, 0.40)	0.47 (-0.06 to 0.08, 0.03)	-0.08 (-0.89 to 0.54, 0.80)
Adjusted linear regression analysis (baseline BCTQ, baseline symptom severity score, neck and upper limb symptoms) of six-week BCTQ outcome: Adjusted mean difference (95% confidence interval, *P* value)						
Treatment effect (injection versus night splinting)	-0.30 (-0.47 to -0.13, <0.01)	-0.32 (-0.50 to -0.14, <0.01)	-0.32 (-0.50 to -0.14, <0.01)	-0.31 (-0.49 to -0.14, <0.01)	-0.32 (-0.50 to -0.14, <0.01)	-0.31 (-0.48 to -0.13,<0.01)
Effect of candidate predictor	-0.28 (-0.69 to 0.14, 0.19)	-0.03 (-0.27 to 0.22, 0.84)	-0.08 (-0.29 to 0.14, 0.48)	0.29 (0.05 to 0.52, 0.02)	0.06 (-0.13 to 0.24, 0.56)	0.06 (-0.20 to 0.32, 0.67)
Effect of treatment x predictor	-0.23 (-1.01 to 0.55, 0.57)	0.30 (-0.19 to 0.79, 0.23)	0.19 (-0.19 to 0.57, 0.33)	0.08 (-0.40 to 0.55, 0.75)	-0.15 (-0.50 to 0.20, 0.40)	-0.27 (-0.78 to 0.23, 0.29)
Subgroup analysis, to show mean difference in effect of injection compared to splinting, adjusted for the prognostic model (baseline BCTQ, baseline SSS and presence of neck or upper limb symptoms) in sub-group stratified by the candidate predictor.						
Group where predictor **'yes'**	-0.07 (-0.59 to 0.46, 0.77) n = 16	-0.52 (-1.03 to -0.01, 0.05) n = 36	-0.38 (-0.57 to -0.19, <0.01) n = 167	-0.19 (-0.62 to 0.24, 0.38) n = 54	-0.23 (-0.50 to 0.04, 0.09) n = 114	-0.28 (-0.47 to -0.09, <0.01) n = 203
Group where predictor **'no'**	-0.32 (-0.50 to -0.14, <0.01) n = 218	-0.27 (-0.46 to -0.07, <0.01) n = 196	-0.19 (-0.58 to 0.21, 0.34) n = 67	-0.33 (-0.52 to -0.14, <0.01) n = 180	-0.39 (-0.63 to -0.16, <0.01) n = 120	-0.51 (-1.01 to 0.00, 0.05) n = 31
Crude difference between groups	0.25	0.25	0.19	0.14	0.16	0.23

8.3.1.1 Interactions between candidate predictor and intervention and subgroup analyses (six-week follow-up)

In each imputed data-set, as per the main trial result, CSI favoured NS at six weeks. There were no significant interactions noted between candidate predictors and treatment intervention when adjusted for confounding. CSI favoured NS in each subgroup, however some subgroups appear to gain more benefit form CSI compared to NS. The minimal important difference (within group change) used in the main INSTINCTS trial was 15%, as measured by the BCTQ from an expected baseline of 2.9 (scale 1-5, SD 1.0).[58] According to these results, only patients with a short duration of symptoms and who have had recurrent CTS reach this threshold (-0.44). Descriptively, those with daytime symptoms as opposed to those with night or wakening symptoms only; those with no depression on screening compared with depression on screening; those with intermittent as opposed to constant symptoms; and those with bilateral symptoms as opposed to unilateral symptoms seemed to receive a greater benefit from injection than from splinting.

Table 8-6 Six-month subgroup analysis

	Nocturnal or symptoms on wakening only	Short duration of symptoms (< 3 months)	No depression	Constant symptoms	Unilateral symptoms	First episode
Unadjusted regression analysis of six-month BCTQ outcome: Adjusted mean difference (95% confidence interval, *P* value)						
Treatment effect (injection versus night splinting)	0.13 (-0.10 to 0.35, 0.26)	0.12 (-0.10 to 0.33, 0.29)	0.11 (-0.10 to 0.32, 0.30)	0.10 (-0.11 to 0.32, 0.34)	0.13 (-0.09 to 0.35, 0.24)	0.12 (-0.11 to 0.35, 0.32)
Moderator effect	-0.38 (-0.86 to 0.10, 0.12)	-0.01 (-0.32 to 0.30, 0.97)	-0.35 (-0.60 to -0.11, <0.01)	0.45 (0.17 to 0.73. <0.01)	-0.28 (-0.51 to -0.05, 0.02)	-0.20 (-0.57 to 0.17, 0.30)
Effect of interaction adjusted for treatment and moderator	-0.39 (-0.88 to 0.09, 0.11)	0.40 (-0.21 to 1.0, 0.20)	0.21 (-0.28 to 0.70, 0.40)	-0.14 (-0.69 to 0.41, 0.62)	0.51 (0.09 to 0.94, 0.02)	0.34 (-0.32 to 1.00, 0.31)
Analysis adjusted for prognostic model (baseline BCTQ, baseline symptom severity score, neck and upper limb symptoms)						
Treatment effect (injection versus night splinting)	0.14 (-0.05 to 0.33, 0.15)	0.12 (-0.06 to 0.31, 0.19)	0.11 (-0.06 to 0.30, 0.21)	0.11 (-0.07 to 0.28, 0.22)	0.13 (-0.04 to 0.31, 0.14)	0.11 (-0.08 to 0.31, 0.24)
Moderator effect	0.22 (-0.20 to 0.64, 0.30)	0.19 (-0.69 to 0.46, 0.15)	-0.01 (-0.24 to 0.21, 0.90)	0.11 (-0.16 to 0.39, 0.41)	-0.15 (-0.35 to 0.04, 0.12)	-0.03 (-0.36 to 0.30, 0.86)
Effect of interaction adjusted for treatment and moderator	0.20 (-0.22 to 0.62, 0.35)	0.25 (-0.25 to 0.75, 0.33)	0.25 (-0.17 to 0.66, 0.24)	0.05 (-0.42 to 0.53, 0.84)	0.22 (-0.13 to 0.58, 0.22)	0.11 (-0.45 to 0.67, 0.70)
Subgroup analysis, to show mean difference of injection compared to splinting, adjusted for the prognostic model (baseline BCTQ, baseline SSS and presence of neck or upper limb symptoms) in sub-group with and without the candidate predictor						
Group where predictor **'yes'**	0.26 (-0.60 to 1.13, 0.49)	0.30 (-0.25 to 0.86, 0.27)	0.05 (-0.15 to 0.25, 0.64)	0.05 (-0.50 to 0.61, 0.83)	0.28 (0.00 to 0.55, 0.05)	0.10 (-0.09 to 0.31, 0.29)
Group where predictor **'no'** **Crude difference between groups**	0.09 (-0.10 to 0.29, 0.30) 0.17	0.09 (-0.11 to 0.28, 0.39) 0.21	0.29 (-0.13 to 0.70, 0.17) 0.24	0.12 (-0.08 to 0.31, 0.23) 0.07	0.04 (-0.20 to 0.28, 0.75) 0.24	0.23 (-0.46 to 0.91, 0.70) 0.13

8.3.1.2 Interactions between candidate predictor and intervention and subgroup analyses (six-month follow-up)

In each dataset, as per the main trial result, there was no significant difference in outcome between patients receiving CSI compared to NS at six months. In fact, whilst not significant, the direction of effect seemed to change. Likewise, no significant interactions between candidate predictor and intervention were identified when adjusted for the prognostic model. Patients with unilateral symptoms did appear to have a significantly less favourable outcome following CSI at six months when compared with NS. Whilst not statistically significant and based on very small subgroup differences, CSI may be less favourable than NS by six months in the following subgroups: those with nocturnal symptoms or symptoms on wakening only; those with a symptom duration of < 3 months; those with depression on screening and those with a recurrent episode.

8.4 Discussion

8.4.1 Summary of main findings

In summary, whilst no significant interaction between candidate predictor and intervention was found at either the six-week or six-month time-point, all sub-groups of participants showed a greater improvement at six-weeks if they received a CSI compared to those who were allocated to NS. By six-months, as per the main trial, no significant difference between the treatment groups were observed apart from patients with unilateral symptoms seemingly having a poorer outcome if they received CSI compared to NS. What is not known is which further interventions (contralateral interventions or CTR) were received, hence unmeasured competing benefits may have influenced results. Alternatively, it may be possible that CSI leads to a higher risk of relapse following an initial short-term improvement.

8.4.2 Interpretation of results

8.4.2.1 Nocturnal or symptoms on wakening only / constant symptoms

Subgroups of patients with 'nocturnal or symptoms on wakening only' and with 'constant' (as opposed to intermittent) symptoms were defined based on questions within the BCTQ and can be considered as descriptors of severity. Patients with severe CTS (including constant paraesthesia) were excluded from the trial. This will have had the effect of reducing the heterogeneity of the severity of CTS seen within the sample, making it difficult to draw conclusions around whether patients with milder CTS can be treated in a different way to those with severe CTS (who should be referred for consideration of surgery). The six-week outcome data suggests that patients with symptoms not limited to night-time but without constant symptoms (i.e. more intermittent symptoms) show a greater improvement with CSI. However, by six months the adjusted mean difference between those that received CSI versus NS in each subgroup, was minimal. It appears possible that by six months, NS may favour patients with night only or intermittent symptoms, however the adjusted mean differences were very small and not significant.

8.4.2.2 Symptom duration

A prolonged duration of symptoms (of which the definition varied), was suggested as a predictor of poor outcome (prognostic factor) in the systematic review presented in chapter 4. Symptom duration was included in the development of the prognostic model developed to predict 6-month outcome, based in the same INSTINCTS data, but was not included in the final model. It has also been tested as a predictor of treatment effect by Atroshi and Celiker as described in chapter 7. However, no convincing evidence of a prognostic or moderating effect was identified. There is some exploratory evidence that patients with a shorter duration of symptoms show a greater improvement at six weeks if they received CSI versus NS but no significant evidence of benefit in the longer term (six-month data).

Whilst it seems clinically reasonable to suppose that prolonged symptoms would expose the nerve to greater pathophysiological damage over time and limit its recovery and rehabilitation potential, this cannot be substantiated by the work presented in this thesis. However, symptom duration could not be identified in CPRD and the INSTINCTS dataset is likely to be homogenous with regard to short versus long duration as patients with a very short duration (< six weeks) were excluded as were patients who had already received treatment. Only 15.4% of participants had a 'short symptom duration.' This is likely due to the fact patients delay presenting initially and then may have had to wait for a referral to an interface service, before recruitment to the trial. Further work could attempt to identify and randomise patients earlier in their course of symptoms and stratify on the basis of symptom duration. This work could also be criticised for categorising a continuous variable; however this was done at baseline as it was felt unlikely that patients would recall in days or indeed weeks how long they had had symptoms for. The decision was made pragmatically to include categories based on months.

8.4.2.3 Depression

The inclusion of depressive symptoms as a candidate predictor of treatment effect was largely based on the opinion of the think-tank and GP survey, rather than on carpal tunnel syndrome literature, although the review of prognosis studies did highlight one study which suggested a better mental health score was associated with being in work with CTS, in a non-operative cohort (P 0.04).[134] It was

felt that patients with depression were less likely to do well overall but also less likely to respond to splinting. This hypothesis was based on the fact that patients with a poor mental health status may have a lower motivation to adhere to a treatment requiring regular application. In fact, the sub-group analysis suggests that whilst patients with no depression at baseline demonstrated a greater improvement with injection versus splinting at six weeks, those with depression showed no significantly greater benefit from either treatment.

Whilst the prognostic study based in the same data did not include depression in the final model, this sub-group analysis suggests that these participants do not do as well with either treatment. However, 29% of patients had responded to the baseline screening questions such that they were considered to have depressive symptoms. This higher than expected figure may be indicative of the effect CTS was having on their experience of symptoms and ability to function or that the screening questions were overly sensitive or non-specific. To test this more fully, a more complete questionnaire such as the Hospital Anxiety and Depression scale could be included, however on this occasion the trial management group and PPIE group felt further lengthy questionnaires at baseline were not appropriate.

8.4.2.4 Laterality of symptoms

The results of this secondary data analysis differ from those reported in the main INSTINCTS trial publication[59] due to the set of variables adjusted for in the linear regression model. In the analysis presented in this chapter, participants with unilateral symptoms appeared to have a less favourable outcome at six months following treatment with CSI compared to NS, than patients with bilateral symptoms (0.28, 95% CI 0.00 to 0.55, P = 0.05 compared to 0.04, -0.20 to 0.28, 0.75).

Participants were asked if they had bilateral CTS at the time of recruitment, and if so which of their wrists was the most severe. The more severe wrist was randomised to an intervention and the participant asked to complete outcome questionnaires based on the symptoms from the more severe wrist. The effect of any additional treatment to the contralateral wrist was not considered in this dataset, neither has the possibility of ipsilateral additional treatments (e.g. CTR or repeat injections).

Furthermore, participants may have found distinguishing the symptoms of one wrist from the other or both combined, difficult.

The contralateral wrist was treated as per 'usual care.' It is difficult to assume that splinting one wrist would have a positive impact on the other, but it is possible to surmise that an injection in one wrist may have an effect on the other via a systemic action of the drug. This is contrary to what was observed however, so perhaps unlikely. Perhaps those who had one CSI had a poorer outcome at six months compared to those who had NS due to the fact the splint users could continue wearing the splint (and perhaps purchased a contralateral splint) for an extended period, longer than the effect of the local corticosteroid. However, this is conjecture.

Following their Cochrane reviews of conservative interventions for CTS,[42, 188, 189] Page et al examined how authors manage the allocation of interventions and the statistical analysis of CTS trials where participants with bilateral CTS are included.[173] Of the 25 trials which included participants with bilateral CTS, 17 (68%) reported the method used to allocate interventions to each wrist and only one (4%) included a statistical method to deal with bilateral involvement. They suggest that not adjusting for non-independence of bilateral observations can lead to a unit-of-analysis error. This type of error can lead to overly narrow confidence intervals and small *P* values and the increase of type 1 errors.[190] Whilst this trial did not attempt to allocate an intervention to each wrist in the case of participants with bilateral CTS, it is possible that the effect of non-independence of bilateral observations may have biased the results and potentially account for the subgroup effect observed. The observation may also represent a type I error in that it is a spurious finding between the other non-significant interactions, secondary to the small sample size.

8.4.2.5 First or recurrent episode

This candidate predictor was a priority for the participants of the think tank and GP survey and had not been identified in previous literature. Clinical experience led to the hypothesis that patients with recurrent symptoms may not benefit from splinting and should be offered a CSI. The exploratory analysis suggests that whilst both groups of patients had a better outcome at six weeks with CSI versus

NS, those with recurrent symptoms showed a greater benefit than those with a first episode. However, the distribution of those with and without recurrent symptoms was not equal between groups, with only small numbers (14%) reporting a recurrent episode. This is possibly due to the fact participants were excluded if they had had treatment in the past six months or carpal tunnel release surgery on that wrist ever in the past.

8.4.3 Methodological considerations

It was accepted a-priori that this study would be an exploratory non-confirmatory exercise to attempt to identify potential predictors of treatment effect that may later be tested in larger trials or IPD meta-analysis of multiple trials. The sample size required to detect a single treatment-predictor interaction may need to be at least four times greater than that required to detect the overall treatment effect.[184] INSTINCTS was not powered to detect treatment*moderator interactions nor designed to stratify by the predictors to be tested.

Attempts were however made to limit the number of candidate predictors, with selection made on the basis of evidence and / or a proposed biological mechanism.[74] Such candidate predictors were measured at baseline using pragmatic yet accepted methods (questionnaire based) and interactions were tested alongside presentation of a stratified analysis. On this basis the methodological criteria developed by Pincus et al. for inclusion in a future meta-analysis were fulfilled.[178]

There is no information available in this study as to what further interventions a patient may have received over the six-month period. The main trial reports that 17 (14.3%) of patients receiving CSI and 14 (11.9%) patients treated with NS had had surgery at six months.[59] It is not possible from the available data to determine if patients with bilateral symptoms were more or less likely to have had surgery or indeed a contralateral intervention.

8.4.4 Conclusion

Whilst this data is not currently helpful in suggesting how conservative management options may be best matched to the baseline characteristics of patients with mild to moderate CTS, it may be of future benefit when taken into account alongside other studies in meta-analysis or used to inform the design of a stratified care trial. Whilst a statistically significant subgroup effect may be observed in patients with unilateral as opposed to bilateral CTS at six months, a unit-of-analysis error may be one of the explanations for this finding.

The next chapter will draw together the results of the preceding studies and discuss the significance of their findings within the context of the literature. The clinical implications of the work will be considered and proposals for further work made.

9 Summary, discussion, implications and conclusions

Summary

The aim of this chapter is to provide a summary of the main findings of the studies presented in this thesis. The findings of these studies are placed in the context of the existing literature and their particular strengths and weakness discussed. The clinical implications and potential opportunities for further research are considered.

9.1 Summary of main findings by thesis objective

9.1.1 Objective 1a. Estimate trends in the prevalence and incidence of CTS diagnosed in primary care between 1993 and 2013 (chapter 3)

The estimated crude prevalence of patients presenting with physician diagnosed carpal tunnel syndrome in a UK primary care setting in 1993 was 26.03 per 10,000 person years (95% CI 25.10 to 27.00), and in 2013, 36.08 per 10,000 person years (95% CI 35.45 to 36.72). Prevalence appeared to decrease between 1993 and 2000 (annual percentage change APC = -0.8%, 95% confidence interval -2.6 to 1.0). It then increased between 2000 and 2004 (APC = 7.8%, 95% CI 3.1 to 12.7) and then increased at a slower rate between 2004 and 2013 (APC = 1.1%, 95% CI 0.4 to 1.8). The female to male ratio reduced over time from 2.74 in 1993 to 1.93 in 2013.

Incidence was derived from the prevalent population and defined as those with a new presentation of CTS during the calendar year in question (no previous CTS code in the prior 2 calendar years). The crude incidence in 1993 was 20.22 per 10,000 person years (95% CI 19.24 to 21.24)), and for 2013, 27.68 per 10,000 person years (95% CI 27.09 to 28.28). The results of the best fitting Joinpoint regression plot suggested the incidence increased between 1993 and 2000 (APC = 0.3, 95% CI -2.3 to 2.9). It then

increased more quickly between 2000 and 2004 (APC = 6.9, 95% CI 0.5 to 13.7), before slowing between 2004 and 2013 (APC = 0.7. 95% CI -0.2 to 1.6).

9.1.2 Objective 1b. Estimate trends in health care use (corticosteroid injection and carpal tunnel release surgery) of patients with CTS between 1993 and 2013 (chapter 3)

The proportion of patients with prevalent CTS with a recorded episode of CTR increased over the total observed study period from 19.35% in 1993 to 27.3 % in 2013. However, whilst the percentage of patients with a coded episode of CTR increased between 1993 and 2007 (annual percentage change APC = 2.6, 95% CI 1.9 to 3.2) the rate of surgical intervention then appeared to decrease between 2007 and 2013 (APC = -1.7, 95% CI -3.3 to -0.3).

Despite multiple methods of identifying the use of corticosteroid injection in the management of CTS, the rates observed were considered to be inaccurately low, suggesting episodes of CSI are not well coded or recorded in CPRD. Using the data available, it was determined that between 5 and 8% of patients received at least 1 injection and that the use of CSI reduced between 1993 and 2005 (APC = -1.29, 95% CI –3.2 to 0.7) and then increased between 2005 and 2013 (APC = 6.56, 95% CI 4.3 to 8.8).

9.1.3 Objective 2a. Summarise available evidence regarding the course of conservatively managed CTS (overall prognosis) and the predictors of long term outcome (prognostic factors) (chapter 4)

A systematic review of the literature identified four studies, which observed patients with untreated CTS. A range of 32% to 58% of participants receiving no formal treatment were reported to have a poor outcome at 12-month follow-up. Studies with a longer term follow up reported poor outcome in 23.4% of patients at 3 years and 50% at 10 years.

Nine further studies were identified which observed patients who received conservative management for CTS. Between-study variation in estimates of prognosis were substantial and particularly dependent on the case definition of CTS and outcome measure applied. Of the four studies reporting

surgery as a marker of inadequate response to conservative management, a range of 57% to 66% of patients required CTR over a period of between 1 and 3 years.

Eleven studies presented data on the association between 39 candidate prognostic factors and a poor outcome from conservative management. Substantial heterogeneity existed between studies in terms of setting, case definition, follow-up period and outcome measures. The studies were judged to be of moderate or high risk of bias. There was agreement in at least three studies that an increasing symptom duration; a positive Phalen's test and the presence of thenar wasting were associated with a poor outcome over variable time periods. However, not all associations were statistically significant and since the studies were not considered to be at low risk of bias, the overall judgement regarding their predictive value remained inconclusive.

9.1.4 Objective 2b. Develop a prognostic model to predict poor outcome in conservatively managed CTS in a cohort of patients identified in CPRD (chapter 5)

17 candidate prognostic factors, derived from the literature and expert opinion, were identified and tested as candidate prognostic factors of future surgery in a cohort of 91,412 patients with physician diagnosed CTS, as recorded in the CPRD. 20.24% of the cohort had a recorded episode of CTR. The median time to surgery was 221 days (IQR 111, 409). Univariable analysis indicated that pregnancy in the preceding year was observed to reduce the risk of future surgery, however as this was not relevant to the majority of the presenting population, it was not included in the final model. The final multivariable Cox regression model performed poorly, C statistic 0.59 (95% CI 0.58 to 0.59) but suggested the likely predictive value of combined prognostic factors including obesity, being an alcohol drinker and having other musculoskeletal pain.

9.1.5 Objective 2c. Develop a prognostic model using individual patient data from an RCT to predict a future change in patient-reported CTS-symptoms (chapter 6)

234 participants from the INSTINCTS trial were observed prospectively over a 6-month period. The BCTQ (a condition-specific patient recorded outcome measure) was completed at baseline, six weeks and six months. By six months, the main trial had reported no significant difference between treatment arms and as such, the participants were observed as a single cohort, while adjusting for treatment allocation. The greatest improvements in terms of symptom severity and function score were seen at six weeks, however further improvement was observed at six months. Multivariable linear regression modelling indicated more severe baseline total BCTQ, less severe symptom severity score, and the absence of any other neck or upper limb symptoms as predictors of improvement in BCTQ score at six months. The small sample size resulted in optimistic predictions, and the optimism-adjusted model calibrated poorly; overestimating the severity of outcome in patients with less severe observed CTS and underestimating the severity of outcome in patients with more severe observed CTS.

9.1.6 Objective 3a. Summarise available evidence regarding predictors of response to specific common primary care treatments of CTS; in particular corticosteroid injection and night splinting (chapter 7)

The systematic review identified four trials which explored predictors (or moderators) of treatment effect. Whilst the quality of the subgroup analyses was judged inadequate in three of the four trials, potential predictors of treatment effect were identified. There is suggestion that the effect of CSI was larger in patients with higher nerve conduction severity and baseline symptom severity scores, however severity was likely to be a prognostic factor of outcome rather than a predictor of a specific treatment effect.[53] Prolonged symptom duration (more than nine months) was also observed by Celiker et al to be a general predictor of poor outcome rather than of treatment effect. Neither patients randomised to wrist splints with acemetacine or a CSI (methylprednisolone 40mg) with a prolonged symptom duration, responded well to treatment.[48] Neither wrist laterality nor patient preference were observed to act as predictors of treatment effect in the other trials included in the review.[140, 179]

9.1.7 Objective 3b. Investigate if a priori defined candidate predictors of treatment effect (effect modifiers), predict a better outcome from either corticosteroid injections or night splinting (chapter 8)

INSTINCTS, an open-label, parallel group, randomised controlled trial compared the effectiveness of CSI to NS. A single local CSI was found to be more effective at reducing symptoms and the functional impact of CTS at six weeks, but by six months there was no significant between-group difference. Further to the subgroup analyses presented in the original trial publication,[59] it was decided to explore whether particular groups of patients did benefit more from one treatment over another. Six candidate moderators were identified from the literature and expert opinion. Moderator*treatment interactions were tested and subgroup analyses carried out. At six months, CSI was significantly less effective than NS in patients with unilateral symptoms compared to those with bilateral CTS, when adjusting for potential confounders (baseline BCTQ, symptom severity and presence of neck and upper limb symptoms). However, there was no significant interaction and a true sub-group effect is unlikely given the small sample size and potential of a unit of analysis error.

9.2 Updates and comparison to findings in the literature

Where relevant, the discussion section of each chapter has reflected on how the findings of the studies presented in this thesis compare to what has been reported in the literature. Below is an update of studies published since the chapters in this thesis were completed and how they might affect the interpretation of findings, with particular reference to the recently published PALMS study.[191]

9.2.1 The epidemiology of carpal tunnel syndrome

The findings of the CPRD epidemiology study presented in chapter 3 have already been discussed in the context of existing literature. In summary, the prevalence and incidence of CTS were observed to have increased in multiple populations. Rates of surgical referrals and episodes of surgery have also increased over time, however the proportion of patients having CTR in the CPRD population was

observed to be in decline and was generally lower than those reported elsewhere in the literature. As in other studies, regional variation was observed in the proportion of patients receiving surgery.[64] Local variation in clinical pathways and restrictions placed on referrals for surgery were likely to explain some of the observed variation. This variation may also partly explain the poor performance of the prediction model presented in chapter 5, which could only account for variation occurring at the level of the older strategic health authorities ('region' variable in CPRD) and not fully adjust for variability at a lower 'practice or Clinical Commissioning Group' level.

9.2.2 Predicting outcome in conservatively managed carpal tunnel syndrome

9.2.2.1 The prognosis of carpal tunnel syndrome

In addition to the studies considered in the systematic review presented in chapter 4, the most relevant study concerning the prognosis of conservatively managed CTS to have been published since its completion, is the PALMS study.[191] PALMS was a large (801 eligible consented participants) prospective, multicentre cohort study designed to predict the outcome of patients recruited in secondary care diagnosed with CTS following clinical review and confirmatory NCS. Patients were treated as per usual care (no treatment, CSI and / or CTR) and observed over an 18-month period. Of the 626 responders, 318 (51%) underwent CTR, 56 (9%) had CSI only and 252 (40%) had had no treatment by six month follow-up. By 18 months, 403 (64%) had undergone surgical management and 21 had had a second injection and three a third. 165 (26%) of participants had no treatment at all. Outcome was judged to be a success if participants reported on a Global Rating of Change scale that they were 'slightly improved, much better or cured.' Predictors of global improvement following injection alone included a positive response to a prior injection (OR 0.18, 95% CI 0.07 to 0.47) and a shorter symptom duration (OR 0.69, 95% CI 0.54 to 0.98). A prognostic model was developed using the CTS-6[34, 192] as an outcome (a shorter form of the BCTQ). The final multivariable linear model predicting symptomatic improvement of CTS treated with injection included a lower symptom severity score at baseline (B=0.55, 95% CI 0.33 to 0.77) with an R^2 of 22.9%.

Whilst the performance of the models were not fully described, similarities to the prognostic model presented in chapter 6 exist. A lower symptom severity score at baseline appears to be predictive of a better outcome. However, the INSTINCTS model is also suggestive of a more severe overall BCTQ score being predictive of a better outcome (adjusting for neck and upper limb symptoms and the independent symptom severity score). Whilst it is established good practice to adjust for baseline severity in prognostic models in order to account for 'regression to the mean,' it is possible that the psychometric properties of certain items included in the full BCTQ led to the variations observed. The utility of the BCTQ and potential implications will be discussed in the next section.

The PALMS study demonstrates how, despite using a similar cohort and similar candidate prognostic factors, the variables included in final prognostic models can vary, depending on the outcome measure applied, length of follow-up, and treatment offered.

9.2.2.2 Comparing the two prognostic models presented in this thesis

This thesis presents two prognostic models, which predict the outcome of conservatively managed CTS. One study used routinely collected primary care data with a very large sample size, but with potential limitations around accuracy and completeness. The other model was set in trial data, with a much smaller sample size but which was more likely to represent data of high quality (intentionally and more precisely measured prognostic factors at baseline). The individual components of the final models were also limited to what was measureable and available in each data set. The CPRD model used a time-dependent binary outcome whilst the INSTINCTS model used a continuous outcome.

In order to systematically compare the risk of bias present in each model, the QUIPS tool used in the systematic review presented in chapter 4, was used to critique and compare each model as shown in Table 9-1. In summary, the application of the QUIPS tool demonstrates that the overall risk of bias of the model developed in CPRD was judged to be high, whilst the risk of bias for the model developed in INSTINCTS data was judged to be low. As previously alluded to, sample size is likely to be a substantial determinant of the poor performance of the INSTINCTS model, but this is not picked up by the QUIPS tool, as it is an issue of precision rather than bias.

Neither model performed well enough to be considered for further clinical development. The CPRD model discriminated between those who experienced the outcome (CTR) and those who did not 59% of the time. The calibration plot for the INSTINCTS model suggested the model tends to underestimate the severity of the more severe cases and overestimate the severity of the milder cases. The PALMS model also exhibits poor performance despite robust methodology, which leads one to question why the outcome of CTS appears to be difficult to predict. The answer is likely to be complex and multi-faceted. Potential reasons for this will now be considered.

Table 9-1 Assessment of the risk of bias in each model presented in the thesis using the QUIPS tool (Hayden et al., 2013)

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of bias
CPRD study	The source of the population is known but not all key characteristics recorded. Adequate participation cannot be measured.	The rate of attrition cannot be measured not the reasons for loss to follow up identified.	The candidate prognostic factors are identified by Read code, which has a risk of misclassification. Appropriate cut-offs are used. The proportion with complete data for prognostic factors is not known.	The outcome was well defined however limitations exist as to whether the method was valid and reliable given it was dependent on medical record coding.	It is likely that some confounders (particularly treatments and local commissioning guidelines) were not identifiable in the data. Imputation4 was not applied for missing data.	Data is presented sufficiently to assess the adequacy of the analysis. The model building strategy is explained and appropriate.	**The relationship between prognostic factors and outcome are likely to be different for participants and eligible nonparticipants, particularly due to the unmeasurable effect of local commissioning policies**
	Moderate risk	**High risk**	**High risk**	**High risk**	**High risk**	**Low risk**	**High risk**
INSTINCTS study	The source of the population is known and well described with good participation.	Study attrition was low and attempts made to collect data from participants who dropped out. Such participants are described.	Important candidate prognostic factors were accurately recorded at baseline.	A valid and reliable outcome measure was used in the same setting for all participants.	The method and setting for measuring confounding was the same for all participants. Missing data was imputed.	Data is presented sufficiently to assess the adequacy of the analysis. The model building strategy is explained and appropriate.	**The relationship between prognostic factors and outcome is unlikely to be different for participants and none participants, however sample size remains a significant limitation**
	Low risk	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

9.2.2.3 Considering carpal tunnel syndrome as a 'generic' musculoskeletal condition

The prospective observational study of primary care patients by Henschke et al aimed to identify generic predictors of poor outcome in patients with musculoskeletal pain, regardless of the location of their pain presentation. They concluded that the region of pain was not a significant predictor of outcome, but that generic predictors of outcome do exist. In chronic non-spinal musculoskeletal pain observed at 12 months: medication use (OR 2.17, 95% CI 1.31 to 3.59) and having the complaint in the previous year (2.0, 95% CI 1.18 to 3.49) were found to be generic predictors of poor outcome.[193] Mallen et al as discussed in chapter 4, also described generic prognostic factors in a cohort of older people presenting with musculoskeletal pain in primary care. In patients presenting for the first time with a musculoskeletal condition: symptom duration (OR 3.26, 95% CI 1.15 to 9.29); pain interference (1.64, 0.62 to 4.33) and multiple-site pain (2.75, 0.91 to 8.33) were found to be important predictors of poor outcome as defined by an unfavourable global rating of change (same, worse or much worse).[194]

A further systematic review of generic prognostic factors for musculoskeletal pain in primary care was conducted by Artus et al. They summarised evidence from 78 prospective cohort studies based in primary care, which reported associations between predictors of outcome of multiple different musculoskeletal conditions. Whilst none of the studies investigated the prognosis of hand or wrist pain specifically, the authors concluded there was high quality evidence that pain intensity, widespread pain, high functional disability, somatisation and movement restriction can be considered generic prognostic factors of poor outcome for musculoskeletal pain.[195]

It has not been shown that CTS can be considered a 'generic' musculoskeletal condition, however it could be assumed that there is some overlap. Symptom duration does appear from these generic studies and the systematic review presented in chapter 4 to be a likely important predictor of outcome in people with musculoskeletal conditions, and hence possibly also in CTS. This evidence was not identifiable in the analysis of CPRD data and the collection of this information in INSTINCTS was likely to have been biased by the inclusion / exclusion criteria. The empirical studies in this thesis have been

unable to substantiate the suggestion from the literature that symptom duration is an important prognostic factor in CTS, which would clinically be important if it could be shown that delaying the surgical treatment of non-responders to primary care management might increase the risk of adverse outcomes.

9.2.2.4 Predicting the outcome of carpal tunnel syndrome considering pathophysiological mechanisms

Although the studies in this thesis could not confirm the predictive value of symptom duration, pathophysiological mechanisms may explain why prolonged exposure of the median nerve to pressure might reduce the chance of recovery.[2, 196] Such mechanisms and the fact that CTS is essentially an entrapment neuropathy rather than a muscle / skeletal condition may lead one to question whether CTS can be considered a 'generic' regional pain syndrome, especially given that pain is not always the predominant symptom.[139]

Schmid et al examined the morphology of small unmyelinated and myelinated axons in patients with and without electrophysiologically diagnosed CTS. They concluded that compression of the median nerve at the wrist affects the small unmyelinated fibres distal to the compression as well as the large myelinated fibres, which are measured by NCS. It is these more distal small unmyelinated fibres that give rise to the neuropathic pain component of CTS. Schmid et al suggest that distal effects of entrapment include a reduction in intraepidermal nerve fibre density. This in turn is independent of electrodiagnostic severity (explaining the mismatch between patient reported severity and electrodiagnostic grading). Elongation of nodes in these small unmyelinated fibres is suggestive of an adaptive change of prolonged nerve compression and may suggest why some patients have fewer positive subjective symptoms (e.g. pain) but more negative objective symptoms (e.g. muscle wasting and weakness leading to functional impairment).[196, 197]

These pathophysiological processes and their relationship with time and exposure question the utility of both symptom severity scales and electrodiagnostics as measures of severity and determinants of qualification for surgical treatment. In addition, Schmid et al also highlight the role of central

sensitisation as being a cause of persistent pain. However, in the case of CTS, even after longer-standing symptoms, treatment of the peripheral trigger has been observed to lead to local and central relief from focal and widespread symptoms. Schmid et al suggest that symptom duration is an important consideration when making definitive treatment decisions (surgery or corticosteroid injection) for patients with CTS.[198]

These observations from basic science studies suggest symptom duration to be an important factor to consider when deciding clinically whether a patient can be reasonably managed using a 'watch and wait approach' or whether a definitive (surgical) intervention is required. Likewise, the use of electrodiagnostics and symptom severity scales to diagnose and stratify patients is questioned as elements of nerve damage will not be measured by nerve conduction studies and the process of neural adaptation may mean that patients with poorer function may have relatively lower symptom severity. Such issues may also partly explain the poor performance of the models and difficulties in predicting outcome.

9.2.2.5 Use of the Boston Carpal Tunnel Questionnaire

The Boston Carpal Tunnel Questionnaire (BCTQ) is the only condition-specific patient recorded outcome measure for carpal tunnel syndrome.[32] The BCTQ has previously been found to have good validity, reliability, responsiveness and interpretability.[159] For this reason, it was used in its entirety as the primary outcome measure for the INSTINTCS trial[58] and therefore the two nested studies presented in this thesis.

Since the development and widespread use of the BCTQ, it has received criticism for its length and redundancy of certain components. Atroshi et al used item response theory to examine the latent trait and differential item functioning of the scale.[34] Their aim was to produce a shorter form of the BCTQ by removing items that were significantly associated with other items and therefore found to be redundant on IRT analysis.

The effect of item redundancy should not have impacted on the optimisation of prediction in the model presented in chapter 6 and the full score remains a valid outcome measure for this purpose. The use of the full score also enabled symptom and function severity to be considered as predictors. Alternative outcome measures could have been used, such as the hand-wrist symptom intensity scale but there would have been no reasoning to do this other than seeking to develop a better performing model – to do this retrospectively could be considered as data-dredging, as it was not included in the a priori investigation plan and approved request for data use.

9.2.3 Update to systematic review of treatment moderators

Other than the INSTINCTS trial itself, a rapid review of the literature for trials investigating the effectiveness of CSI or NS compared to other modes of conservative treatment since the review presented in chapter 7, found one small (25 participants in each arm) randomised clinical trial comparing CSI with NS.[57] The BCTQ at 4 weeks was the primary outcome measure used. There was no significant difference between treatment arms observed (*P*=0.22) at this time point. There was no attempt to investigate for a subgroup effect.

Identifying predictors of treatment effect has been difficult and is likely to require either a purposively designed large stratified care trial or an individual patient data meta-analysis of multiple trials (if suitable trials were to exist), in order to have sufficient power to test treatment*predictor interactions.

9.3 Strengths and limitations

9.3.1 Strengths of the studies included in the thesis

The studies presented in this thesis apply a range of methodologies and have used different study settings in order to describe the epidemiology and prognosis of carpal tunnel syndrome and explore how such evidence may be used to improve the primary care management of patients with CTS.

The thesis follows the PROGRESS framework,[75] as outlined in chapter 1 and attempts to present findings from each of the four types of study in a structured manner. A very large electronic healthcare data set, representative of the general population was used to describe the clinical setting for the further studies, i.e. patients with physician diagnosed carpal tunnel syndrome, presenting in primary care. The same data-set was then used to develop a prognostic model that aimed to identify patients who were likely to require surgical intervention. Multiple sources of candidate prognostic factors were identified and tested in the model development. It was acknowledged that the predictive performance of the model meant it lacked clinical utility. A further model was therefore developed in data with the availability of a patient reported outcome measure and more precisely defined and measured prognostic factors, some of which were felt to be important and not measurable in CPRD data. This model also performed poorly and it was concluded that the prediction of CTS is complex and that the reasons for poor performance are likely to be multifactorial.

Exploratory analysis in the same trial data attempted to identify predictors of treatment effect that might lead clinicians to be better able to discuss the likely benefits of management options particular to a patients' individual profile. It appears that, based on current evidence, patient choice is likely to be the most helpful guide to therapy, given that no such predictors were reliably identified in the trial data.

The use of the literature preceding and contemporaneous to these studies and available data from the empirical studies has been used to attempt to answer the initial research questions posed. Whilst no clinically useful conclusions could be drawn, this in is itself is helpful information. Data presented regarding overall prognosis does offer a helpful estimate for the likely course of symptoms, but clinicians may wish to take into account the potential influence of symptom duration, additional comorbidities / pain elsewhere, and baseline levels of symptoms when considering treatment options and referral.

The overall results of INSTINCTS probably offer the best estimate of likely response to CSI vs NS, regardless of patient characteristics, until such a time when evidence regarding moderators from larger trials or IPD meta-analysis emerge.

9.3.2 Limitations of the studies included in the thesis and alternative approaches

The limitations as well as benefits of using the CPRD as a data source have been discussed in 3.1.3. In summary, whilst the sample sizes it provides can be very large, the quality of the data, in the case of CTS may be more limited. The definition of CTS was restricted to a specific code. It is possible that true cases of CTS were not included in the cohort due to a more generic code or symptom codes being used instead. This would have implications on both the findings of the epidemiology studies as well as the cohort study. Rates of prevalence and incidence would be underestimated, although trends would likely be the same. If the restriction to a single Read code meant that patients with milder or less well defined symptoms were excluded, it is possible that selection bias could have been introduced to the cohort and potentially affected associations within the sample.

In this project, there was no funding to access linked Hospital Episode Statistics data. However, it was anticipated that administration coding of outpatient episodes would be adequate and the primary care data would identify episodes of CTR occurring outside of secondary care that HES would not be able to identify. Such episodes are likely to be increasing, as alternative providers deliver the service in primary care settings. In order to verify this assumption HES linkage would have been required.

The overall prognosis and association between prognostic factors and outcome may have been influenced by various treatments offered to patients in the CPRD cohort. Apart from episodes of CTR, it is likely that un-recorded episodes of CSI, NS and other treatment modalities were used to treat patients. Variation in treatment may have affected both the overall prognosis and the performance of the model. The INSTINCTS cohort however offered the advantage of random treatment allocation, reducing the potential influence of treatment on associations between prognostic factors and outcome, and hence the performance and the model. However, confounding by indication may have

still affected the results after the initial six-week period, when patients were then able to seek other forms of treatment.

INSTINCTS was a high quality randomised control trial providing a priori precise measures of candidate predictors at baseline and patient recorded outcomes at various time points. Whilst pragmatic and relatively non-exclusive, the trial was not designed to investigate prognosis, nor powered to predict treatment effect. CTR was not used as an outcome at six months as there was awareness that availability and criteria varied between centre. Patients who were to have surgery were unlikely all to have had it by six months given the mean time to surgery in CPRD was 9 months from initial presentation. Further work could explore the associations of baseline factors with an episode of surgery at 12 or 24 months. This would then allow the model developed in CPRD to be tested and updated in the higher quality INSTINCTS data, the major limitation still being the restricted sample size.

Stepwise backward elimination procedures using a significance level of 0.1, were used to select variables in both prognostic models presented in the thesis. Multiple strategies for variable selection exist. However, each have their advantages and disadvantages.[199] Despite avoiding univariable selection by starting with the full model, backward elimination can still lead to overfitting and optimism, particularly in smaller datasets. Alternative methods of variable selection include LASSO (least absolute shrinkage and selection operator) and elastic net. These methods also start with a full model but simultaneously penalise each predictor-outcome association, hence addressing the risk of overfitting.[165]

Missing data in the INSTINCTS cohort was assumed to be MAR. In an attempt to reduce the potential bias introduced by missing it data, it was managed using multiple imputation. Lifestyle (smoking, alcohol, BMI and deprivation) data from CPRD was assumed to be MNAR and as such managed using a missing indicator method and complete case analysis. These approaches are subject to criticism. A missing indicator method is limited in a number of ways: bias may be introduced by residual confounding; the magnitude and direction of bias can become difficult to predict and as the results are not theoretically driven, they are potentially meaningless. Complete case analysis is also limited

because the data used in the model is not necessarily representative of the population. Discarding data also means that the sample size and therefore statistical power are reduced and the standard error increased.[200]

Work by Peterson et al has shown that missing data for demographic characteristics (particularly weight) and disease status can be subject to multiple imputation in studies based in primary care data. However, this requires careful consideration of clinical associations and individual longitudinal trajectories.[201] A method of imputation using a two-fold fully conditional algorithm has been proposed and tested.[202]

A further source of bias in the studies described in the thesis is that caused by a unit of analysis error. Page et al suggest that unless considered in the statistical analysis, the non-independency of bilateral observations can increase the chance of type 1 errors (the rejection of a true null hypothesis).[173] Schmid et al suggest that neuro-immunological changes may be a cause of bilateral CTS and that when one wrist is objectively treated, it is possible to see resolution in the other wrist, as the systemic neuro-inflammatory process is reduced.[198] Laterality (i.e. whether the CTS affected one or both hands) could not be identified in CPRD and may have led to the episodes of CTR being underestimated over time. It may also have been an important prognostic factor to consider in the model but was not available. Approximately 50% of patients had bilateral CTS in the INSTINCTS cohort. However, only the worst affected wrist was allocated a treatment and the patient was asked to record their outcomes considering that wrist only. Laterality of symptoms was considered for inclusion in the prognostic model and tested for as a predictor of treatment effect. Whilst considering the very small sample size and lack of significant interaction, it is potentially suggested that patients with unilateral CTS experienced a less favourable outcome at six months if they were initially treated with a single injection rather than splinting. The subgroup difference was very small however and so were subgroup sizes. This result therefore is likely to be spurious.

Poor performance of the models may have been due to missing or inadequately measured prognostic factors at baseline. A further study using data from the PALMS cohort by Jerosch-Herald et al examined

the association of psychological distress at baseline with health-related quality of life and costs of CTS in the subgroup of patients referred to secondary care.[197] They concluded that patient reported symptom severity at baseline was positively associated with anxiety, depression, health-related quality of life (P<.0001 in each case) and societal costs, when adjusting for other important confounders. Anxiety but not depression was also associated with electrophysiological severity (p=0.027).[197] Despite the inclusion of measures of anxiety and depression at baseline in both the CPRD and INSTINCTS model, as with any of the candidate predictors, if they were not measured in an effective manner (for example, due to limitations in the number of further questions added to the trial questionnaire or inadequate identification and coding), this may have further led to the poor performance of the prognostic models.

9.4 Clinical relevance of findings

The studies presented in this thesis suggest that up to 75% of patients presenting in primary care can be reassured that their symptoms are likely to resolve or improve substantially, to the extent that they will not need an operation. This figure is higher than in other studies, which are generally set in secondary care and may therefore already have been pre-stratified by severity. INSTINCTS data does suggest that patients continue to experience improvements in symptom and function beyond six weeks post initial treatment. Whilst the number of patients with CTS presenting in primary care appeared to be increasing, fewer proportionally were observed to receive CTR. This may have been due to changes in access to surgery. The group of patients who were more likely to have surgery included those who were older, obese, drink alcohol, smoke and had other musculoskeletal pain and inflammatory conditions (adjusted for region and deprivation). A more severe overall BCTQ (with a lower SSS) and the absence of neck and upper limb symptoms may also predict a less favourable patient reported outcome score at six months. CTR is accepted to be an effective treatment and patients with severe or non-responsive symptom or functional disturbance should be provided with access to this treatment without undue delay or inappropriate dependence on electrodiagnostic findings. For patients with mild to moderate CTS, CSI and NS can be considered but it has not been possible to identify which patients are more likely to benefit from each treatment.

The assertion that there exists a group of patients for whom conservative management will not sufficiently help and who are likely to require surgical intervention, does not consider the health economics of treating CTS. Such a health economic analysis is beyond the scope of this thesis but has been considered in the INSTINCTS. The studies presented may however contribute to the further debate around the rationalisation of healthcare and the restrictions imposed on clinicians as to which patients with what characteristics can be referred for surgery.

9.5 Contribution to future work

Given that CSI and NS remain the mainstay of interventions available for CTS managed in primary care, the evidence base for any medium to longer-term benefit remains unclear. This evidence may be generated by the 12 and 24 month follow up of the INSTINCTS trial, although this is still unlikely to provide any clinically meaningful recommendations regarding targeting treatment to patients based on their baseline presentation.

Considerations for further work may therefore include the design and testing of a stratified care intervention for CTS. This work has provided exploratory evidence of potential moderators to include in such an intervention, however additional research would be needed to further test the predictive value of baseline characteristics to confidently inform the design of such a stratified intervention.

9.6 Thesis conclusion

Carpal tunnel syndrome is a bothersome condition, which affects patients' ability to function. The number of patients presenting in primary care with CTS was increasing whilst the proportion of patients accessing surgical treatment decreased. A substantial proportion of patients can be observed to improve over the short to medium term following conservative management, however some will not respond to treatment and have persisting symptoms. These patients are likely to include those with a higher combined symptom and function severity score at baseline and no other neck and upper limb symptoms. A combination of increasing age, obesity, being an alcohol drinker, smoker and having other neck, inflammatory or multisite pain can help predict the need for future surgery. All patients receiving primary care management for CTS should be observed and referred for consideration of surgical treatment if they fail to respond to corticosteroid injection or night splinting.

10 References

1 Keith MW, Masear V, Chung K, et al. Diagnosis of carpal tunnel syndrome. *J Am Acad Orthop Surg* 2009;17:389-96.

2 Padua L, Coraci D, Erra C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. *Lancet Neurol* 2016;15:1273-84 doi:S1474-4422(16)30231-9 [pii].

3 Paget J. Lectures on surgical pathology. Philadelphia: Lindsay & Blakinston 1854.

4 Putnam J. A series of cases of parethesias, mainly of the hand, orperiodic recurrence, and possibly of vaso-motor origin. *Archives of Medical Science* 1880;4:147-62.

5 Stecco C, Aldegheri R. Historical review of carpal tunnel syndrome. *Chir Organi Mov* 2008;92:7-10 doi:10.1007/s12306-008-0033-8; 10.1007/s12306-008-0033-8.

6 Learmonth JR. The principle of decompression in the treatmnet of certain diseases of peripheral nerves. *Surgery Clinics of North America* 1933;13:905-13.

7 Chow JC. Endoscopic release of the carpal tunnel ligament: a new technique for carpal tunnel syndrome. *Arthroscopy* 1989;6:288-96.

8 Simpson JA. Electrical signs in the diagnosis of carpal tunnel and related syndromes. *Journal of Neurology, Neurosurgery & Psychiatry* 1956;19:275-80.

9 Mitchell R, Chesney A, Seal S, et al. Anatomical variations of the carpal tunnel structures. *Canadian Journal of Plastic Surgery* 2009;17:e3-7.

10 Anatomy of the Human Body. Available at: http://www.bartleby.com/107/. Accessed November 11, 13.

11 Ibrahim I, Khan WS, Goddard N, et al. Carpal tunnel syndrome: a review of the recent literature. *Open Orthop J* 2012;6:69-76 doi:10.2174/1874325001206010069; 10.2174/1874325001206010069.

12 Mackinnon SE. Pathophysiology of nerve compression. *Hand Clin* 2002;18:231-41.

13 Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. *Clinical Neurophysiology* 2002;113:1373-81 doi:http://dx.doi.org/10.1016/S1388-2457(02)00169-4.

14 Alfonso C, Jann S, Massa R, et al. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: A review. *Neurological Sciences* 2010;31:243-52.

15 Ferry S, Pritchard T, Keenan J, et al. Estimating the prevalence of delayed median nerve conduction in the general population. *Br J Rheumatol* 1998;37:630-5.

16 Graham B. The value added by electrodiagnostic testing in the diagnosis of carpal tunnel syndrome. *J Bone Joint Surg Am* 2008;90:2587-93 doi:10.2106/JBJS.G.01362.

17 Boocock MG, Collier JM, McNair PJ, et al. A framework for the classification and diagnosis of work-related upper extremity conditions: systematic review. *Semin Arthritis Rheum* 2009;38:296-311 doi:10.1016/j.semarthrit.2007.10.006; 10.1016/j.semarthrit.2007.10.006.

18 Descatha A, Dale AM, Franzblau A, et al. Comparison of research case definitions for carpal tunnel syndrome. *Scand J Work Environ Health* 2011;37:298-306 doi:10.5271/sjweh.3148.

19 Latinovic R, Gulliford MC, Hughes RA. Incidence of common compressive neuropathies in primary care. *J Neurol Neurosurg Psychiatry* 2006;77:263-5 doi:10.1136/jnnp.2005.066696.

20 Bland JD. Treatment of carpal tunnel syndrome. *Muscle Nerve* 2007;36:167-71.

21 Keith MW, Masear V, Chung KC, et al. American Academy of Orthopaedic Surgeons Clinical Practice Guideline on diagnosis of carpal tunnel syndrome. *J Bone Joint Surg Am* 2009;91:2478-9 doi:10.2106/JBJS.I.00643.

22 Carpal Tunnel Syndrome (CTS) - The Map of Medicine. Available at: http://app.mapofmedicine.com/mom/127/page.html?department-id=8&specialty-id=1037&pathway-id=3411&page-id=8741&history=clear. Accessed 25/10/2012, 2012.

23 Carpal Tunnel Syndrome. Available at: http://cks.nice.org.uk/carpal-tunnel-syndrome#!scenariorecommendation:1. Accessed 05/14, 2013.

24 Rempel D, Evanoff B, Amadio PC, et al. Consensus criteria for the classification of carpal tunnel syndrome in epidemiologic studies. *Am J Public Health* 1998;88:1447-51.

25 Katz JN, Stirrat CR. A self-administered hand diagram for the diagnosis of carpal tunnel syndrome. *J Hand Surg Am* 1990;15:360-3.

26 Wainner RS, Fritz JM, Irrgang JJ, et al. Development of a clinical prediction rule for the diagnosis of carpal tunnel syndrome. *Arch Phys Med Rehabil* 2005;86:609-18 doi:10.1016/j.apmr.2004.11.008.

27 Graham B, Regehr G, Naglie G, et al. Development and Validation of Diagnostic Criteria for Carpal Tunnel Syndrome. *J Hand Surg* 2006;31:919.e1,919.e2,919.e3,919.e4,919.e5,919.e6,919.e7.

28 Graham B. The diagnosis and treatment of carpal tunnel syndrome. *BMJ* 2006;332:1463-4 doi:10.1136/bmj.332.7556.1463.

29 Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline. Available at: www.aaos.org/ctsguideline. Accessed 05/02, 2019.

30 BSSH Evidence for Surgical Treatment 1 Carpal Tunnel Syndrome. Available at: http://www.bssh.ac.uk/education/guidelines/carpal_tunnel_syndrome.pdf. Accessed 22/10/2012, 2012.

31 Burton C, Chesterton L, Davenport G, et al. Developing Agreed Clinical Criteria for the Diagnosis of Carpal Tunnel Syndrome in Primary Care - A Clinical Consensus Exercise 2013.

32 Levine DW, Simmons BP, Koris MJ, 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;75:1585-92.

33 Kamath V, Stothard J. A clinical questionnaire for the diagnosis of carpal tunnel syndrome. *J Hand Surg Br* 2003;28:455-9.

34 Atroshi I. Lyren PE. Gummesson,C. The 6-item CTS symptoms scale: a brief outcomes measure for carpal tunnel syndrome. *Quality of Life Research* 2009;18:347-58.

35 Bland JD. Carpal tunnel syndrome. *Curr Opin Neurol* 2005;18:581-5.

36 Concannon MJ, Gainor B, Petroski GF, et al. The predictive value of electrodiagnostic studies in carpal tunnel syndrome. *Plast Reconstr Surg* 1997;100:1452-8.

37 Jablecki CK, Andary MT, Floeter MT, et al. Second AAEM literature review of the usefulness of nerve conduction studies and needle electromyography for the evaluation of patients with carpal tunnel syndrome. *Muscle Nerve Supplement* 2002;2002:918-22.

38 Jordan R, Carter T, Cummins C. A systematic review of the utility of electrodiagnostic testing in carpal tunnel syndrome. *British Journal of General Practice* 2002;52:670-3.

39 Jeremy D P Bland. Carpal tunnel syndrome. *BMJ* 2007;335:343-6 doi:10.1136/bmj.39282.623553.AD.

40 Royal College of Surgeons. Commissioning Guide: Treatment of Carpal Tunnel Syndrome 2016.

41 Descatha A, Huard L, Aubert F, et al. Meta-analysis on the performance of sonography for the diagnosis of carpal tunnel syndrome. *Semin Arthritis Rheum* 2012;41:914-22 doi:10.1016/j.semarthrit.2011.11.006.

42 Page MJ, Massy-Westropp N, O'Connor D, et al. Splinting for carpal tunnel syndrome. *Cochrane Database of Systematic Reviews* 2012:CD010003-NaN.

43 Huisstede BM, Hoogvliet P, Randsdorp MS, et al. Carpal Tunnel Syndrome. Part I: Effectiveness of Nonsurgical Treatments–A Systematic Review. *Arch Phys Med Rehabil* 2010;91:981-1004 doi:10.1016/j.apmr.2010.03.022.

44 Gelberman RH, Aronson D, Weisman MH. Carpal-tunnel syndrome. Results of a prospective trial of steroid injection and splinting. *Journal of Bone & Joint Surgery - American Volume* 1980;62:1181-4.

45 Marshall SC, Tardif G, Ashworth NL. Local corticosteroid injection for carpal tunnel syndrome. *Cochrane Database of Systematic Reviews* 2007:CD001554-NaN.

46 J W H H Dammers, M M Veering, M Vermeulen. Injection with methylprednisolone proximal to the carpal tunnel: randomised double blind trial. *BMJ* 1999;319:884-6 doi:10.1136/bmj.319.7214.884.

47 Wong SM, Hui AC, Lo SK, et al. Single vs. two steroid injections for carpal tunnel syndrome: a randomised clinical trial. *Int J Clin Pract* 2005;59:1417-21 doi:10.1111/j.1368-5031.2005.00696.x.

48 Celiker R, Arslan S, Inanici F. Corticosteroid injection vs. nonsteroidal antiinflammatory drug and splinting in carpal tunnel syndrome. *Am J Phys Med Rehabil* 2002;81:182-6.

49 Lucantoni C, Grottoli S, Gaetti R. Comparison between He-Ne laser therapy and steroid injections in the treatment of idiopathic carpal tunnel syndrome [Confronto tra laserterapia HE–NE infiltrativa steroidea nel trattamento della sindrome idiopatica del tunnel carpale]. *La Riabilitazione ;25(4):249–56.* 1992;25:249-56.

50 Habib GS, Badarny S, Rawashdeh H. A novel approach of local corticosteroid injection for the treatment of carpal tunnel syndrome. *Clin Rheumatol* 2006;25:338-40 doi:10.1007/s10067-005-0002-7.

51 Gokoglu F, Fndkoglu G, Yorgancoglu ZR, et al. Evaluation of iontophoresis and local corticosteroid injection in the treatment of carpal tunnel syndrome. *Am J Phys Med Rehabil* 2005;84:92-6.

52 Wong SM, Hui AC, Tang A, et al. Local vs systemic corticosteroids in the treatment of carpal tunnel syndrome. *Neurology* 2001;56:1565-7.

53 Atroshi I, Flondell M, Hofer M, et al. Methylprednisolone injections for the carpal tunnel syndrome: a randomized, placebo-controlled trial. *Ann Intern Med* 2013;159:309-17.

54 Karadas O, Tok F, Ulas UH, et al. The effectiveness of triamcinolone acetonide vs. procaine hydrochloride injection in the management of carpal tunnel syndrome: a double-blind randomized clinical trial. *American Journal of Physical Medicine & Rehabilitation* 2011;90:287-92.

55 Sevim S, Dogu O, Camdeviren H, et al. Long-term effectiveness of steroid injections and splinting in mild and moderate carpal tunnel syndrome. *Neurol Sci* 2004;25:48-52 doi:10.1007/s10072-004-0229-0 [doi].

56 Ucan H, Yagci I, Yilmaz L, et al. Comparison of splinting, splinting plus local steroid injection and open carpal tunnel release outcomes in idiopathic carpal tunnel syndrome. *Rheumatol Int* 2006;27:45-51 doi:10.1007/s00296-006-0163-y [doi].

57 So H, Chung VCH, Cheng JCK, et al. Local steroid injection versus wrist splinting for carpal tunnel syndrome: A randomized clinical trial. *Int J Rheum Dis* 2018;21:102-7 doi:10.1111/1756-185X.13162.

58 Injection Versus Splining in Carpal Tunnel Syndrome (INSTinCTS). Available at: https://www.clinicaltrials.gov/ct2/show/NCT02038452. Accessed 13 May 2014, 2014.

59 Chesterton LS, Blagojevic-Bucknall M, Burton C, 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;392:1423-33.

60 Middleton SD, Anakwe RE. *BMJ* 2014;349 doi:10.1136/bmj.g6437.

61 Scholten RJ, Mink van der Molen A, Uitdehaag BM, et al. Surgical treatment options for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2007;(4):CD003905 doi:10.1002/14651858.CD003905.pub3 [doi].

62 Turner A, Kimble F, Gulyás K, et al. Can the outcome of open carpal tunnel release be predicted?: a review of the literature. *ANZ J Surg* 2010;80:50-4 doi:10.1111/j.1445-2197.2009.05175.x.

63 Louie DL, Earp BE, Collins JE, et al. *The Journal of Bone & Joint Surgery* 2013;95:1067-73 doi:10.2106/JBJS.L.00903.

64 Ryan D, Shaw A, Graham S, et al. Variation in CCG policies for the treatment of carpal tunnel syndrome. *Bulletin* 2017;99:28-31 doi:10.1308/rcsbull.2017.28.

65 Palmer,D.H., Hanrahan,L.P. Social and economic costs of carpal tunnel surgery. *Instructional course lectures* 1995;44:167-72.

66 **Days away from work highest for Carpal Tunnel Syndrome**. Available at: Days away from work highest for carpal tunnel syndrome. Accessed 11/10/2012, 2012.

67 Hospital Episode Statistics, Admitted Patient Care, England, 2012-13: Procedures and Interventions. Available at: http://www.hscic.gov.uk/catalogue/PUB12566/hosp-epis-stat-admi-proc-2012-13-tab.xlsx. Accessed 03/24, 2015.

68 Miranda BH, Asaad K, Cerovac S. Carpal tunnel syndrome study: Local corticosteroids, conversion to surgery and NHS implications. *Journal of Plastic Reconstructive and Aesthetic Surgery* 2013;66:1432-3 doi:10.1016/j.bjps.2013.04.005.

69 Padua L, Padua R, Aprile I, et al. Multiperspective follow-up of untreated carpal tunnel syndrome: a multicenter study. *Neurology* 2001;56:1459-67.

70 The Oxford English Dictionary. Available at: http://www.oxforddictionaries.com/definition/english. Accessed April 2015, 2015.

71 Harry Hemingway, Peter Croft, Pablo Perel, et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. *BMJ* 2013;346 doi:10.1136/bmj.e5595.

72 Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380 doi:10.1371/journal.pmed.1001380; 10.1371/journal.pmed.1001380.

73 Steyerberg EW, Moons KGM, van dW, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. *PLoS Med* 2013;10:e1001381.

74 Hingorani AD, Windt DA, Riley RD, et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ* 2013;346:e5793 doi:10.1136/bmj.e5793 [doi].

75 Riley DR, van der Windt DA, Croft P, et al., eds. Prognosis research in healthcare: concepts, methods and impact. Oxford, UK: Oxford University Press 2019.

76 Szklo M, Javier Nieto f. Measuring Disease Occurrence. In: Jones & Bartlett Learning, ed. Epidemiology. Beyond the Basics 2014:47-77.

77 Browsing Disease Prevalence Models. Available at: http://www.apho.org.uk/DISEASEPREVALENCEMODELS. Accessed 09/25, 2014.

78 Wallace P, Delaney B, Sullivan F. Unlocking the research potential of the GP electronic care record. *Br J Gen Pract* 2013;63:284-5 doi:10.3399/bjgp13X668023.

79 Shephard E, Stapley S, Hamilton W. The use of electronic databases in primary care research. *Family Practice* 2011;28:352-4 doi:10.1093/fampra/cmr039.

80 SAIL Databank. Available at: https://saildatabank.com/. Accessed 09/26, 2019.

81 Attribution Data Set GP-Registered Populations Scaled to ONS Population Estimates – 2011 2012 . Available at: http://www.hscic.gov.uk/catalogue/PUB05054. Accessed 01/17, 2017.

82 Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827-36 doi:10.1093/ije/dyv098 [doi].

83 Benson T. The history of the Read codes. *Informatics in Primary Care* 2011;19:173-82.

84 SNOMED CT. Available at: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct. Accessed May 28, 2019.

85 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;60:e128-36 doi:10.3399/bjgp10X483562.

86 Jordan K, Clarke AM, Symmons DP, et al. Measuring disease prevalence: a comparison of musculoskeletal disease using four general practice consultation databases. *Br J Gen Pract* 2007;57:7-14.

87 Clinical Practice Research Datalink. Available at: https://www.cprd.com/linked-data. Accessed May 28, 2019.

88 Davis L, Vedanarayanan VV. Carpal Tunnel Syndrome in Children. *Pediatr Neurol* 2014;50:57-9 doi:10.1016/j.pediatrneurol.2013.08.019.

89 BMJ Group, Pharmaceutical Press. 10.1.2.2 Local Corticosteroid Injections. In: Anonymous . British National Formulary: BMJ Group; Pharmaceutical Press 2013.

90 Population Estimates. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates. Accessed 02/16, 2017.

91 National Cancer Institute. Joinpoint Regression Program - Surveillance Research Program 2017.

92 NHS Executive. *Information for Health: An Information Strategy for the Modern NHS 1998–2005. A National Strategy for Local Implementation* 1998.

93 Porcheret M, Hughes R, Evans D, et al. Data quality of general practice electronic health records: the impact of a program of assessments, feedback, and training. *Journal of the American Medical Informatics Association* 2004;11:78-86 doi:http://dx.doi.org/10.1197/jamia.M1362.

94 Lewis R, Appleby J. Can the English NHS meet the 18-week waiting list target?. *J R Soc Med* 2006;99:10-3.

95 Roquelaure Y, Ha C, Nicolas G, et al. Attributable risk of carpal tunnel syndrome according to industry and occupation in a general population. *Arthritis Rheum* 2008;59:1341-8 doi:10.1002/art.24002.

96 Gelfman R, Melton LJ,3rd, Yawn BP, et al. Long-term trends in carpal tunnel syndrome. *Neurology* 2009;72:33-42.

97 Shiri R, Pourmemari MH, Falah-Hassani K, et al. The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies. *Obes Rev* 2015;16:1094-104 doi:10.1111/obr.12324 [doi].

98 Pourmemari MH, Shiri R. Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis. *Diabetic Med* 2016;33:10-6 doi:10.1111/dme.12855.

99 Bongers FJ, Schellevis FG, van den Bosch WJ, et al. Carpal tunnel syndrome in general practice (1987 and 2001): incidence and the role of occupational and non-occupational factors. *Br J Gen Pract* 2007;57:36-9.

100 Roquelaure Y, Chazelle E, Gautier L, et al. Time trends in incidence and prevalence of carpal tunnel syndrome over eight years according to multiple data sources: Pays de la Loire study. *Scand J Work Environ Health* 2017:75-85.

101 Foot C, Naylor C, Imison C. The Quality of GP Diagnosis and Referral 2010.

102 Imison C, Naylor C. Referral Management 2010.

103 Gerritsen AM, de Vet HCW, Scholten RJPM, et al. Splinting vs surgery in the treatment of carpal tunnel syndrome: a randomized controlled trial. *JAMA* 2002;288:1245-51.

104 Wildin C, Dias JJ, Heras-Palou C, et al. Trends in elective hand surgery referrals from primary care. *Ann R Coll Surg Engl* 2006;88:543-6 doi:10.1308/003588406X117070.

105 Tadjerbashi K, Åkesson A, Atroshi I. Incidence of referred carpal tunnel syndrome and carpal tunnel release surgery in the general population: Increase over time and regional variations. *J Orthop Surg (Hong Kong)* 2019;27:2309499019825572 doi:10.1177/2309499019825572.

106 Bebbington E, Furniss D. Linear regression analysis of Hospital Episode Statistics predicts a large increase in demand for elective hand surgery in England. *J Plast Reconstr Aesthet Surg* 2015;68:243-51 doi:10.1016/j.bjps.2014.10.011 [doi].

107 Henderson R, Keiding N. Individual survival time prediction using statistical models. *J Med Ethics* 2005;31:703-6 doi:31/12/703 [pii].

108 Louie D, Earp B, Blazar P. Long-term outcomes of carpal tunnel release: a critical review of the literature. *Hand* 2012;7:242-6.

109 Tang CQY, Lai SWH, Tay SC. Long-term outcome of carpal tunnel release surgery in patients with severe carpal tunnel syndrome. *Bone Joint J* 2017;99-B:1348-53 doi:10.1302/0301-620X.99B10.BJJ-2016-0587.R2 [doi].

110 Burton CL, Chesterton LS, Chen Y, et al. Clinical Course and Prognostic Factors in Conservatively Managed Carpal Tunnel Syndrome: A Systematic Review. *Arch Phys Med Rehabil* 2016;97:836,852.e1 doi:10.1016/j.apmr.2015.09.013 [doi].

111 MEDLINE. Available at: http://www.nlm.nih.gov/pubs/factsheets/medline.html. Accessed 06/05, 2014.

112 Embase Product. Available at: http://site.ovid.com/pdf/collateral_2014/Embase_FS_0314_FINAL.pdf. Accessed 06/05, 2014.

113 AMED. Available at: http://www.ebscohost.com/corporate-research/amed. Accessed 06/05, 2014.

114 Journals and Databases. Available at: http://www.library.nhs.uk/help/resource/. Accessed 06/05, 2014.

115 About the Cochrane Library. Available at: http://www.thecochranelibrary.com/view/0/AboutTheCochraneLibrary.html. Accessed 06/05, 2014.

116 About Trip. Available at: http://www.tripdatabase.com/about. Accessed 06/05, 2014.

117 Science Citation Index Expanded. Available at: http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/science-citation-index-expanded.html. Accessed May / 07, 2015.

118 Conference Proceedings Citations Index. Available at: http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/conference-proceedings-citation-index.html. Accessed May / 07, 2015.

119 Cochrane Handbook for Systematic Reviews of Interventions. Available at: http://handbook.cochrane.org/. Accessed May / 12, 2015.

120 Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280-6 doi:10.7326/0003-4819-158-4-201302190-00009; 10.7326/0003-4819-158-4-201302190-00009.

121 **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses**. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 06/03, 2014.

122 Sackett DL, Straus SE, Richardson WS. Evidence-Based Medicine. How to Practice and Teach EMB. Edinburgh: Churchill Livingstone 2000.

123 Ariens GA, van Mechelen W, Bongers PM, et al. Physical risk factors for neck pain. *Scandinavian Journal of Work, Environment and Health* 2000;26:7-19.

124 DeStefano F, Nordstrom DL, Vierkant RA. Long-term symptom outcomes of carpal tunnel syndrome and its treatment. *Journal of Hand Surgery - American Volume* 1997;22:200-10.

125 Padua L, Padua R, Lo Monaco M, et al. Natural history of carpal tunnel syndrome according to the neurophysiological classification. *Ital J Neurol Sci* 1998;19:357-61.

126 OrtizCorredor F, Enriquez F, DiazRuiz J, et al. Natural evolution of carpal tunnel syndrome in untreated patients. *Clinical Neurophysiology* Jun 2008;119:1373-8.

127 Resende LAL, Tahara A, Fonseca RG, et al. The natural history of carpal tunnel syndrome: A study of 20 hands evaluated 4 to 9 years after initial diagnosis. *Electromyogr Clin Neurophysiol* 2003;43:301-4.

128 Beaton DE, Wright JG, Katz JN, et al. Development of the QuickDASH: comparison of three item-reduction approaches. *J Bone Joint Surg Am* 2005;87:1038-46 doi:87/5/1038 [pii].

129 Gianinni F. Quantative Assessment of Historical and Objective Findings: A New Clinical Severity Scale of CTS. In: Luchetti R, Amadio P, eds. Carpal Tunnel Syndrome: Springer Berlin Heidelberg 2007:82-8.

130 Lian BT, Urkude R, Verma KK. Clinical profile, electrodiagnosis and outcome in patients with carpal tunnel syndrome: A Singapore perspective. *Singapore Med J* 2006;47:1049-52.

131 Kiylioglu N, Bicerol B, Ozkul A, et al. Natural course and treatment efficacy: one-year observation in diabetic and idiopathic carpal tunnel syndrome. *Journal of Clinical Neurophysiology* 2009;26:446-54.

132 Kaplan SJ, Glickel SZ, Eaton RG. Predictive factors in the non-surgical treatment of carpal tunnel syndrome. *Journal of Hand Surgery - British Volume* 1990;15:106-8.

133 Muhlau G, Both R, Kunath H. Carpal tunnel syndrome--course and prognosis. *J Neurol* 1984;231:83-6.

134 Katz JN, Lew RA, Bessette L, et al. Prevalence and predictors of long-term work disability due to carpal tunnel syndrome. *Am J Ind Med* 1998;33:543-50.

135 Katz JN, Keller RB, Simmons BP, et al. Maine Carpal Tunnel Study: outcomes of operative and nonoperative therapy for carpal tunnel syndrome in a community-based cohort. *Journal of Hand Surgery - American Volume* 1998;23:697-710.

136 Goodwill CJ. THE CARPAL TUNNEL SYNDROME. LONG-TERM FOLLOW-UP SHOWING RELATION OF LATENCY MEASUREMENTS TO RESPONSE TO TREATMENT. *Ann Phys Med* 1965;8:12-21.

137 Kouyoumdjian JA, Morita MPA, Molina AFP, et al. Long-term outcomes of symptomatic electrodiagnosed carpal tunnel syndrome. *Arq Neuropsiquiatr* 2003;61:ate of Pubaton: June 2003.

138 Boyd KU, Gan BS, Ross DC, et al. Outcomes in carpal tunnel syndrome: symptom severity, conservative management and progression to surgery. *Clinical & Investigative Medicine* 2005;28:254-61.

139 Duckworth AD, Jenkins PJ, Roddam P, et al. Pain and carpal tunnel syndrome. *Journal of Hand Surgery - American Volume* 2013;38:1540-6.

140 Gerritsen AAM, Korthals-De Bos IBC, Laboyrie PM, et al. Splinting for carpal tunnel syndrome: prognostic indicators of success. *Journal of Neurology, Neurosurgery & Psychiatry* 2003;74:1342-4 doi:10.1136/jnnp.74.9.1342.

141 Graham RG, Hudson DA, Solomons M, et al. A prospective study to assess the outcome of steroid injections and wrist splinting for the treatment of carpal tunnel syndrome. *Plastic & Reconstructive Surgery* 2004;113:550-6.

142 Jenkins PJ, Duckworth AD, Watts AC, et al. Corticosteroid injection for carpal tunnel syndrome: a 5-year survivorship analysis. *Hand (N Y)* 2012;7:151-6 doi:10.1007/s11552-012-9390-8; 10.1007/s11552-012-9390-8.

143 Meys V, Thissen S, Rozeman S, et al. Prognostic factors in carpal tunnel syndrome treated with a corticosteroid injection. *Muscle and Nerve* 2011;44:763-8.

144 Page MJ, O'Connor DA, Pitt V, et al. Reporting of allocation method and statistical analyses that deal with bilaterally affected wrists in clinical trials for carpal tunnel syndrome. *Am J Phys Med Rehabil* 2013;92:1012-9 doi:10.1097/PHM.0b013e31828cd3e7 [doi].

145 Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD StatementThe TRIPOD Statement. *AIM* 2015;162:55-63 doi:10.7326/M14-0697.

146 Mallen CD. The prognosis of musculoskeletal pain in older adults in general practice 2009.

147 Burton C, Campbell P, Jordan K, et al. The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care. *Family Practice* 2012 doi:10.1093/fampra/cms044.

148 Peduzzi DH, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis . *Journal of clinical epidemiology* 1996;49:1373-9.

149 Cox DR. Regression models and life-tables (with discussion). *Journal of the Royal Statistical Society* 1972;34:187-220.

150 Riley RD, Snell KIE, Moons KGM, et al. Fundamental statistical methods for prognosis research. In: Riley RD, van der Windt DA, Croft P, et al., eds. Prognosis research in healthcare: Concepts, methods and impact: Oxford University Press 2019:37-68.

151 Schoenfeld D. Partial residuals for the propotional hazards regression model. *Biometrika* 1982;69:239-41.

152 GRAMBSCH PM, THERNEAU TM. Proportional hazards tests and diagnostics based on weighted residuals. *biomet* 1994;81:515-26 doi:10.1093/biomet/81.3.515.

153 Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. *BMJ* 2009;338 doi:10.1136/bmj.b604.

154 Harrell FE,Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87 doi:10.1002/(SICI)1097-0258(19960229)15:43.0.CO;2-4 [pii].

155 Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338 doi:10.1136/bmj.b2393.

156 Padua L, Di Pasquale A, Pazzaglia C, et al. Systematic review of pregnancy-related carpal tunnel syndrome. *Muscle Nerve* 2010;42:697-702 doi:10.1002/mus.21910 [doi].

157 Moons KGM, Altman DG, Vergouwe Y, et al. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009;338 doi:10.1136/bmj.b606.

158 Schuit E, Groenwold RH, Harrell FE,Jr, et al. Unexpected predictor-outcome associations in clinical prediction research: causes and solutions. *CMAJ* 2013;185:E499-505 doi:10.1503/cmaj.120812 [doi].

159 Leite JC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. *BMC Musculoskeletal Disorders* 2006;7:78.

160 Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R). *Psychology and Health* 2002;17:1-16.

161 Jenkins CD, Stanton BA, Niemcryk SJ, et al. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988;41:313-21 doi:0895-4356(88)90138-2 [pii].

162 van Windt,D A W M der, Koes BW, Devillé W, et al. Effectiveness of corticosteroid injections versus physiotherapy for treatment of painful stiff shoulder in primary care: randomised trial. *BMJ* 1998;317:1292-6 doi:10.1136/bmj.317.7168.1292.

163 Foster NE, Bishop A, Thomas E, et al. Illness perceptions of low back pain patients in primary care: what are they, do they change and are they associated with outcome?. *Pain* 2008;136:177-87 doi:10.1016/j.pain.2007.12.007 [doi].

164 Malchaire J, Roquelaure Y, Cock N, et al. Musculoskeletal complaints, functional capacity, personality and psychosocial factors. *Int Arch Occup Environ Health* 2001;74:549-57.

165 Riley RD, Moons KGM, DeBray TPA, et al. Chapter 7: Prognostic model research. In: Riley RD, van der Windt DA, Croft P, et al., eds. Prognosis Research in Healthcare: Concepts, Methods and Impact: Oxford University Press 2019:139,- 187.

166 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377-99 doi:10.1002/sim.4067 [doi].

167 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statist Med* 2011;30:377-99 doi:10.1002/sim.4067.

168 Groenwold RH, Moons KG, Pajouheshnia R, et al. Explicit inclusion of treatment in prognostic modeling was recommended in observational and randomized settings. *J Clin Epidemiol* 2016;78:90-100 doi:S0895-4356(16)30030-0 [pii].

169 Stein C. Inadmissibility of the usual estimator for the mean of a multivariatedistribution 1956:197,-206.

170 Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. *Statist Med* 1990;9:1303-25 doi:10.1002/sim.4780091109.

171 Ensor J. PMPSAMPSIZE: Stata module to calculate the minimum sample size required for developing a multivariable prediction model 2018.

172 Riley RD, Snell KIE, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: Part I – Continuous outcomes. *Statistics in Medicine* 2019;38:1262-75 doi:10.1002/sim.7993.

173 Page J, O'Connor A, Pitt V, et al. Reporting of Allocation Method and Statistical Analyses That Deal with Bilaterally Affected Wrists in Clinical Trials for Carpal Tunnel Syndrome. *American Journal of Physical Medicine & Rehabilitation* 2013;92:1012-20.

174 Hill JC, Fritz JM. Psychosocial influences on low back pain, disability, and response to treatment. *Phys Ther* 2011;91:712-21 doi:10.2522/ptj.20100280 [doi].

175 Hancock M, Herbert RD, Maher CG. A Guide to Interpretation of Studies Investigating Subgroups of Responders to Physical Therapy Interventions. *Physical Therapy* 2009;89:698-704 doi:10.2522/ptj.20080351.

176 Aboonq MS. Pathophysiology of carpal tunnel syndrome. *Neurosciences (Riyadh, Saudi Arabia)* 2015;20:4-9.

177 O'Connor D, Marshall S, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. *Cochrane Database of Systematic Reviews* 2003:003219.

178 Pincus T, Miles C, Froud R, et al. Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: a consensus study. *BMC Med Res Methodol* 2011;11:14,2288-11-14 doi:10.1186/1471-2288-11-14; 10.1186/1471-2288-11-14.

179 Ly-pen D, Andreu J-, Millan I, et al. Comparison of surgical decompression and local steroid injection in the treatment of carpal tunnel syndrome: 2-year clinical results from a randomized trial. *Rheumatology (United Kingdom)* 2012;51:Arte Number: kes053. ate of Pubaton: August 2012.

180 Ly-Pen D, Andreu J, de Blas G, et al. Surgical decompression versus local steroid injection in carpal tunnel syndrome - A one-year, prospective, randomized, open, controlled clinical trial. *Arthritis Rheum* 2005;52:612-9 doi:10.1002/art.20767.

181 Wang R, Ware J. Detecting Moderator Effects Using Subgroup Analyses. *Prevention Science* 2013;14:111-20 doi:10.1007/s11121-011-0221-x.

182 Sun X, Briel M, Busse JW, et al. Subgroup Analysis of Trials Is Rarely Easy (SATIRE): a study protocol for a systematic review to characterize the analysis, reporting, and claim of subgroup effects in randomized trials. *Trials* 2009;10:101- doi:10.1186/1745-6215-10-101.

183 Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005:365 176-86.

184 Brookes ST, Whitely E, Egger M. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 2004;57 doi:10.1016/j.jclinepi.2003.08.009.

185 Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ* 2012;344 doi:10.1136/bmj.e1553.

186 Assmann SF, Pocock SJ, Enos LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355 doi:10.1016/S0140-6736(00)02039-0.

187 Kasenda B, Schandelmaier S, Sun X, et al. Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications. *BMJ* 2014;349 doi:10.1136/bmj.g4539.

188 Page MJ, O'Connor D, Pitt V, et al. Exercise and mobilisation interventions for carpal tunnel syndrome. *Cochrane Database of Systematic Reviews* 2012:CD009899-NaN.

189 Page MJ, O'Connor D, Pitt V, et al. Therapeutic ultrasound for carpal tunnel syndrome. *Cochrane Database of Systematic Reviews* 2013:CD009601-NaN.

190 Altman DG, Bland JM. Statistics notes. Units of analysis. *BMJ* 1997;314:1874- doi:10.1136/bmj.314.7098.1874.

191 Jerosch-Herold C, Shepstone L, Houghton J, et al. Prognostic factors for response to treatment by corticosteroid injection or surgery in carpal tunnel syndrome (palms study): A prospective multicenter cohort study. *Muscle Nerve* 2019;60:32-40 doi:10.1002/mus.26459.

192 Atroshi I, Lyren PE, Ornstein E, et al. The six-item CTS symptoms scale and palmar pain scale in carpal tunnel syndrome. *J Hand Surg Am* 2011;36:788-94 doi:10.1016/j.jhsa.2011.02.021.

193 Henschke N, Ostelo RWJG, Terwee CB, et al. Identifying generic predictors of outcome in patients presenting to primary care with nonspinal musculoskeletal pain. *Arthritis Care Res* 2012;64:1217-24 doi:10.1002/acr.21665.

194 Mallen CD, Thomas E, Belcher J, et al. Point-of-Care Prognosis for Common Musculoskeletal Pain in Older AdultsMusculoskeletal Pain in Older Adults. *INTEMED* 2013;173:1119-25 doi:10.1001/jamainternmed.2013.962.

195 Artus M, Campbell P, Mallen CD, et al. Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. *BMJ Open* 2017;7:e012901 doi:10.1136/bmjopen-2016-012901.

196 Schmid AB, Bland JD, Bhat MA, et al. The relationship of nerve fibre pathology to sensory function in entrapment neuropathy. *Brain* 2014;137:3186-99 doi:10.1093/brain/awu288 [doi].

197 Jerosch-Herold C, Houghton J, Blake J, et al. Association of psychological distress, quality of life and costs with carpal tunnel syndrome severity: a cross-sectional analysis of the PALMS cohort. *BMJ Open* 2017;7:e017732,2017-017732 doi:10.1136/bmjopen-2017-017732 [doi].

198 Schmid AB, Hailey L, Tampin B. Entrapment Neuropathies: Challenging Common Beliefs With Novel Evidence. *J Orthop Sports Phys Ther* 2018;48:58-62 doi:10.2519/jospt.2018.0603 [doi].

199 Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med* 2007;26:5512-28 doi:10.1002/sim.3148 [doi].

200 Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clinical epidemiology* 2017;9:157-66 doi:10.2147/CLEP.S129785.

201 Petersen I, Welch CA, Nazareth I, et al. Health indicator recording in UK primary care electronic health records: key implications for handling missing data. *Clinical epidemiology* 2019;11:157-67 doi:10.2147/CLEP.S191437.

202 Welch C, Bartlett J, Petersen I. Application of multiple imputation using the two-fold fully conditional specification algorithm in longitudinal clinical data. *The Stata journal* 2014;14:418-31.

203 AAOS Guideline on the Treatment of Carpal Tunnel Syndrome 2011 Report for the "Re-issue" of the Original Guideline . Available at: http://www.aaos.org/Research/guidelines/CTS_Treatment_REIssue.pdf. Accessed 28/11/12, 2012.

204 Jordan K, Porcheret M, Kadam UT, et al. The use of general practice consultation databases in rheumatology research. *Rheumatology* 2006;45:126-8 doi:10.1093/rheumatology/kei265.

205 Jordan KP, Kadam UT, Hayward R, et al. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010;11:144,2474-11-144 doi:10.1186/1471-2474-11-144 [doi].

206 Jordan K, Porcheret M, Croft P. Quality of morbidity coding in general practice computerized medical records: a systematic review. *Fam Pract* 2004;21:396-412 doi:10.1093/fampra/cmh409 [doi].

207 Topic referral form: Carpal tunnel syndrome. Available at: file:///S:/Downloads/Topic%20referral%20form%20carpal%20tunnel%20syndrome.pdf. Accessed 05/15, 2014.

208 Surgery in Primary Care (SIPC) for CTS. Available at: http://www.carpal-tunnel.net/kentinfo/surgery. Accessed 05/15, 2014.

209 Community Carpal Tunnel Decompression Surgery Service. Available at: https://www.supply2health.nhs.uk/CPI/Lists/AQPOffers/Attachments/24/Document%202%20Carpal%20Tunnel%20Decompression%20Surgery%20Service%20Specification.pdf. Accessed 05/15, 2014.

11 Appendices

A. ISAC Protocol

ISAC APPLICATION FORM PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted	....	**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

1. Study Title

The Epidemiology, Prognosis and Management of Carpal Tunnel Syndrome in Primary Care

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Dr Claire Burton, NIHR In Practice Fellow, Arthritis Research UK Primary Care Centre, Keele University.
Email: c.burton@keele.ac.uk

3. Affiliation (full address)

Arthritis Research UK Primary Care Centre, Keele University, Keele, Staffordshire ST5 5BG

4. Protocol's Author (if different from the principal investigator)

5. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Dr Linda Chesterton, Keele University, email: l.s.chesterton@keele.ac.uk
Dr Ying Chen, Keele University, email: y.chen1@keele.ac.uk
Dr Kelvin Jordan, Keele University, email: k.p.jordan@keele.ac.uk
Professor Danielle van der Windt, Keele University, email: d.van.der.windt@keele.ac.uk

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

6. Type of Institution (please tick one box below)

Academia	☒	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

7. Financial Sponsor of study

Pharmaceutical Industry *(please specify)*	☐	Academia*(please specify)*	☒
Keele University			
Government / NHS *(please specify)*	☐	None	☐
Other *(please specify)*	☒ submitted)		

8. Data source *(please tick one box below)*

Sponsor has on-line access	☒	Purchase of ad hoc dataset	☐
Commissioned study	☐		
Other	☐ *(please specify)*		

9. Has this protocol been peer reviewed by another Committee?

Yes*	☒	No	☐

** Please state in your protocol the name of the reviewing Committee(s) and provide an outline of the review process and outcome.*

This protocol has been reviewed by the Keele CPRD steering group housed at the Arthritis Research UK Primary Care Centre.

10. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety ☐ Drug Use ☐ Disease Epidemiology ☒
Drug Effectiveness ☐ Pharmacoeconomic ☐ Other ☐

11. This study is intended for:

Publication in peer reviewed journals ☒ Presentation at scientific conference ☒
Presentation at company/institutional meetings ☐ Other
Inclusion in MPhil thesis

12. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ No ☒

13. If you are seeking access to data held under the CPRD Data Linkage Scheme*, please select the source(s) of linked data being requested.

☐ Hospital Episode Statistics ☐ Cancer Registry Data**
☐ MINAP ☐ ONS Mortality Data
☒ Index of Multiple Deprivation/ Townsend Score
☐ Mother Baby Link ☐ Other: (please specify)

** As part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.*

***Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.*

14. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ No* ☐

**Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*

Please list below the name of the person/s at the CPRD with whom you have discussed your request.

15. If you are seeking access to data held under the CPRD Data Linkage Scheme, please provide the following information:

The number of linked datasets requested: 1

A synopsis of the purpose(s) for which the linkages are required:
We wish to access the Index of Multiple Deprivation in order to assess the prognostic value of deprivation as a predictor of surgery in patient s diagnosed with CTS.

Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

16. If you have requested linked data sets, please indicate whether the Principal Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

    Yes* ☐ No ☒

** If yes, please provide further details:*

17. Does this protocol involve requesting any additional information from GPs?

    Yes* ☐ No ☒

    * *Please indicate what will be required:*

Completion of questionnaires by the GP$^{\Psi}$ Yes ☐ No ☐
Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐
Other (please describe)

$^{\Psi}$ *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

18. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

    Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

19. Does this study involve linking to patient *identifiable* data from other sources?

    Yes ☐ No ☒

20. Does this study require contact with patients in order for them to complete a questionnaire?

    Yes ☐ No ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

21. Does this study require contact with patients in order to collect a sample?

    Yes* ☐ No ☒

** Please state what will be collected*

22. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☒	☒
> 3	☐	☐

Yes

No

Is statistical expertise available within the research team? ☒ ☐

If yes, please outline level of experience

Ying Chen is a Research Associate in Biostatistics, with a PhD in Genetic Epidemiology and is currently working on a different study within CPRD.
Kelvin Jordan is a Reader in Biostatistics, with a PhD in Medical Statistics and 20 years of experience.

Is experience of handling large data sets (>1 million records) available within the research team? ☒ ☐

If yes, please outline level of experience

Kelvin Jordan has analysed 2 previous GPRD datasets and 1 current CPRD dataset and is also principal investigator of a number of research studies utilising a regional GP database (CiPCA) consisting of consultation data covering more than 10 years from 13 general practices.

Is UK primary care experience available within the research team? ☒ ☐

If yes, please outline level of experience

Claire Burton has been a practicing GP since completion of her training in 2011. She works in a Practice with significant involvement and expertise in primary care research.

23. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study

Gelfman, R., L. J. Melton 3rd, B. P. Yawn, P. C. Wollan, P. C. Amadio, and J. C. Stevens. 2009. "Long-Term Trends in Carpal Tunnel Syndrome." *Neurology* 72 (1): 33-41.

Padua, L., R. Padua, I. Aprile, P. Pasqualetti, and P. Tonali. 2001. "Multiperspective Follow-Up of Untreated Carpal Tunnel Syndrome: A Multicenter Study." *Neurology* 56 (11): 1459-1467.

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	Yes	No	If no, reason for omission
Lay Summary (max.200 words)	☒	☐	
Background	☒	☐	
Objective, specific aims and rationale	☒	☐	
Study Type *Descriptive* *Hypothesis Generating* *Hypothesis Testing*	 ☒ ☐ ☒	 ☐ ☒ ☐	 Prognostic analysis
Study Design	☒	☐	
Sample size/power calculation (Please provide justification of sample size in the protocol)	☒	☐	
Study population (including estimate of expected number of relevant patients in the CPRD)	☒	☐	
Selection of comparison group(s) or controls	☐	☒	Not applicable to this study
Exposures, outcomes and covariates *Exposures are clearly described* *Outcomes are clearly described*	☒ ☒ ☒	☐ ☐ ☐	
Use of linked data (if applicable)	☒	☐	
Data/ Statistical Analysis Plan *There is plan for addressing confounding* *There is a plan for addressing missing data*	☒ ☒ ☒	☐ ☐ ☐	
Patient/ user group involvement [†]	☒	☐	
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

[†] ***It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.***

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

Lay Summary

Carpal Tunnel Syndrome (CTS) is a common condition in which a nerve (known as the median nerve) is squeezed as it passes through the wrist. CTS can cause pain or aching, tingling and numbness in the affected hand. It may disturb sleep and affect people's ability to do day to day activities.

It is not clear how many people in the UK have CTS or consult their GP for this problem. We are also unsure how patients with CTS are being treated in primary care nor how they respond, for example how many are given injections by their GP, how many need surgery and how they respond to these treatments in the long term.

This study will aim to:

- show how many people are getting carpal tunnel syndrome, describe how they are being treated and how this has been changing over a period of 24 years
- show what usually happens to people's symptoms and predict which patients will have more severe disease and need an operation

The CPRD (a large database of healthcare information from general practice) will be used to estimate how many people each year develop CTS and to describe how they are treated. We will then examine these patient's records, in the database, to see if there are features that suggest which patients are likely to need surgery.

Background

Carpal tunnel syndrome (CTS) is a symptomatic compression neuropathy of the median nerve at the level of the wrist [203]. CTS is characterised by numbness, tingling, hand and arm pain and muscle dysfunction and is a recognised work-related musculoskeletal disorder (WMSD) caused by strain and repeated movements (biomechanical overload) and is hence more common in manual workers [11]. CTS can be associated with pregnancy and a number of co-morbidities such as diabetes and hypothyroidism. Work absence due to CTS appears to cause a significant socio-economic burden [66], although we are not aware of UK based data.

A study from the UK General Practice Research Database in 2000, calculated the incidence in men to be 8.8 per 10,000 person-years and in women to be 19.3 per 10,000 person-years, with new presentations being most frequent at ages 45-54 in women and 75-84 in men [19]. Evidence from the US based Rochester Epidemiology Project suggested the annual adjusted incidence rates of medically diagnosed CTS was higher than in the UK and increased significantly from 25.9 per 10,000 person-years in 1981-1985 to 42.4 in 2000-2005 [96]. Although there was a report of referrals for elective carpal tunnel surgery to one major UK hand centre rising by 88% between 1989-1990 and 2000 (5.97 to 11.2 per 10,000 person-years) [104], there is no more recent data regarding the UK incidence of CTS or how this, alongside management, may have changed over time.

To further explore the current evidence base of the likely outcome (prognosis) of patients presenting with CTS, a structured literature search was carried out. The course of untreated CTS was studied by Padua *et al* (2001) in a relatively short follow-up study over a 10 to 15 month period. The authors found clinical and neurophysiological measures improved in patients with more severe initial impairment compared with milder initial impairment and the main positive prognostic factors were short symptom duration and younger age. Bilateral symptoms and a positive Phalen's test predicted poor prognosis [69]. Predictors of post-surgical outcome have been investigated extensively; however there has been little discussion in the literature regarding the value of clinical indicators at diagnosis to predict the outcome of conservatively managed CTS or to predict the need for surgical intervention. None of the papers found were set in the consulting primary care population, suggesting that there is a significant opportunity to further investigate the course and prognosis of CTS presenting in primary care, particularly over the longer term.

With previous evidence of an increasing incidence of CTS in the US over a period of 20 years [96] and evidence of an increasing rate of surgical referrals in the UK over a period of 10 years[104], the proposed studies will therefore provide the new and updated epidemiological data required to describe the current prevalence, incidence and management of carpal tunnel syndrome in the UK. This research

will also help to map the likely outcome of patients presenting in primary care with CTS and identify factors that may predict the need for surgical intervention. Such evidence will help inform the commissioning of appropriate evidence based services in primary care or the primary / secondary care interface, where the majority of the management of CTS occurs.

Objective, specific aims and rationale

The proposed research aims to describe the prevalence, incidence and management of CTS over a period of 24 years and will provide information currently lacking on the outcomes of patients presenting in primary care. Results will inform further research into how treatments may be targeted to individual patients.

Our specific objectives are to:

1. Describe the patterns of the age- and sex-standardised annual prevalence of CTS diagnosed in primary care between calendar year 1987 and calendar year 2013
2. Describe the patterns of the age- and sex- standardised incidence of CTS diagnosed in primary care between calendar year 1989 and calendar year 2013
3. Describe the patterns of health care use (corticosteroid injection and decompression surgery) of patients with CTS between calendar year 1987 and 2013
4. Identify the prognostic value of candidate factors available in primary care consultation data to predict the risk of poor outcome in CTS over time, as defined by an episode of carpal tunnel release surgery

Study Type

This will be a descriptive study illustrating epidemiological patterns and a prognostic analysis aiming to identify factors predicting long-term outcome in primary care patients with CTS.

Study Design

This study will have two components, which will be described separately:

Part 1. A series of descriptive analyses estimating the annual incidence, prevalence and management of patients with CTS

Part 2. A retrospective cohort study for identifying prognostic factors for long-term outcome in CTS. This study will be used to observe a cohort of primary care patients with incident carpal tunnel syndrome over a maximum period of 24 years (1989 to 2013). We aim to determine the predictors of surgical intervention, based on data available from the primary care medical records.

The methods for these analyses have been developed following a pilot study of consultation data from 11 general practices in North Staffordshire, who contribute to the Consultations in Primary Care Archive (CiPCA). CiCPA is a high quality, validated database, containing recorded data from 13 general practices in North Staffordshire, UK from 2000 to 2011 (at the time of data collection). [204-206]

The primary outcome for the prognostic study will be carpal tunnel release surgery (CTR). National recommendations suggest that CTR is reserved for patients who have severe disease or for those who have failed conservative treatment. It is therefore of interest to patients, clinicians and commissioners to know which patients are likely to require surgery.[207] CTR is a procedure that does take place in primary care, for example in North Staffordshire, East Kent [208] and Tyne and Wear [209] and as such does not necessitate a hospital admission. We therefore aim to use coded entries of CTR recorded in general practice data to capture surgical episodes as we believe using HES data to capture CTR is likely to underestimate the true frequency.

Using coded entries to record CTR was the approach used by Latinovic in their analysis of GPRD [19] and has been shown to provide results in agreement with the literature .[96] In the CiPCA pilot study,

between 2000 and 2010, the percentage of patients with prevalent CTS with a coded episode of CTR increased from 10% to 26% (29% - 42% of the incident population of the corresponding calendar year).

We aim to include area deprivation in our description of prevalence and incidence of CTS and as one of the potential predictors of surgery. So as not to reduce our sample size, the main analysis will be run on all CPRD Gold practices (not including deprivation in the analysis), and a subgroup analysis based on practices to which linkage is possible, run to analyse the influence of deprivation. Linkage will therefore be required to the ITownsend Score (IMD).

Part 1: Incidence, prevalence and management of CTS

Sample size/power calculation (Please provide justification of sample size in the protocol)

From CiPCA we determined the annual prevalence of CTS in 2000 as 20.0 per 10,000 individuals. Given an estimated CPRD annual registered population of 5.5 million, this would suggest we would identify around 11,000 patients with a recorded consultation for CTS per year.
Previous work indicates figures in CPRD may be lower compared to CiPCA, so feasibility work within CPRD GOLD has been carried out. This work has shown that between 1987 and 2013 there have been 203,803 individuals consulting with CTS giving a minimum annual prevalence of 14.25 per 10,000 (it is possible individuals presented on multiple occasions over the study period). Using a 95% confidence level, the size of population within CPRD allows estimation of annual prevalence with a margin of error of less than 1 per 10,000 assuming actual prevalence is around 14 per 10,000.

With regard to the number of patients receiving surgery, 134,761 episodes of carpal tunnel release (9.4 per 10,000 individuals per annum) were recorded in general practice records during the same period. Using CiPCA data for 2010, 6 per 10,000 individuals per annum were recorded as having a CTR.

Conducting the analyses in CiPCA has provided a description of prevalence and practice in a local area. However, care pathways for patients with CTS vary significantly between healthcare localities. It is possible that incidence will also vary between regions due to factors such as local industry. Analysis using CPRD will therefore provide a description of prevalence, incidence and management of CTS generalizable to the national population.

Study population
Inclusion criteria / exclusion criteria

The denominator population for calculation of prevalence and incidence will be the total person-years contributed to the database by patients over the age of 18 years with up-to-standard data for each annual period between 1 January 1987 and 31 December 2013.

Selection of comparison group(s) or controls
Not applicable

Exposures, outcomes and covariates
Not applicable

Data / Statistical Analysis Plan
Data will be managed and analysed in SPSS version 21 and STATA Intercooled 13.1. For fitting of complex models, STATA MP4 is available for use by the study team.

Distinguishing incident from prevalent cases
The prevalence of individuals consulting with CTS will be calculated per annum. The numerator for prevalence will be all individuals aged 18 years and over having a record of a carpal tunnel syndrome diagnosis or evidence of a carpal tunnel release or carpal tunnel injection in a given calendar year. The Read codes used to identify patients with CTS can be found in appendix 1.

For determination of the annual incidence of CTS, the numerator will be all patients aged 18 years and over having a record of CTS or evidence of carpal tunnel release or carpal tunnel injection, without a prior record of these codes during a run-in period of two years. This two year run-in period is based on expert consensus in that it was felt unlikely that a patient with ongoing bothersome symptoms would not have consulted within this period. CTS can present as a new episode in the contralateral wrist sometime after the initial presentation, hence it was not felt possible to use the criteria as 'no previous recorded episode' to define incidence.

Age and sex specific annual prevalence and incidence will be determined for each year, from 1987 (or 1989 in the case of incidence) to 2013. For confidence interval calculation and subsequent regression modelling, a Poisson or negative binomial distribution will be used as appropriate. Age and sex standardised annual figures of CTS prevalence and incidence for each year will also be calculated. These figures will be directly standardised to the general age-sex population structure of the UK in each calendar year using population estimates provided by the website of the Office of National Statistics.

Cases have been described as those with either a specific CTS diagnostic code, or a CTS specific treatment code. Using treatment codes as well as diagnostic codes is due to the fact patients may be allocated a less specific hand pain code prior to referral or treatment and hence only be identifiable after a CTR has been carried out. In part 2, this will not be possible as we need to identify time to surgery from diagnosis. This precludes the use of a treatment specific code being used to identify cases with CTS. To ensure the use of treatment codes in this manner does not affect the overall trend, a sensitivity analysis calculating incidence and prevalence with and without using treatment codes, will be performed.

Estimating change in the age-sex standardised annual prevalence and incidence of CTS (objectives 1-2)
Emerging patterns will be described and regional variation explored to identify any marked differences. We will apply Joinpoint regression to determine average annual percentage change and assess if and when there are changes in the underlying trend. This will also be used to explore the potential influence of changes in practice, for example the introduction of the 18-week wait target in 2010.
Describing the patterns of health care use (corticosteroid injection and decompression surgery) of patients with CTS between calendar year 1987 and 2013 (objective 3)

Evidence of the use of management options for CTS will be obtained by using Read coded entries (see Appendix 2). Specific interest will be paid to carpal tunnel release surgery and carpal tunnel injection. We expect carpal tunnel release to be coded in the patient record. Episodes of carpal tunnel injection will also be identified by Read code and by identifying the prescription of an injectable corticosteroid (see Appendix 4) within 4 weeks of an index CTS consultation. This time period has been agreed through clinical consensus. Feasibility work within CPRD has shown that by using Read coded data 1,608 patients out of 11,305 with a diagnosis of CTS, received a carpal tunnel injection in primary care, in one annual period.

We will also seek evidence of the use of splints by identifying Read coded entries. We are aware however of the potential limitation of patients acquiring splints from other sources e.g. 'over the counter' but hope to capture some detail of their use over time. Evidence of referral to secondary care, the utilisation of nerve conduction studies and sickness certification will also be measured through Read coded entries (Appendix 5).

We will calculate the use of these interventions per patient with CTS per annum and describe how these proportions change over the study period.

Part 2: Identifying predictors of carpal tunnel release

Sample size/power calculation (Please provide justification of sample size in the protocol)

We aim to describe the prognostic value of 17 previously identified potential predictors of the outcome of CTS. From our feasibility work we know CPRD will provide us with a sufficient number of events (carpal tunnel release) to develop a prediction model considering these 17 variables (>10 events per variable).

Study population (including estimate of expected number of relevant patients in the CPRD)

Inclusion criteria
The study population will be the incident cases with a diagnostic Read code for CTS as identified in part 1, using the same inclusion criteria. Patients with a Read code only for a CTS intervention (carpal tunnel release or carpal tunnel injection) will not be included in the cohort as there would be no identifiable baseline to measure time to surgery from.

Selection of comparison group(s) or controls
Not applicable

Exposures, outcomes and covariates
Exposures (Potential prognostic factors to be tested)
The following variables will be tested as prognostic factors. They have been defined by a review of the literature and clinical consensus and reduced to items that are felt likely to be recorded in CPRD. The Read codes to be used are shown in Appendix 3.

Prognostic factor	**Method of measurement**	**Time period to be applied**	**Source of Read code list (where applicable)**
Age at diagnosis	Routinely recorded data	At time of index date	
Gender	Routinely recorded data	At time of index date	
GP Practice	Routinely recorded data	At time of index date	
Region	Routinely recorded data	At time of index date	
Deprivation score	Routinely recorded data for practices which provide Index of Multiple Deprivation scores	2010 quintile score	
Obesity	Read code or from the Test table	The recorded value closest to the index date	
Alcohol status	Read code or from the Test table	The recorded value closest to the index date	
Smoking status	Read code or from the Test table	The recorded value closest to the index date	
Pregnancy	Read code	Read code within a 1 year period prior to the index date	Code list developed for purpose of this study using the Clinical Terminology Browser
Affective disorders	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies. through clinical consensus [147]

Hypothyroidism	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies [147]
Diabetes	Read code	Read code within a 2 year period prior to the index date	Code list developed for previous studies [147]
Inflammatory conditions	Read code	Read code within a 2 year period prior to the index date	Code list developed for purpose of this study
Neck or upper limb conditions	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Arthritis Research UK Primary Care Centre
Multi-site pain (including osteoarthritis)	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Arthritis Research UK Primary Care Centre
Tendonitis / epicondylitis	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Arthritis Research UK Primary Care Centre and developed for purpose of this study
Previous wrist trauma	Read code	Read code within a 2 year period prior to the index date	Code list developed for use in the Arthritis Research UK Primary Care Centre and developed for purpose of this study

Outcomes
Due to the retrospective design of the study and use of healthcare data, it will not be possible to utilise patient reported outcome measures for carpal tunnel syndrome that are commonly used in research, such as the Boston Carpal Tunnel Questionnaire (BCTQ)[32]. Time to carpal tunnel release (CTR) surgery will therefore be used as the primary outcome measure and proxy of a poor outcome as it suggests that symptoms have either been severe or not responded to conservative management.

Data/ Statistical Analysis Plan

1. Estimating the prognostic value of consultation data used to predict long-term outcome in CTS
Incident CTS cases over each of the annual periods will form a retrospective cohort and be followed for at least a one year with a total possible follow up period of 24 years. Only patients with a diagnostic Read code for CTS will be included in the cohort. We will exclude cases defined based on a condition specific treatment code only to prevent treatment bias and ensure an identifiable baseline.

Proportional hazard assumption will be tested in Cox models. Cox proportional hazards models will then be used to determine the association between potential prognostic factors (listed above) and surgical intervention, whereby the first episode of CTR will be used as the endpoint (we are aware patients may require further surgery for revision or treatment of the contralateral hand, but for the purposes of this study we will focus on the initial surgical episode). This will be a time to event analysis in which patients will be censored at the point they receive CTR or are recorded as deceased, leave the practice or the practice no longer contributes to CPRD.

The determination of the prognostic value of a factor will be based on two phases. First the correlational structure of the variables will be observed. Provided there is no strong inter-correlation, each variable will be added into a multivariable model. A backward selection procedure will then be used to determine the prognostic factors in the final multivariable model. Variables eliminated will be re-entered in the final multivariable model with adjustment for the remaining significant variables (determined prognostic factors) to ensure that no omitted variable significantly reduces the log likelihood chi-square of the model. The performance of the multivariable model will be quantified by sensitivity/specificity and by concordance statistics (C-statistics), which is analogous to the receiver operating characteristics (ROC) curve for binary data. A C-statistic can be interpreted as the probability that the model predicts a higher risk of severe outcome for those who actually receive CTR compared to those that didn't receive CTR over the follow-up time.

Limitations of the study design, data sources and analytic methods / missing data / confounding

CTS may present bilaterally and the methodology of this study (use of Read codes to identify prevalent and incident cases and to describe their prognosis with regard to surgery) does not allow for 'wrists' as opposed to 'individual patients' to be described. This is unlikely to be a significant issue when describing the prevalence and incidence of the disease or the healthcare use over time. It may however impact upon the measurement of time to surgical treatment, where we will be unsure of which wrist is being operated on in cases of bilateral CTS.

We are also assuming that surgery is a marker of severe or non-responsive disease. This does not allow for the fact that some patients with severe disease or very significant co-morbidities may choose not to undertake surgery.

There is potential for the misclassification of cases, in that some individuals may receive a diagnosis of CTS when they do not have the condition. It is however more likely that patients with CTS receive a less descriptive diagnostic code, such as 'hand pain.' We will therefore use condition specific treatment codes including 'carpal tunnel release' and 'carpal tunnel injection' to capture those who may previously have been assigned a broader code but go onto to receive condition specific treatment, when calculating prevalence and incidence.

We are also aware from our work within CiPCA that splinting and injection interventions are not comprehensively coded. We have shown within CPRD however that by identifying prescription codes for injectable steroids linked to patients consulting with CTS, we can identify a more likely number of patients receiving injections within primary care (of the 11,305 patients consulting with CTS in a 1 year period, 1,608 were also prescribed an injectable steroid). We will further clarify the criteria for assuming a prescription to be for the purpose of treating CTS by ensuring the prescription occurs within 4 weeks of a consultation tagged with a diagnostic CTS Read code and that there is an absence of any other musculoskeletal code within that same 4 week period.

By using CPRD data to capture surgical intervention, we hope to identify operations occurring in all healthcare sectors. It remains possible however that some interventions communicated to primary care will not be satisfactorily coded and is hence an important limitation. There are likely to be patients with missing information on smoking alcohol and BMI status, especially in the earlier years. We will compare the effects on our results of excluding those patients with missing information to an analysis including these patients in a missing category. It is also possible that there will be missing prognostic factors not coded or recorded in consultation data, such as symptom severity and clinical findings (e.g. muscle wasting).

Plans for disseminating and communicating study results
Patients and stake-holders will be involved in the interpretation and dissemination of study findings through our Research User and Implementation Groups. We aim to publish the findings in internationally recognised journals. Our findings will be presented through international musculoskeletal and primary care conferences for example, Society of Academic Primary Care.

Appendix 1: CTS Read codes

Read Code	Term
F340	Carpal tunnel syndrome
85BE.00	Injection of carpal tunnel
70560	Carpal tunnel release
70564	Endoscopic carpal tunnel release

Appendix 2: Treatment codes

Read Code	Term
7056000	Carpal tunnel release
7056011	Carpal tunnel decompression
85BE.00	Injection of carpal tunnel
7L19F	Injection of steroid NEC
7K6ZF	Injection of steroid into wrist joint
7056200	Re-release of carpal tunnel
7056400	Endoscopic carpal tunnel release
705A100	Revision of carpal tunnel release

Appendix 3: Terms for potential prognostic factors

Pregnancy (and associated antenatal terms)

62	Antenatal care
621	Patient currently pregnant
6211	Pregnant - urine test confirms
6212	Pregnant - blood test confirms
6213	Pregnant - V.E. confirms
6214	Pregnant - on history
6215	Pregnant - on abdom. palpation
6216	Pregnant - planned
6217	Pregnant - unplanned - wanted
6218	Pregnant -unplanned-not wanted
6219	Patient ? pregnant
621A	Pregnancy unplanned ? wanted
621B	Pregnant - ? planned
621C	Unplanned pregnancy
621Z	Patient pregnant NOS
622	Antenatal care: gravida No.
6221	Antenatal care: primigravida
6222	Antenatal care: 2nd pregnancy
6223	Antenatal care: 3rd pregnancy
6224	Antenatal care: multip
622Z	Antenatal care: gravida NOS

623	A/N care: obstetric risk
6231	A/N care: uncertain dates
6232	A/N care: recurrent aborter
6233	A/N care: grand multip
6234	A/N care: H/O stillbirth
6235	A/N care: H/O perinatal death
6236	A/N care: poor obstetr history
6237	A/N care: H/O trophoblast.dis.
623Z	A/N care: obstetric risk NOS
624	A/N care: precious pregnancy
6241	A/N care: elderly primip.
6242	A/N care: H/O infertility
624Z	A/N care: precious preg. NOS
625	A/N care: social risk
6251	A/N care: poor home conditions
6252	A/N care: poor A/N attender
6253	A/N care: late booker
6254	A/N care: H/O child abuse
625Z	A/N care: social risk NOS
626	A/N care: medical risk
627	A/N care: gynae. risk
628	A/N care: risk NOS
6281	A/N care: under 5ft tall
6282	A/N care:10yrs+since last preg
6283	A/N care: primip. < 17 years
6284	A/N care: primip. > 30 years
6285	A/N care: multip. > 35 years
628Z	A/N risk NOS
629	No ante-natal care
6291	Ante-natal care: not offered
6292	Ante-natal care: not wanted
6293	Ante-natal care: not attended
6294	No A/N care: not known preg.
629Z	No ante-natal care NOS
62A	A/N care provider
62A1	A/N care from G.P.
62A2	A/N care from consultant
62A3	A/N - shared care
62A4	A/N care midwifery led
62AZ	A/N care provider NOS
62B	Delivery booking place
62B1	Delivery: no place booked
62B2	Home delivery booked
62B3	G.P. unit delivery booking
62B4	Consultant unit booking
62B5	Private home delivery booking
62B6	Delivery booking place changed
62B7	Domino delivery
62B8	Midwife unit delivery booking
62BZ	Delivery booking - place NOS
62C	Deliv.booking - length of stay
62C1	Short stay delivery booking
62C2	Full stay delivery booking
62CZ	Delivery booking - stay NOS

62D	Parent craft classes
62D1	Parent craft classes offered
62D2	Parent craft class not offered
62D3	Parent craft not wanted
62D4	Parent craft class attended
62D5	Parent craft -individual class
62D6	Parent craft - group class
62DZ	Parent craft class NOS
62E	Feeding intention
6.20E+02	Feeding intention - not known
6.20E+03	Feeding intention - unsure
6.20E+04	Feeding intention - breast
6.20E+05	Feeding intention - bottle
62EZ	Feeding intention - NOS
62F	Antenatal amniocentesis
62F1	A/N amniocentesis -not offered
62F2	A/N amniocentesis - offered
62F3	A/N amniocentesis - not wanted
62F4	A/N amniocentesis wanted
62F5	A/N amniocentesis - awaited
62F6	A/N amniocentesis - normal
62F7	A/N amniocentesis - abnormal
62F8	A/N amnio. for ? chrom.abnorm.
62F9	A/N amnio. for ? neural tube
62FZ	Antenatal amniocentesis NOS
62G	Antenatal ultrasound scan
62G1	A/N U/S scan not offered
62G2	A/N U/S scan offered
62G3	A/N U/S scan not wanted
62G4	A/N U/S scan wanted
62G5	A/N U/S scan awaited
62G6	A/N U/S scan normal += dates
62G7	A/N U/S scan normal +? dates
62G8	A/N U/S scan abnormal
62G9	A/N U/S scan for ? abnormality
62GA	A/N U/S scan for slow growth
62GB	Antenatal ultrasounds scan at 4-8 weeks
62GC	Antenatal ultrasound scan at 9-1six weeks
62GD	Antenatal ultrasound scan at 17-22 weeks
62GE	Antenatal ultrasound scan at 22-40 weeks
62GZ	Antenatal ultrasound scan NOS
62H	A/N Rh antibody screen
62H1	A/N Rh screen not offered
62H2	A/N Rh screen offered
62H3	Rh screen - 1st preg. sample
62H4	Rh screen - 2nd preg. sample
62H5	Rh screen - 3rd preg. sample
62H6	Rh screen - cord blood sample
62H7	Rh - 6/12 after anti-D sample
62H8	Rh - random, non-preg. sample
62HZ	A/N Rh antibody screen NOS
62I	Alpha-feto protein blood test
62I1	AFP blood test offered
62I2	AFP blood test not offered

62I3	AFP blood test wanted
62I4	AFP blood test not wanted
62I5	AFP - blood sent
62IZ	AFP blood test NOS
62J	Rubella screen
62J1	Rubella screen not offered
62J2	Rubella screen offered
62J3	Rubella screen not wanted
62J4	Rubella screen wanted
62J5	Rubella screen - blood sent
62J6	Rubella status not known
62JZ	Rubella screen NOS
62K	Antenatal syphilis screen
62K1	A/N syphilis screen not done
62K2	A/N syphilis screen-blood sent
62KZ	Antenatal syphilis screen NOS
62L	Antenatal blood group screen
62L1	A/N blood gp screen not done
62L2	A/N blood group screen done
62LZ	A/N blood group screen NOS
62M	Antenatal sickle cell screen
62M1	A/N sickle screen not done
62M2	A/N sickle cell screen done
62MZ	A/N sickle cell screen NOS
62N	Antenatal examinations
62N1	A/N booking examination
62N2	A/N 12 weeks examination
62N3	A/N 1six week examination
62N4	A/N 20 week examination
62N5	A/N 24 week examination
62N6	A/N 28 week examination
62N7	A/N 30 week examination
62N8	A/N 32 week examination
62N9	A/N 34 week examination
62NA	A/N 35 week examination
62NB	A/N 3six week examination
62NC	A/N 37 week examination
62ND	A/N 38 week examination
62NE	A/N 39 week examination
62NF	A/N 40 week examination
62NG	A/N 41 week examination
62NH	A/N 42 week examination
62NJ	Antenatal 22 week examination
62NK	Antenatal 25 week examination
62NL	Antenatal 31 week examination
62NZ	Antenatal examination NOS
62O	Misc. antenatal data
62O1	Fetal movements felt
62O2	Fetal movements seen
62O3	Fetal maturity: dates = size
62O4	Fetal maturity: dates not=size
62O5	Spontaneous membrane rupture
62O6	Vaginal show
62O7	Pregnancy prolonged - 41 weeks

62O8	Pregnancy prolonged - 42 weeks
62O9	Initial booking of patient
62OZ	Misc. antenatal data NOS
62U	Downs screen - blood test
62U0	Triple test offered
62U1	Double test offered
62U2	Triple test not offered
62U3	Double test not offered
62U4	Triple test wanted
62U5	Double test wanted
62U6	Triple test not wanted
62U7	Double test not wanted
62U8	Downs screening - blood sent
62U9	Downs screen blood test normal
62UA	Downs screen blood test abnormal
62Uz	Downs screening blood test NOS
62V	Delivery place planned
62V0	Home delivery planned
62W	Antenatal blood tests
62X	Length of gestation
62X0	Gestation <24 weeks
62X1	Gestation = 24 weeks
62X2	Gestation >24 weeks
62X3	Full term gestation - 40 weeks
62X4	Length of gestation at birth
62X5	Length of gestation at time of test
62Y	Routine antenatal care
62Z	Maternal care NOS
62c0	Crown rump length

Affective disorders

E200	Anxiety states
E2000	Anxiety state unspecified
E2001	Panic disorder
E2002	Generalised anxiety disorder
E2003	Anxiety with depression
E2004	Chronic anxiety
E2005	Recurrent anxiety
E200z	Anxiety state NOS
Eu41	[X]Other anxiety disorders
Eu410	[X]Panic disorder [episodic paroxysmal anxiety]
Eu411	[X]Generalized anxiety disorder
Eu412	[X]Mixed anxiety and depressive disorder
Eu413	[X]Other mixed anxiety disorders
Eu41y	[X]Other specified anxiety disorders
Eu41z	[X]Anxiety disorder, unspecified
Eu32	[X]Depressive episode
Eu320	[X]Mild depressive episode
Eu321	[X]Moderate depressive episode
Eu322	[X]Severe depressive episode without psychotic symptoms
Eu323	[X]Severe depressive episode with psychotic symptoms
Eu324	[X]Mild depression
Eu32y	[X]Other depressive episodes
Eu32z	[X]Depressive episode, unspecified

Eu33	[X]Recurrent depressive disorder
Eu330	[X]Recurrent depressive disorder, current episode mild
Eu331	[X]Recurrent depressive disorder, current episode moderate
Eu332	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
Eu333	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
Eu334	[X]Recurrent depressive disorder, currently in remission
Eu33y	[X]Other recurrent depressive disorders
Eu33z	[X]Recurrent depressive disorder, unspecified
Eu34	[X]Persistent mood affective disorders
Eu340	[X]Cyclothymia
Eu341	[X]Dysthymia
Eu34y	[X]Other persistent mood affective disorders
Eu34z	[X]Persistent mood affective disorder, unspecified
Eu3y	[X]Other mood affective disorders
Eu3y0	[X]Other single mood affective disorders
Eu3y1	[X]Other recurrent mood affective disorders
Eu3yy	[X]Other specified mood affective disorders

Hypothyroidsim

C04..	Hypothyroidism
C040.00	Postsurgical hypothyroidism
C041.00	Other postablative hypothyroidism
C041000	Irradiation hypothyroidism
C041z00	Postablative hypothyroidism NOS
C042.00	Iodine hypothyroidism
C043.00	Other iatrogenic hypothyroidism
C043000	Hypothyroidism resulting from para-aminosalicylic acid
C043100	Hypothyroidism resulting from phenylbutazone
C043200	Hypothyroidism resulting from resorcinol
C043z00	Iatrogenic hypothyroidism NOS
C044.00	Postinfectious hypothyroidism
C045.00	Acquired atrophy of thyroid
C046.00	Autoimmune myxoedema
C047.00	Subclinical hypothyroidism
C04y.00	Other acquired hypothyroidism
C04z.00	Hypothyroidism NOS
C04z000	Premature puberty due to hypothyroidism
C04z100	Myxoedema coma
1432.00	H/O: hypothyroidism
C04..00	Acquired hypothyroidism
C03y000	Congenital hypothyroidism with diffuse goitre
C03y100	Congenital hypothyroidism without goitre
C03z.00	Congenital hypothyroidism NOS
66BB.00	Hypothyroidism annual review
9Oj..00	Hypothyroidism monitoring administration
9Oj0.00	Hypothyroidism monitoring first letter
9Oj1.00	Hypothyroidism monitoring second letter
9Oj2.00	Hypothyroidism monitoring third letter
9Oj3.00	Hypothyroidism monitoring verbal invite
9Oj4.00	Hypothyroidism monitoring telephone invitation
C0A5.00	Subclinical iodine-deficiency hypothyroidism
9Oj4.00	Hypothyroidism monitoring telephone invitation

Diabetes

Read Code	Term
C10E.	Type 1 diabetes mellitus
C10E0	Type 1 diabetes mellitus with renal complications

C10E1	Type 1 diabetes mellitus with ophthalmic complications
C10E2	Type 1 diabetes mellitus with neurological complications
C10E3	Type 1 diabetes mellitus with multiple complications
C10E4	Unstable type 1 diabetes mellitus
C10E5	Type 1 diabetes mellitus with ulcer
C10E6	Type 1 diabetes mellitus with gangrene
C10E7	Type 1 diabetes mellitus with retinopathy
C10E8	Type 1 diabetes mellitus - poor control
C10E9	Type 1 diabetes mellitus maturity onset
C10EA	Type 1 diabetes mellitus without complication
C10EB	Type 1 diabetes mellitus with mononeuropathy
C10EC	Type 1 diabetes mellitus with polyneuropathy
C10ED	Type 1 diabetes mellitus with nephropathy
C10EE	Type 1 diabetes mellitus with hypoglycaemic coma
C10EF	Type 1 diabetes mellitus with diabetic cataract
C10EG	Type 1 diabetes mellitus with peripheral angiopathy
C10EH	Type 1 diabetes mellitus with arthropathy
C10EJ	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK	Type 1 diabetes mellitus with persistent proteinuria
C10EL	Type 1 diabetes mellitus with persistent microalbuminuria
C10EM	Type 1 diabetes mellitus with ketoacidosis
C10EN	Type 1 diabetes mellitus with ketoacidotic coma
C10EP	Type 1 diabetes mellitus with exudative maculopathy
C10EQ	Type 1 diabetes mellitus with gastroparesis
C10ER	Latent autoimmune diabetes mellitus in adult

C10F	Type 2 diabetes mellitus
C10F0	Type 2 diabetes mellitus with renal complications
C10F1	Type 2 diabetes mellitus with ophthalmic complications
C10F2	Type 2 diabetes mellitus with neurological complications
C10F3	Type 2 diabetes mellitus with multiple complications
C10F4	Type 2 diabetes mellitus with ulcer
C10F5	Type 2 diabetes mellitus with gangrene
C10F6	Type 2 diabetes mellitus with retinopathy
C10F|	Type 2 diabetes mellitus - poor control
C10F8	Reaven's syndrome
C10F9	Type 2 diabetes mellitus without complication
C10FA	Type 2 diabetes mellitus with mononeuropathy
C10FB	Type 2 diabetes mellitus with polyneuropathy
C10F|	Type 2 diabetes mellitus with nephropathy
C10FD	Type 2 diabetes mellitus with hypoglycaemic coma
C10FE	Type 2 diabetes mellitus with diabetic cataract
C10FF	Type 2 diabetes mellitus with peripheral angiopathy
C10FG	Type 2 diabetes mellitus with arthropathy
C10FH	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ	Insulin treated Type 2 diabetes mellitus
C10FK	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL	Type 2 diabetes mellitus with persistent proteinuria
C10FM	Type 2 diabetes mellitus with persistent microalbuminuria
C10FN	Type 2 diabetes mellitus with ketoacidosis
C10FP	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ	Type 2 diabetes mellitus with exudative maculopathy
C10FR	Type 2 diabetes mellitus with gastroparesis

C10FS	Maternally inherited diabetes mellitus

Inflammatory conditions

Read Code	Term
N10	Inflammatory spondylopathies
N100	Ankylosing spondylitis
N101	Spinal enthesopathy
N102	Sacroiliitis NEC
N10y	Other inflammatory spondylopathies
N10y0	Inflammatory spondylopathies in diseases EC
N10yz	Other inflammatory spondylopathies NOS
N10z	Spondylitis NOS
N04	Inflammatory polyarthropathy
N040	Rheumatoid arthritis
N0400	Rheumatoid arthritis of cervical spine
N0401	Other rheumatoid arthritis of spine
N0402	Rheumatoid arthritis of shoulder
N0403	Rheumatoid arthritis of sternoclavicular joint
N0404	Rheumatoid arthritis of acromioclavicular joint
N0405	Rheumatoid arthritis of elbow
N0406	Rheumatoid arthritis of distal radio-ulnar joint
N0407	Rheumatoid arthritis of wrist
N0408	Rheumatoid arthritis of metacarpophalangeal joint
N0409	Rheumatoid arthritis of proximal interphalangeal joint of finger
N040A	Rheumatoid arthritis of distal interphalangeal joint of finger
N040B	Rheumatoid arthritis of hip
N040C	Rheumatoid arthritis of sacro-iliac joint
N040D	Rheumatoid arthritis of knee
N040E	Rheumatoid arthritis of tibio-fibular joint
N040F	Rheumatoid arthritis of ankle
N040G	Rheumatoid arthritis of subtalar joint
N040H	Rheumatoid arthritis of talonavicular joint
N040J	Rheumatoid arthritis of other tarsal joint
N040K	Rheumatoid arthritis of 1st metatarsophalangeal joint
N040L	Rheumatoid arthritis of lesser metatarsophalangeal joint
N040M	Rheumatoid arthritis of interphalangeal joint of toe
N040N	Rheumatoid vasculitis
N040P	Seronegative rheumatoid arthritis
N040Q	Rheumatoid bursitis
N040R	Rheumatoid nodule
N040S	Rheumatoid arthritis - multiple joint
N040T	Flare of rheumatoid arthritis
N041	Felty's syndrome
N042	Other rheumatoid arthropathy with visceral or systemic involvement
N0420	Rheumatic carditis
N0421	Rheumatoid lung disease
N0422	Rheumatoid nodule
N042z	Rheumatoid arthropathy with visceral or systemic involvement NOS
N043	Juvenile rheumatoid arthritis - Still's disease
N0430	Juvenile rheumatoid arthropathy unspecified
N0431	Acute polyarticular juvenile rheumatoid arthritis
N0432	Pauciarticular juvenile rheumatoid arthritis
N0433	Monarticular juvenile rheumatoid arthritis

N043z	Juvenile rheumatoid arthritis NOS
N044	Chronic post-rheumatic arthropathy
N045	Other juvenile arthritis
N0450	Juvenile ankylosing spondylitis
N0451	Juvenile seronegative polyarthritis
N0452	Juvenile arthritis in psoriasis
N0453	Juvenile arthritis in Crohn's disease
N0454	Juvenile arthritis in ulcerative colitis
N0455	Juvenile rheumatoid arthritis
N0456	Pauciarticular onset juvenile chronic arthritis
N047	Seropositive errosive rheumatoid arthritis
N04X	Seropositive rheumatoid arthritis, unspecified
N04y	Other specified inflammatory polyarthropathy
N04y0	Rheumatoid lung
N04y1	Sero negative arthritis
N04y2	Adult-onset Still's disease
N04y3	Remitting seronegative symmetrical synovitis with pitting oedema
N04yz	Other specified inflammatory polyarthropathy NOS
N04z	Inflammatory polyarthropathy NOS

Neck and upper limb conditions

Read Code	Term
16A	Stiff neck symptom
16A1	No stiff neck
16A2	Stiff neck
16A3	Torticollis - symptom
16A3	Wry neck symptom
16A3	Wry neck/torticollis
16AZ	Stiff neck symptom NOS
EGTON309	Sore Neck
EMISR4QFU1	Fusion Of Cervical Spine
N0400	Rheumatoid arthritis-Cx spine
N110	Cervical spond.- no myelopathy
N110	Cervical spond.-no myelopathy
N110	Cervical spondylosis
N110	Cervical spondylosis without myelopathy
N110	Osteoarthritis cervical spine
N1100	One lev Cx spondyl-no myelop
N1101	Two lev Cx spondyl-no myelop
N1102	Mult lev Cx spondyl-no myelop
N111	Cervical spond.+ myelopathy
N111	Cervical spond.with myelopathy
N111	Cervical spondylosis with myelopathy
N1110	One lev Cx spondyl + myelop
N1111	Two lev Cx spondyl + myelop
N1112	Mult lev Cx spondyl + myelop
N1113	Cervical myelopathy
N119	Cervical spondylosis with radiculopathy
N119	Cx spondylosis + radiculopathy
N1190	One lev Cx spondyl + radiculop
N1191	Two lev Cx spondyl + radiculop
N1192	Mult lev Cx spondyl+radiculop
N11A	Cx spondyl + vasc compression

N11D0	Osteoarthritis of cervical spine
N11E	Cervical spondylosis
N120	Cervical disc displ.-no myelop
N120	Cervical disc displacement
N120	PID - prol cerv disc,no myelop
N120	PID - prol cerv discno myelop
N125	Cervical disc degeneration
N1291	Cervical disc disord.+myelop.
N12A1	Cervical postlaminectomy syndr
N12B0	Cx disc prolapse + myelopathy
N12C0	Cx disc prolapse+radiculopathy
N12z1	Other cervical disc disorders
N12z4	Cervical discitis
N12z5	Annular tear of cervical disc
N12z6	Resorption of cervical disc
N12z7	Calcification of cervical disc
N12zH	Cerv disc disord + radiculopth
N12zH	Cervical disc disorder with radiculopathy
N13	Cervical disorder NOS
N13	Other cervical disorders
N130	Cervical spinal stenosis
N1300	Idiopathic Cx spinal stenosis
N1301	Degenerativ Cx spinal stenosis
N1302	Iatrogenic Cx spinal stenosis
N1303	Cx spin stenos due to oth dis
N131	Cervicalgia
N131	Cervicalgia - pain in neck
N131	Pain in cervical spine
N135	Torticollis unspecified
N1350	Intermittent torticollis
N1351	Rheumatic torticollis
N135z	Stiff neck NOS
N135z	Torticollis NOS
N135z	Wry neck
N136	Panniculitis of neck
N137	Cervical post.long.lig.ossific
N138	Cervicalgia
N13y	Other cervical syndromes
N13y0	Cervical syndrome NEC
N13y1	Klippel's disease
N13y2	Crick in neck
N13y3	Cervical root syndrome
N13yz	Other cervical syndromes NOS
N13z	Cervical and neck disorders NOS
N13z	Cervical/neck disorder NOS
N1480	Atlanto-occipital ankylosis
N1481	Atlanto-axial ankylosis
N1482	Cervical spine ankylosis
N1487	Atlanto-occipital instability
N1488	Atlanto-axial instability
N1489	Cervical spine instability
N1y0	Rec atlantoax subl + myelopath
N2300	Infective myositis-neck
N230B	Muscle abscess-neck

N2405	Fibrositis of neck
N300A	Acute osteomyelitis-cerv spine
N301A	Chronic osteomyelitis-Cx spine
N301F	Brodie's abscess-cervic spine
N302A	Infection of cervical spine
N303A	Periostitis, no osteomye-Cx sp
N3040	Tuberculosis of cervical spine
N3080	Subacute osteomyelitis-Cx spin
N3100	Paget's disease-cervical spine
N331A	Osteopor path # cerv vertebrae
N331C	Pathological # cervical vert
N331E	Collapse of cervical vertebra
N331H	Collap cerv vert due to osteop
N382	Acquired deformity of neck
N391	Nonallopathic lesion-cervical
Nyu57	[X]O recur atlantoaxl subluxtn
Nyu70	[X]Oth cervicl disc displacmnt
Nyu71	[X]Oth cervicl disc degeneratn
Nyu72	[X]Oth cervical disc disorders
Nyu7B	[X]Cervical disc disord, unsp
OX7131A	Osteoarthrosis Cervical Spine /ox
OX7280AD	Pain Neck /ox
R042	[D]Neck swelling/mass/lump
S100	Closed # cervical spine
S100	Closed fracture of cervical spine
S1000	Clsd # unsp cerv vertebra
S1001	Closed fracture atlas
S1002	Closed fracture axis
S1003	Clsd # third cerv vertebra
S1004	Clsd # fourth cerv vertebra
S1005	Clsd # fifth cerv vertebra
S1006	C6 closed # - no cord lesion
S1006	Clsd # sixth cerv vertebra
S1007	C7 closed # - no cord lesion
S1007	Clsd # seventh cerv vertebra
S1008	Cls # atlas-isol arch/art prcs
S1009	Clsd # atlas, comminuted
S100A	Clsd # axis odontoid process
S100A	Clsd # axis, odontoid process
S100B	Clsd # axis, spondylolysis
S100C	Clsd # axis, spinous process
S100D	Clsd # axis, transvrse process
S100E	Clsd # axis, posterior arch
S100F	Clsd # axis, tricolumnar
S100G	Clsd # cerv vert, burst
S100H	Clsd # cerv vert, wedge
S100J	Cls # cerv vert, spondylolysis
S100K	Cls # cerv vert, spinous prcss
S100L	Cls # cerv vert, trnsvrse prcs
S100M	Cls # cerv vert, post arch
S100N	Cls # cerv vert, tricolumnar
S100x	Multiple clsd # cerv vert
S100z	Clsd # cerv spine NOS
S101	Open fracture cervical spine

S1010	Open # unsp cerv vertebra
S1011	Open fracture atlas
S1012	Open fracture axis
S1013	Open # third cerv vertebra
S1014	Open # fourth cerv vertebra
S1015	Open # fifth cerv vertebra
S1016	Open # sixth cerv vertebra
S1017	Open # seventh cerv vert
S1018	Opn # atlas-isol arch/art prcs
S1019	Open # atlas, comminuted
S101A	Open # axis, odontoid prcss
S101B	Open # axis, spondylolysis
S101C	Open # axis, spinous procss
S101D	Opn # axis, trnsvrse process
S101E	Open # axis, posterior arch
S101F	Open # axis, tricolumnar
S101G	Open # cerv vert, burst
S101H	Open # cerv vert, wedge
S101J	Opn # cerv vert, spondylolysis
S101K	Opn # cerv vert, spinous prcs
S101L	Opn # cerv vert, trnsvrse prcs
S101M	Opn # cerv vert, post arch
S101N	Opn # cerv vert, tricolumnar
S101x	Multiple open # cerv vert
S101z	Open # cerv spine NOS
S10A	Fracture of neck
S10A0	Fracture/1st cervical vertebra
S10A1	Fracture/2nd cervical vertebra
S10A2	Multip fracture/cervical spin
S10A2	Multip fracture/cervical spine
S110	Closed cervical #+cord lesion
S1100	Clsd # C1-C4 unspec cord les
S1101	Clsd # C1-C4 complete cord les
S1102	Clsd # C1-C4 ant cord lesion
S1103	Clsd # C1-C4 cent cord lesion
S1104	Clsd # C1-C4 post cord lesion
S1105	Clsd # C1-C4 incomp cord les
S1106	Clsd # C5-C7 unspec cord les
S1107	Clsd # C5-C7 complete cord les
S1108	Clsd # C5-C7 ant cord lesion
S1109	Clsd # C5-C7 cent cord lesion
S110A	Clsd # C5-C7 post cord lesion
S110B	Clsd # C5-C7 incomp cord les
S110z	Closed cervical#+cord lesn.NOS
S111	Open cervical #+cord lesion
S1110	Op # C1-C4 unspec cord les
S1111	Op # C1-4 compl cord lesion
S1112	Op # C1-4 ant cord lesion
S1113	Op # C1-4 cent cord lesion
S1114	Op # C1-4 post cord lesion
S1115	Op # C1-4 cord les. NOS
S1116	Op # C5-7 unspec cord lesion
S1117	Op # C5-7 compl cord lesion
S1118	Op # C5-7 anterior cord les

S1119	Op # C5-7 central cord les
S111A	Op # C5-7 posterior cord lesn
S111B	Op # C5-7 incomp cord les NOS
S111z	Open cervical#+cord lesion NOS
S1250	Closed fracture larynx
S1251	Closed #hyoid bone
S1252	Closed #thyroid cartilage
S1253	Closed #trachea
S125z	Closed #larynx/trachea NOS
S126	Open # larynx and trachea
S1260	Open fracture larynx
S1261	Open #hyoid bone
S1262	Open #thyroid cartilage
S1263	Open #trachea
S126z	Open #larynx/trachea NOS
S490	Closed dislocation cervical spine
S490	Cls dslc cervical spine
S4900	Closed disloc.cerv.spine unsp.
S4901	Cls dslc atlanto-occipital jnt
S4902	Cls dslc atlanto-axial joint
S4903	Closed dislocation C2/C3
S4904	Closed dislocation C3/C4
S4905	Closed dislocation C4/C5
S4906	Closed dislocation C5/C6
S4907	Closed dislocation C6/C7
S4908	Closed dislocation C7/T1
S4909	Cl spnl dslc+cerv crd lsn,unsp
S490A	Cl spnl dslc+comp cerv crd lsn
S490B	Cls spnl dslc+ant cerv crd lsn
S490C	Cl spn dslc+cntrl cerv crd lsn
S490D	Cls spn dslc+post cerv crd lsn
S490x	Closed disloc.mult.cerv.vert.
S490z	Closed disloc.cervic.vert.NOS
S491	Open dislocation of neck
S4910	Open disloc.cerv.spine unspec.
S4911	Open dslc atlanto-occipital jt
S4912	Open dslc atlanto-axial jt
S4913	Open dislocation C2/C3
S4914	Open dislocation C3/C4
S4915	Open dislocation C4/C5
S4916	Open dislocation C5/C6
S4917	Open dislocation C6/C7
S4918	Open dislocation C7/T1
S4919	Opn spnl dsl+cerv crd lsn,unsp
S491A	Opn spn dslc+comp cerv crd lsn
S491B	Opn spnl dslc+ant cerv crd lsn
S491C	Opn spn dslc+ctrl cerv crd lsn
S491D	Opn spnl dsl+post cerv crd lsn
S491x	Open disloc.mult.cerv.vertebra
S491z	Open disloc.cervical vert.NOS
S4965	Cls trm dslc laryngl cartilage
S4975	Opn dslc laryngl cartilage
S498	Cls sublux cervical spine
S4980	Cls sublux cervical spine,unsp

S4981	Cls sublux atlanto-occiptl jt
S4982	Cls sublux atlanto-axial jt
S4983	Closed subluxation C2/C3
S4984	Closed subluxation C3/C4
S4985	Closed subluxation C4/C5
S4986	Closed subluxation C5/C6
S4987	Closed subluxation C6/C7
S4988	Closed subluxation C7/T1
S4989	Cl spn sublx+cerv crd lsn,unsp
S498A	Cl spn sublx+comp cerv crd lsn
S498B	Cl spn sublux+ant cerv crd lsn
S498C	Cl spn sublx+cntrl crv crd lsn
S498D	Cl spn sublux+post crv crd lsn
S498x	Cls sublux mlti cerv vertebrae
S498z	Cls sublux cerv vertebra NOS
S499	Open sublux cerv spine
S4990	Open sublux cerv spine, unsp
S4991	Opn sublux atlanto-occipitl jt
S4992	Open sublux atlanto-axial jt
S4993	Open subluxation C2/C3
S4994	Open subluxation C3/C4
S4995	Open subluxation C4/C5
S4996	Open subluxation C5/C6
S4997	Open subluxation C6/C7
S4998	Open subluxation C7/T1
S4999	Op spn sublx+cerv crd lsn,unsp
S499A	Op spn sublx+comp cerv crd lsn
S499B	Op spn sublux+ant cerv crd lsn
S499C	Op spn sublx+cntrl crv crd lsn
S499D	Op spn sublux+post crv crd lsn
S499x	Opn sublux mlti cerv vertebrae
S499z	Opn sublux cerv vertebra NOS
S49E5	Cls trm sublux laryngl cart
S49F5	Opn trm sublux laryngl cartlge
S570	Neck sprain
S570	Sprained neck
S5700	Neck sprain unspecified
S5700	Torticollis - traumatic
S5700	Whiplash injury
S5701	Cervical ant.longit.lig.sprain
S5702	Atlanto-axial joint sprain
S5703	Atlanto-occipital joint sprain
S5704	Whiplash injury
S570z	Neck sprain NOS
S5E1	Cmplt tr,thyroid region lgmt
S5N0	Open dvsn, neck ligament
S5P1	Opn dvsn,thyroid region lgmt
S5P10	Opn dvsn,cricoarytenoid lgmt
S5P11	Opn dvsn,cricothyroid ligament
S5P12	Opn dvsn,thyroid cartilge lgmt
S5P1z	Opn dvsn,thyroid regn lgmt NOS
S84	Open wound of neck
SC010	Late effect # cervic vertebra
SD0	Superficial Injury: Neck

SD097	SuperficialInjury:Neck
SE08	Othercontusionneck
SF021	Crush injury larynx
SJ30	Cervical nerve root injury
SJ30	Cervicalnerverootinjury
SJ303	Cervical nerve root injury - C4
SJ304	Cervical nerve root injury - C5
SJ305	Cervical nerve root injury - C6
SJ306	Cervical nerve root injury - C7
SK10y	Other neck injuries
SK10y	Otherneckinjuries
SK10z	OtherfaceandneckinjuriesNOS
Syu1	[X]Injuries to the neck
Syu12	[X]Superf inj neck part unsp
Syu15	[X]Fract oth spec cervic vert
Syu16	[X]Fracture other parts neck
Syu17	[X]Disloc oth unsp parts neck
Syu18	[X]Spr/str jt/lg ot/un pt neck
14G8	H/O: vertebral fracture
N111	Vertebral artery compr.syndr.
N148	Ankylosis/instab Cx,Th,Lu spin
S1	Fracture of neck and trunk
S1z	Fracture of neck and trunk NOS
N1483	Cervico-thoracic ankylosis
N148A	Cervico-thoracic instability
N133	Cervicobrachial syndrome
N132	Cervicocranial syndrome
R04	[D]Head and neck symptoms
R042	[D]Swell.masslump head/neck
R0420	[D]Swelling in head or neck
R04z	[D]Head and neck other sympt.
R04zz	[D]Head and neck symptoms NOS
S8	Open wound head/neck/trunk
S8	Open wound of head neck and trunk
S8z	Open wound head/neck/trunk NOS
SE0z	Contusion face scalp+neck NOS
SK10z	Other face and neck injuries NOS
SK10z	Other face/neck injuries NOS
SR10	Fracture involv head with neck
SR100	Cls fract invol head with neck
SR101	Op fract invol head with neck
SR20	Disloc,sprns+strns inv hd+neck
SR20	Dislocations, sprains and strains involving head with neck

Multisite pain

Read Code	Term
1D12	C/O: stiffness
1DCC	Aching muscles
N04y1	Sero negative arthritis
N05	Osteoarthritis
N050	Generalised osteoarthritis - OA
N0500	Generalised OA-site unspecif.
N0502	Generalised OA-multiple sites

N0504	Primary general osteoarthrosis
N0505	Secondary multiple arthrosis
N050z	Generalised osteoarthritis NOS
N05z	Joint degeneration
N05z0	Osteoarthritis NOS-site unspec
N05z8	Osteoarthritis - other joint
N05zz	Osteoarthritis NOS
N06	Other/unspecif. arthropathies
N063	Menopausal arthritis
N0630	Climacteric arthr.-site unsp.
N0638	Climacteric arthr.-other spec.
N0639	Climacteric arthr.-multip.site
N063z	Climacteric arthr.-NOS
N065	Polyarthropathy NEC
N0650	Unsp.polyarthr.-site unspecif.
N0658	Unsp.polyarthr.-other specif.
N0659	Unsp.polyarthr.-multiple site
N065A	Generalised arthritis
N065z	Polyarthritis
N2y	Nonarticular rheumatism OS
N2z	Nonarticular rheumatism NOS
N06z	Arthritis
N06z0	Arthropathy NOS-site unspecif.
N06z8	Arthropathy NOS-other specif.
N06z9	Arthropathy NOS-multiple sites
N06zB	Chronic arthritis
N06zz	Arthropathy NOS
N09	Other/unspecif.joint disorders
N094	Ache in joint
N0940	Arthralgia - site unspecified
N0948	Arthralgia - other specified
N0949	Arthralgia of multiple joints
N094z	Arthralgia NOS
N095	Joint stiffness NEC
N0950	Stiff joint NEC-site unspecif.
N0958	Stiff joint NEC-other specif.
N0959	Multiple stiff joints
N095z	Joint stiffness NEC NOS
N096	Musculoskeletal pain - joints
N0968	Other joint sympt.-other spec.
N0969	Other joint sympt.-multip.site
N096z	Other joint symptoms NOS
N09y	Other spec. joint disorders
N09y0	Other joint dis.-site unspec.
N09y8	Other joint dis.-other specif.
N09y9	Other joint dis.-multiple site
N09yz	Other joint disorders NOS
N09z	Joint disorders NOS
N09zz	Joint disorders NOS
N0z	Arthropathies NOS
N2	Rheumatism, excl.the back
N22yz	Other tendon disorder NOS
N22z	Synovium/tendon/bursa dis.NOS
N23	Muscle/ligament/fascia disord.

N233z	Other specif.musc.disorder NOS
N239	Fibromyalgia
N23y	Other muscle/ligament/fascia
N23yz	Other musc./lig./fasc.dis.NOS
N23z	Muscle/ligament/fascia dis.NOS
N24	Other soft tissue disorders
N240	Rheumatism/fibrositis unspecif
N2400	Rheumatism unspecified
N2401	Fibrositis unspecified
N2402	Muscular rheumatism
N2403	Rheumatic pain
N240z	Rheumatism/fibrositis NOS
N241	Myalgia/myositis unspecified
N2410	Muscle pain
N2411	Myositis unspecified
N2412	Fibromyositis NOS
N241z	Myalgia/myositis NOS
N247	Other musculoskel.limb sympts.
N248	Fibromyalgia
N24z	Polyalgia
N09z0	Joint disord.NOS-site unspecif

Tendonitis / epicondylitis

Read Code	Term
N21z2	Tendonitis NOS
N2125	Shoulder tendonitis
MHTBAGO1	Golfers Elbow-Epicondylitis
N2131	Medial epicondylitis of the elbow
N2131	Golfer's elbow
N2131	Medial epicondylitis - elbow
N2131	Medial epicondylitis of the elbow
N2132	Lateral epicondylitis of the elbow
N2132	Lateral epicondylitis - elbow
N2132	Lateral epicondylitis of the elbow
N2132	Tennis elbow
N2132	Tennis elbow - epicondylitis
N21z2	Tendonitis adductor
N21z2	Tendonitis bicepital
N2205	Tendonitis of thumb

Previous wrist trauma

Read Code	Term
SK132	Otherwristinjuries
SK133	Unspecified injury of wrist
SK133	Unspecifiedinjuryofwrist
Syu63	[X]Fract other carpal bone(s)
UNMAPPC4	Wrist injury
S242	Fracture at wrist and hand level
S242	Fracture/wrist and hand level
S52	Sprain of wrist and hand
S52	Sprain wrist/hand
S524	Sprain tendon wrist or hand
S52z	Wrist and hand sprain NOS
S52z	Wrist/hand sprain NOS

S5A	Complete tear, wrist or hand
S5Az	Complete tear wrist/hand NOS
S5H	Open division wrist/hand lgmt
S5Hz	Open dvsn wrist/hand lig NOS
S5Rz	Rupture tendon hand/wrist NOS
SE32	Bruise - wrist/hand
SE32	Contusion wrist or hand
SE32z	Contusion wrist and hand NOS
SF22	Crush injury wrist or hand
SJ528	Inj/ulnar nerve/wrist+hand lev
SJ53	Radial nerve injury
SJ534	Inj/radial nerv/wrist+hand lev
Syu6	[X]Injuries to the wrist and hand
Syu65	[X]Frac oth uns part wrist/hnd
Syu66	[X]Spr/str ot/uns prt wris/hnd
Syu6C	[X]Inj int mus/tn ot finwt/hd
Syu6M	[X]Unsp injury wrist and hand
Syu6M	[X]Unspecified injury of wrist and hand

Appendix 4: Injectable Steroids

Product code	Product name
925	Depo-medrone with lidocaine 40mg/ml+10mg/ml Injection (Pharmacia Ltd)
1133	Depo-medrone 40mg/ml Injection (Pharmacia Ltd)
14982	Depo-Medrone 40mg/1ml suspension for injection vials (Pfizer Ltd)
7405	Depo-Medrone with Lidocaine suspension for injection 1ml vials (Pfizer Ltd)
16583	Kenalog Intra-articular / Intramuscular 40mg/1ml suspension for injection vials (Bristol-Myers Squibb Pharmaceuticals Ltd)
20157	Depo-Medrone with Lidocaine suspension for injection 2ml vials (Pfizer Ltd)
1893	Hydrocortistab 25mg/1ml suspension for injection ampoules (Amdipharm Plc)
768	Kenalog 40mg/ml Injection (E R Squibb and Sons Ltd)
8864	Adcortyl 10mg/ml Intraarticular / intradermal injection (E R Squibb and Sons Ltd)
27413	Depo-Medrone 80mg/2ml suspension for injection vials (Pfizer Ltd)
8108	Hydrocortisone acetate 25mg/1ml suspension for injection ampoules
9026	Lederspan 20mg/ml Injection (Wyeth Pharmaceuticals)
14335	Adcortyl Intra-articular / Intradermal 10mg/1ml suspension for injection ampoules (Bristol-Myers Squibb Pharmaceuticals Ltd)
18660	Deltastab 25mg/1ml suspension for injection ampoules (Amdipharm Plc)
4123	Kenalog 40mg/ml Intraarticular injection (E R Squibb and Sons Ltd)
3703	Kenalog 80mg/2ml Intramuscular injection (E R Squibb and Sons Ltd)
33132	Methylprednisolone acetate 40mg/1ml suspension for injection vials
16582	Triamcinolone acetonide 40mg/ml suspension for injection
4488	Triamcinolone acetonide 40mg/ml IA/IM
5493	Methylprednisolone acetate 40mg/ml Injection
4687	Methylprednisolone acetate with lidocaine 40mg/ml + 10mg/ml Injection
35156	Methylprednisolone 40mg/1ml / Lidocaine 10mg/1ml (1%) suspension for injection vials
35040	Depo-Medrone 120mg/3ml suspension for injection vials (Pfizer Ltd)
14906	Dexamethasone 4mg/1ml solution for injection ampoules
35349	Methylprednisolone acetate 80mg/2ml suspension for injection vials
35154	Methylprednisolone 80mg/2ml / Lidocaine 20mg/2ml (1%) suspension for injection vials
48406	Triamcinolone acetonide 40mg/1ml suspension for injection vials
14958	Triamcinolone acetonide 10mg/1ml suspension for injection ampoules
14962	Adcortyl Intra-articular / Intradermal 50mg/5ml suspension for injection vials (Bristol-Myers Squibb Pharmaceuticals Ltd)

4233	Dexamethasone sodium phosphate 4mg/ml injection
4125	Triamcinolone acetonide 80mg/2ml intramuscular injection
11123	Triamcinolone acetonide 10mg/ml IA/ID
16815	Triamcinolone hexacetonide 20mg/ml Injection
9368	Triamcinolone acetonide 10mg/ml IA/ID
7992	Lederspan 5mg/ml Injection (Wyeth Pharmaceuticals)
8306	Prednisolone 25mg/1ml suspension for injection ampoules
13981	Adcortyl 10mg/ml Intradermal injection (E R Squibb and Sons Ltd)
35688	Methylprednisolone acetate 120mg/3ml suspension for injection vials
13972	Dexamethasone sodium phosphate 5mg/ml injection
30244	Triamcinolone acetonide 40mg/ml injection
13952	Decadron 4mg/ml Injection (MSD Thomas Morson Pharmaceuticals)
14188	Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials
35453	Dexamethasone 3.3mg/1ml solution for injection ampoules
13397	Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials
15717	Betamethasone 4mg/1ml solution for injection ampoules
37500	Dexamethasone 6.6mg/2ml solution for injection vials
22577	Betnesol 4mg/1ml solution for injection ampoules (Focus Pharmaceuticals Ltd)
15016	Triamcinolone hexacetonide 5mg/ml Injection
18266	Methylprednisolone sodium succinate 125mg powder and solvent for solution for injection vials
11334	Dexamethasone sodium phosphate iv 4mg/ml injection
25226	Solu-Medrone 125mg powder and solvent for solution for injection vials (Pfizer Ltd)
23511	Solu-Medrone 40mg powder and solvent for solution for injection vials (Pfizer Ltd)
10657	Dexamethasone sodium phosphate 4mg/ml intra-artic injection
21540	Solu-Medrone 500mg powder and solvent for solution for injection vials (Pfizer Ltd)
35578	Triamcinolone acetonide 50mg/5ml suspension for injection vials
18765	Methylprednisolone sodium succinate 40mg powder and solvent for solution for injection vials
25839	Solu-Medrone 1g powder and solvent for solution for injection vials (Pfizer Ltd)
34083	Dexamethasone 5mg/ml Injection (Organon Laboratories Ltd)
48746	Depo-Medrone 40mg/1ml suspension for injection vials (Mawdsley-Brooks & Company Ltd)
31948	Dexamethasone 4mg/ml Injection (Mayne Pharma Plc 1)
37737	Kenalog 40mg/ml Injection (E R Squibb and Sons Ltd)
56940	Dexamethasone 6.6mg/2ml solution for injection ampoules
48800	Depo-Medrone 40mg/1ml suspension for injection vials (Doncaster Pharmaceuticals Ltd)
49076	Depo-Medrone with Lidocaine suspension for injection 1ml vials (Lexon (UK) Ltd)
50253	Depo-Medrone with Lidocaine suspension for injection 1ml vials (Doncaster Pharmaceuticals Ltd)
24224	Codelsol 16mg/ml Injection (MSD Thomas Morson Pharmaceuticals)
48748	Depo-Medrone 40mg/1ml suspension for injection vials (Lexon (UK) Ltd)
50734	Depo-Medrone with Lidocaine suspension for injection 1ml vials (Mawdsley-Brooks & Company Ltd)
12405	Methylprednisolone sodium succinate 2g powder and solvent for solution for injection vials
26454	Decadron 4mg/ml Injection (MSD Thomas Morson Pharmaceuticals)
26299	Oradexon-organon 4mg/ml Intraarticular injection (Organon Laboratories Ltd)
53173	Dexamethasone 4mg/1ml solution for injection ampoules (Merck Sharp & Dohme Ltd)

Appendix 5: Referrals and investigations

8H54	Orthopedic referral
8H4B	Referred to rheumatologist
8HTd	Referral to rheumatology clinic
8HRE	Referral for nerve conduction studies
70652	Nerve conduction studies

FEED-BACK TO APPLICANTS

CONFIDENTIAL		*by e-mail*	
PROTOCOL NO:	**14_167**		
PROTOCOL TITLE:	The Epidemiology, Prognosis and Management of Carpal Tunnel Syndrome in Primary Care		
APPLICANT:	Dr Claire Burton, NIHR In Practice Fellow, Arthritis Research UK Primary Care Centre, Keele University		
APPROVED ☐	**APPROVED WITH COMMENTS (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:
Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.
Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC

REVIEWER COMMENTS:

Protocol 14_167 is approved with the following comments:
1. Linkage to HES data could be considered as an additional means of identifying patients undergoing carpal tunnel release surgery in practices eligible for the linkage scheme or for the purposes of a sensitivity analysis. Should you decide to link to HES data, submission of an amendment will be required (see below).
2. The study time period is 24 years during which time the management of carpal tunnel syndrome may have changed considerably. Consideration could be given to be taking into account year of diagnosis in the model.

DATE OF ISAC FEEDBACK:	16 September 2014
DATE OF APPLICANT FEEDBACK:	

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted

B. Tables associated with figures displayed in chapter 3

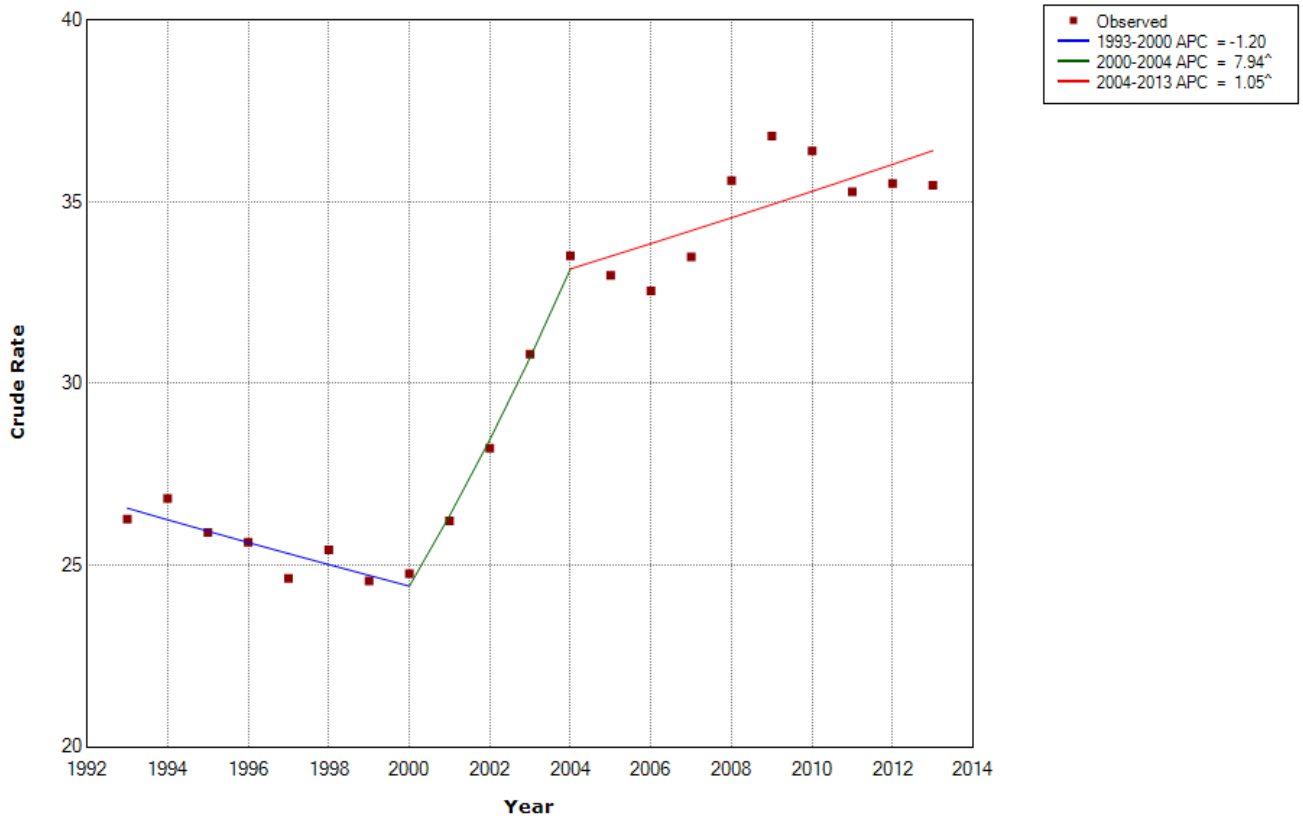
B1. Prevalence of carpal tunnel syndrome (n/10,000 person years) stratified by age and gender

Prevalence of carpal tunnel syndrome (n/10,000 person years) stratified by age and gender																					
Year	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Female 18-29	14.66	15.22	16.72	14.60	13.97	13.74	11.98	10.71	9.78	11.87	13.44	13.23	13.28	13.02	13.46	13.49	15.54	14.84	14.30	14.48	13.79
Female 30-39	42.21	36.87	37.37	36.04	33.57	36.34	34.20	31.94	32.55	36.57	38.21	38.97	39.67	39.34	41.98	42.99	45.15	44.34	41.87	41.24	38.78
Female 40-49	50.08	53.46	44.75	49.95	46.04	49.25	43.91	43.88	43.57	46.22	47.23	49.51	48.66	47.80	52.37	55.67	54.90	54.84	53.87	56.71	53.94
Female 50-59	59.46	56.02	57.71	56.78	55.46	56.23	57.87	54.94	58.40	61.41	71.39	78.41	76.71	73.29	70.77	73.87	75.44	73.46	70.48	67.67	70.60
Female 60-69	31.26	36.03	32.47	32.60	28.06	33.34	31.91	33.92	37.71	40.10	47.64	56.92	52.16	50.23	48.61	56.21	55.19	54.01	50.21	48.92	50.48
Female 70+	33.13	31.28	33.53	32.65	32.44	31.40	31.76	34.13	37.52	39.92	44.97	49.08	49.73	53.28	52.85	55.85	61.06	59.96	59.47	58.25	58.05
Male18-29	5.04	4.00	3.93	4.00	3.55	2.78	2.88	2.42	2.74	2.80	3.22	3.69	3.34	3.31	3.95	3.70	3.41	3.76	4.36	4.21	4.12
Male 30-39	9.95	11.02	11.36	11.19	11.11	10.60	8.61	10.32	10.78	11.75	12.00	13.06	12.23	11.57	11.30	11.78	12.17	12.94	11.67	12.29	12.55
Male 40-49	15.85	17.59	17.65	15.30	16.00	16.33	16.73	16.81	17.71	20.15	20.18	22.04	20.02	18.45	21.06	23.14	22.93	24.87	23.06	23.21	22.58
Male 50-59	18.72	21.66	21.08	20.23	20.36	19.03	19.51	19.64	22.12	24.46	25.71	26.68	26.55	26.62	28.09	29.90	31.06	30.86	31.16	28.64	32.01
Male 60-69	17.64	19.92	16.22	16.78	15.68	17.62	19.27	19.99	22.91	23.93	24.61	29.08	28.71	28.87	30.73	31.59	34.81	31.41	31.71	34.84	34.75
Male 70+	20.95	24.12	22.16	21.69	23.71	23.65	22.11	25.86	27.93	28.43	31.65	34.51	37.91	37.76	39.16	43.19	44.93	45.60	46.33	46.05	49.14

B2. Incidence of carpal tunnel syndrome (n/10,000 person years) stratified by age and gender

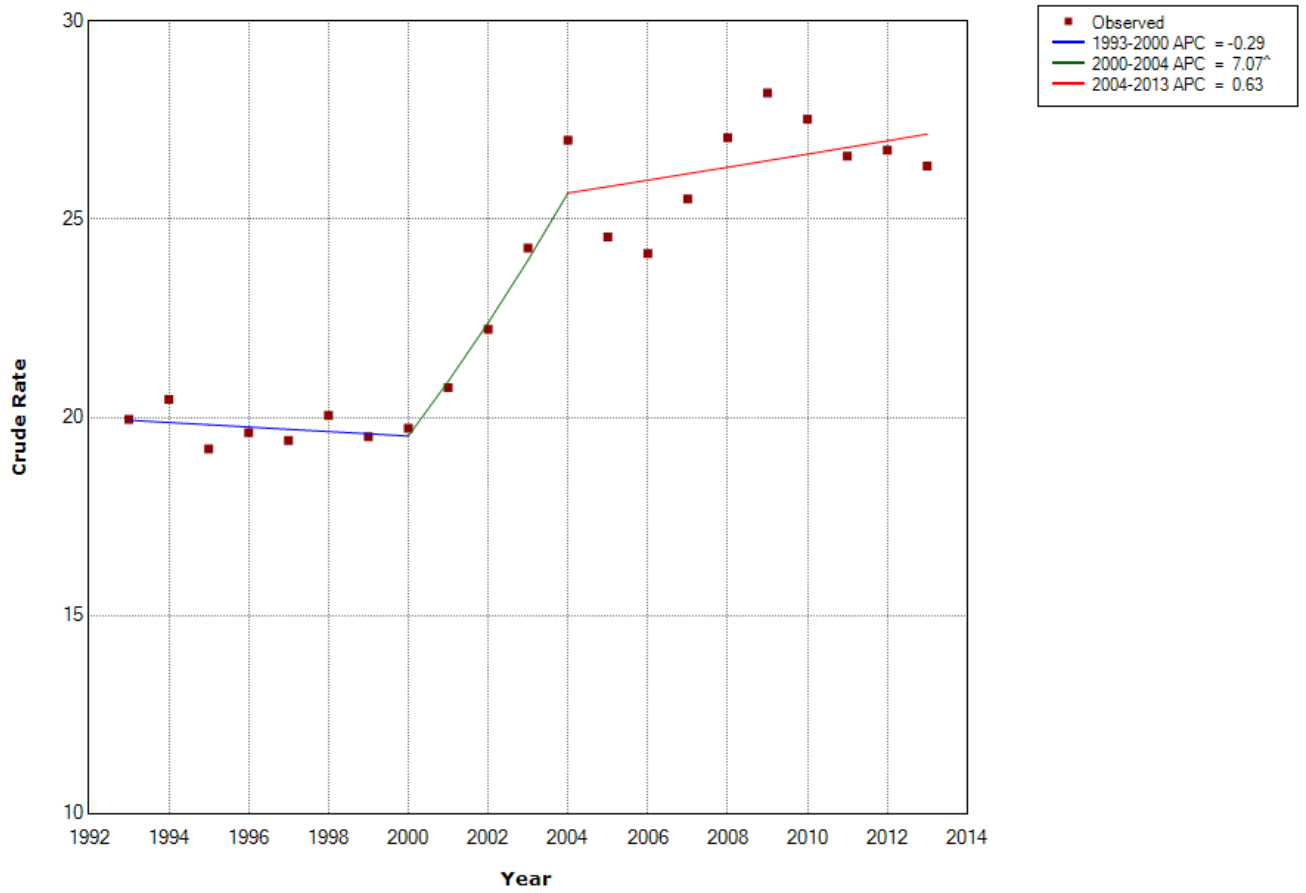
Incidence of carpal tunnel syndrome (n/10,000 person years) stratified by age and gender																					
Year	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Female 18-29	12.69	12.69	12.84	12.88	11.45	12.32	11.77	10.14	8.63	10.23	11.54	12.26	10.70	10.48	11.61	9.96	13.90	12.19	11.55	11.89	10.68
Female 30-39	31.40	28.58	28.00	27.62	28.09	30.09	27.83	25.88	27.18	28.31	30.31	33.31	30.53	30.06	32.17	33.13	34.97	33.96	32.51	31.72	28.69
Female 40-49	38.43	37.75	33.08	36.31	35.17	37.42	31.74	34.72	34.05	34.94	35.63	37.37	36.27	35.62	40.06	42.51	40.89	40.86	40.05	42.06	39.50
Female 50-59	39.86	41.02	41.93	40.82	41.44	43.24	44.70	42.33	43.94	46.44	54.52	61.11	54.56	52.25	58.55	54.70	56.14	54.10	51.62	50.07	50.97
Female 60-69	25.54	29.79	24.64	25.70	25.08	26.41	26.43	26.86	30.23	32.54	39.12	46.20	38.44	36.30	31.00	42.47	42.24	41.87	37.74	35.80	37.32
Female 70+	24.45	22.29	24.21	25.28	26.17	25.09	25.25	27.67	29.29	32.87	34.96	39.57	37.78	39.60	39.13	41.89	46.03	44.89	44.46	42.29	43.53
Male18-29	3.58	3.69	3.09	3.02	2.32	2.29	2.35	1.44	2.24	2.75	2.60	3.14	2.60	2.58	3.33	3.13	2.77	3.00	3.56	3.51	3.35
Male 30-39	9.09	8.63	8.63	10.67	7.82	8.45	5.92	8.74	8.60	10.01	10.72	11.28	9.76	8.80	9.53	9.16	9.90	10.30	9.19	9.67	9.72
Male 40-49	14.23	14.35	12.63	11.83	11.86	12.41	13.43	13.26	14.39	16.32	16.08	17.78	14.28	14.25	16.36	18.23	17.76	19.58	17.15	18.13	17.63
Male 50-59	13.90	17.40	17.11	15.36	16.26	15.17	16.54	15.87	18.00	18.59	19.87	21.36	20.23	20.02	22.30	23.69	23.38	23.91	23.51	24.40	25.45
Male 60-69	13.62	15.14	11.42	12.22	13.02	13.48	15.58	15.96	18.78	18.49	19.80	23.71	21.12	21.81	23.95	24.79	27.56	23.24	24.59	27.90	26.23
Male 70+	14.88	18.38	15.72	16.64	18.34	18.06	17.29	19.27	20.53	21.95	24.71	27.24	27.92	26.94	29.67	31.84	33.81	32.52	33.23	33.78	33.83

B3. Joinpoint analysis plot of the age and gender standardised prevalence of carpal tunnel syndrome between 1993 and 2013



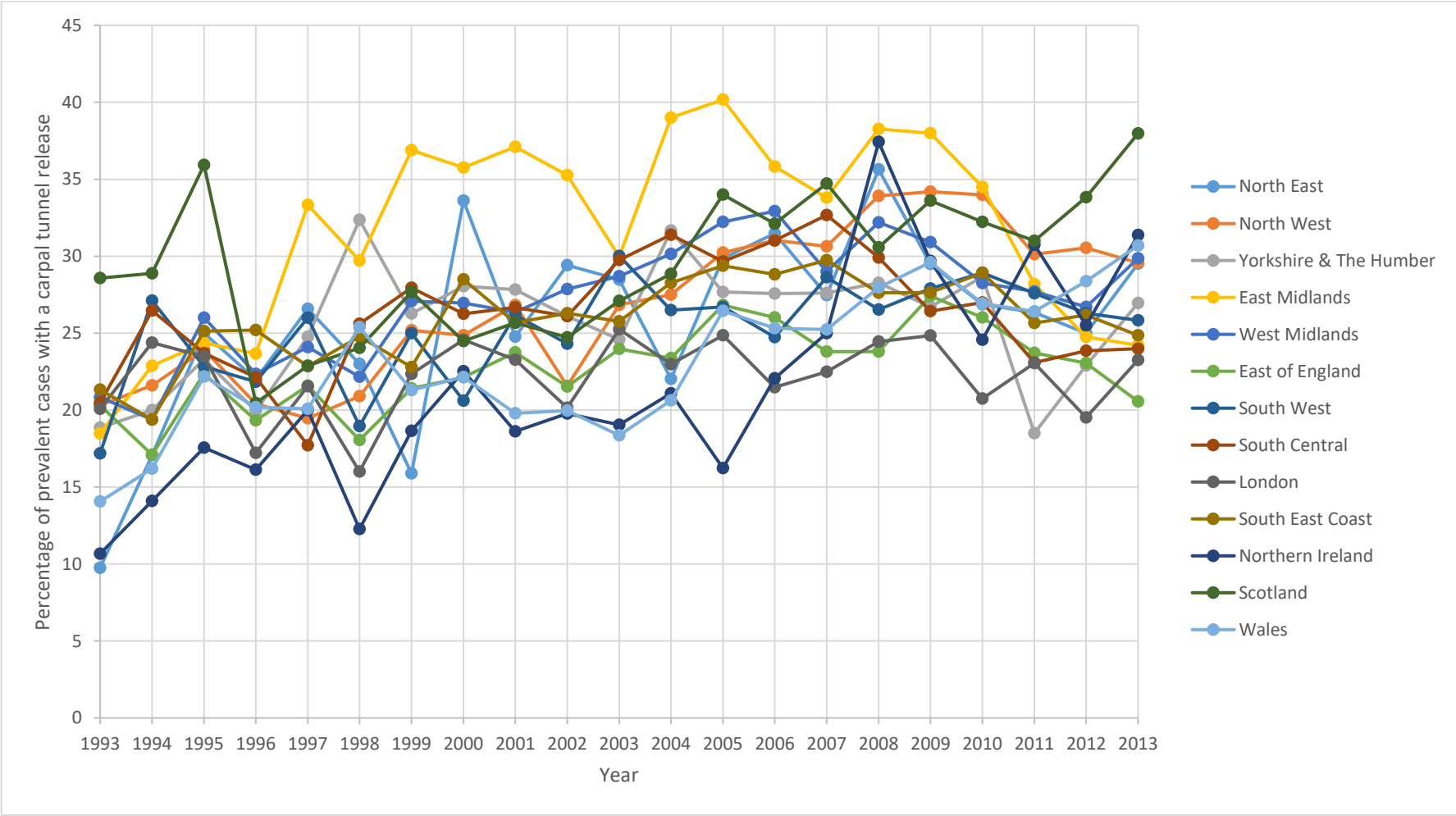
^ The Annual Percent Change (APC) is significantly different from zero at alpha = 0.05

B4. Joinpoint analysis plot of the age and gender standardised incidence of carpal tunnel syndrome between 1993 and 2013



^ The Annual Percent Change (APC) is significantly different from zero at alpha = 0.05

B5. Episodes of carpal tunnel surgery as a percentage of prevalent cases in each calendar year, over time, by region



C. Systematic review search terms

Search Terms for Carpal Tunnel Syndrome	
1	carpal tunnel syndrome .mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2	CTS.mp.
3	carpal channel mp.
4	nerve compression*.mp.
5	entrapment neuropath*.mp.
6	nerve entrapment*.mp.
7	hand pain.mp.
8	wrist pain.mp.
9	Or/1-8
Medline Search Filter on OVIDsp for Epidemiology / Prognostic Studies (from Centre Database)	
10	exp EPIDEMIOLOGY/
11	exp PROGNOSIS/
12	exp DISEASE PROGRESSION/
13	predict$.mp.
14	factor$.mp.
15	risk$.mp.
16	model$.mp.
17	evolution.mp.
18	history.mp.
19	indicator$.mp.
20	course.mp.
21	rule$.mp.
22	transition$.mp.
22	determinant$.mp.
23	pattern$.mp.
24	subgroup$.mp.
25	sub-groups.mp.
26	screen$.mp.
27	long-term.mp.
28	progress$.mp.
29	modif$.mp.
30	mediat$.mp.
31	rate$.mp.
32	occurrence$.mp.

33	preval$.mp.
34	inciden$.mp.
35	epidemiol$.mp.
36	epidemiology.fs
37	etiology.fs.
38	OR/10-37
39	exp EPIDEMIOLOGIC STUDIES/
40	cohort$.mp.
41	follow-up.mp.
42	("case control" or "case controlled").mp.
43	retrospective$.mp.
44	prospective$.mp.
45	((patient$ or medical) adj3 (record$ or review$ or histor$)).mp.
46	longitudinal$.mp.
47	inception.mp.
48	observation$.mp.
49	time series.mp.
50	OR/39-49
51	38 and 50
	EMBASE search filter on OVIDsp for Epidemiology / Prognostic Studies (from Centre Database)
52	exp DISEASE COURSE/
53	predict$.mp.
54	factor$.mp.
55	risk$.mp.
56	model$.mp.
57	evolution.mp.
58	history.mp.
59	indicator$.mp.
60	course.mp.
61	rule$.mp.
62	transition$.mp.
63	determinant$.mp.
64	pattern$.mp.
65	subgroup$.mp.
66	sub-group$.mp.
67	screen$.mp.
68	long-term.mp.
69	progress$.mp.

70	modif$.mp.
71	mediat$.mp.
72	Or/52-71
73	exp COMPARATIVE STUDY/ or exp
74	CONTROLLED STUDY/ or exp MODEL/ or OBSERVATIONAL STUDY/ or TREND STUDY/
75	COHORT ANALYSIS/ or CORRELATIONAL STUDY/ or CROSS-SECTIONAL STUDY/ or exp DATA COLLECTION METHOD/ or EXPLORATORY RESEARCH/ or MULTIMETHOD STUDY/ or QUANTITATIVE STUDY/ or SECONDARY ANALYSIS/
76	cohort$.mp.
77	follow-up.mp.
78	("case control" or "case controlled").mp.
79	retrospective$.mp.
80	prospective$.mp.
81	(study or studies).mp.
82	((patient$ or medical) adj3 (record$ or review$ or histor$)).mp.
83	longitudinal$.mp.
84	inception.mp.
85	observation$.mp.
86	time series.mp.
87	outcome$.mp.
88	Or/73-87
89	72 and 88
Search Filter used by SIGN for RCTs for MEDLINE	
90	Randomized Controlled Trials as Topic/
91	randomized controlled trial/
92	Random Allocation/
93	Double Blind Method/
94	Single Blind Method/
95	clinical trial/
96	clinical trial, phase i.pt
97	clinical trial, phase ii.pt
98	clinical trial, phase iii.pt
99	clinical trial, phase iv.pt
100	controlled clinical trial.pt
101	randomized controlled trial.pt
102	multicenter study.pt
103	clinical trial.pt
104	exp Clinical Trials as topic/

105	or/90-104
106	(clinical adj trial$).tw
107	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
108	PLACEBOS/
109	placebo$.tw
110	randomly allocated.tw
111	(allocated adj2 random$).tw
112	or/1106-111
113	105 or 112
114	case report.tw
115	letter/
116	historical article/
117	or/114-116
118	113 not 117
Search Filter used by SIGN for RCTs for EMBASE	
119	Clinical trial/
120	Randomized controlled trial/
121	Randomization/
122	Single blind procedure/
123	Double blind procedure/
124	Crossover procedure/
125	Placebo/
126	Randomi?ed controlled trial$.tw.
127	Rct.tw.
128	Random allocation.tw.
129	Randomly allocated.tw.
130	Allocated randomly.tw.
131	(allocated adj2 random).tw.
132	Single blind$.tw.
133	Double blind$.tw.
134	((treble or triple) adj (blind$).tw.
135	Placebo$.tw.
136	Prospective study/
137	Or/119-136
138	Case study/
140	Case report.tw.
141	Abstract report/ or letter/
142	Or/138-141

143	137 not 142

D. Tables relating to the identification of candidate prognostic factors and predictors of treatment effect used in chapters 4 & 8

D1. Table of candidate prognostic factors and predictors of treatment effect identified by GP's in response to a survey

Suggested candidate prognostic factors of a good outcome from carpal tunnel syndrome managed conservatively	Sum score of graded responses	Suggested candidate prognostic factors of a poor outcome from carpal tunnel syndrome managed conservatively	Sum score of graded responses
Short history	15	Thenar muscle weakness or wasting	9
No thenar muscle weakness or wasting	6	Longer symptom duration	8
Non severe symptoms	5	Continuous numbness / symptoms	8
Good work ethic	4	Unemployed / On sickness benefit / Off work because of CTS	7
Nocturnal or wakening symptoms only	4	Greater symptom severity	5
Acute onset	4	Underlying osteoarthritis	4
Symptoms not related to work	3	Co-morbidity	4
Postural symptoms only	3	Vague description of pain and paraesthesia / Diagnosis unclear	3
Intermittent symptoms	3	Symptoms related to work	3
Good function / coping with day to day activities	3	Poor sleep because of CTS	3
Good patient education	3	Poor patient education/ expectation	3
No previous anxiety / depression	2	History of anxiety / depression	3
Symptoms not present at time of examination (may be evident on provocation)	2	Slow insidious worsening	2
Well defined median nerve distribution	2	Previous surgery on the effected side	2
Early intervention	2	Previous failed treatment	2
Good quality sleep	2	Late intervention	2
Isolated condition with positive diagnostic tests (Phalen’s etc)	2	Mildly abnormal or normal NCS	1
No co-morbidity	1		
Unilateral	1		
Associated with RA	1		
Previous good outcome with CTS	1		

Clearly abnormal NCS	1		
Suggested candidate predictors of a good treatment effect from a corticosteroid injection		**Suggested candidate predictors of a poor treatment effect from a corticosteroid injection**	
Patients willing to try (for 2 weeks) / Good compliance / Motivation	9	Previous failure of splint to other wrist	9
Previous benefit from splint (to other wrist)	8	Thenar muscle weakness or wasting	6
Early morning pain and numbness predominate	7	Splinting at night is not acceptable / not willing to try	6
Pregnant	6	Long history	6
Nocturnal or wakening symptoms only	5	History of anxiety / depression	4
Short history	5	Continuous numbness	4
No thenar muscle weakness or wasting	4	Patients find splints uncomfortable	4
Good work ethic	3	Daytime symptoms	4
Postural symptoms only	3	Poor compliance	4
Patient asks for splint	3	Unemployed / On sickness benefit	3
Good patient education	3	Poor education	3
Symptoms not related to work	2	Symptoms related to work	2
Symptoms not present at time of examination (may be evident on provocation)	2	Previous surgery on the effected side	2
Unilateral symptoms	2	Poor sleep because of CTS	2
Intermittent night symptoms	2	Long time interval before commencing treatment	1
Milder symptoms	2	Patients who normally fail to improve no matter what you offer them	1
No previous anxiety / depression	1		
Suggested candidate predictors of a good treatment effect from night splinting		**Suggested candidate predictors of a poor treatment effect from night splinting**	
Previous benefit from injection (to other wrist)	11	Previous failure of injection (to other wrist)	15
Severe / clear symptoms with defined distribution of symptoms	6	Continuous numbness / symtpoms	8
No thenar muscle weakness or wasting	5	Thenar muscle weakness or wasting	5
Inflammatory arthritis causing CTS	5	Underlying OA	4
Nocturnal or wakening symptoms only	4	Diagnostic uncertainty	4
Short duration of symptoms	4	Previous failure of injection to another joint	3
Good education	4	Muscle wasting	3
Previous benefit from injection to another joint	3	Recurrent symptoms	3
Postural symptoms only	3	Needle phobia	3

Accuracy of siting injection	3	Co-existing WRULD or radiculopathy	3
Intermittent symptoms / mild to moderate symptoms	3	Unemployed / On sickness benefit	2
Good post injection advice	3	Previous surgery on the effected side	2
Patient requests	3	Slow progression of symptoms over long period of time	2
Self-limiting history like pregnancy	3	Severe symptoms	2
Good work ethic	2	Symptoms related to work	1
Symptoms not present at time of examination (may be evident on provocation)	2		
Patients flexible to ideas of management	2		
Symptoms not related to work	1		
Positive provocation tests	1		
First attendance	1		
Abnormality in wrist like a previous fracture	1		
Suggested candidate predictors of a good treatment effect from carpal tunnel release surgery		**Suggested candidate predictors of a poor treatment effect from carpal tunnel release surgery**	
Successful surgery on contralateral side	11	Thenar muscle weakness or wasting	10
Good work ethic	7	Unemployed / On sickness benefit / Poor work ethic	7
Nocturnal or wakening symptoms only	4	Previous surgery on the effected side	6
A postive approach to surgery	4	Continuous numbness	4
Recurrent injections / splints	4	Tethering of the nerve	4
Short history	4	Those with previous negative response to surgery	4
Symptoms not related to work	3	Long history	4
Postural symptoms only	3	Symptoms related to work	3
Male gender	3	OA wrist	3
Abnormal NCS	3	Those with a fear of surgery/surgeons	3
Post op hand therapy	3	Normal or slightly abnormal NCS	3
No previous anxiety / depression	2	History of anxiety / depression	2
Symptoms not present at time of examination (may be evident on provocation)	2	Poor post-operative care and poor instruction about the post-operative period	2
Occupation and activities allowing good post-op care	2	On-going work related upper limb disorder	2
No wasting	2	Co-morbidity	1
Severe symptoms	2	Female gender	1

No co-morbidity	1	On-going litigation	1
No thenar muscle weakness or wasting	1		
Correct diagnosis	1		

D2. Table summarising the candidate predictors of outcome and treatment effect

Table summarising candidate predictors of outcome and response to different treatment modalitiesCandidate variable	**Source**	**Predictor of overall outcome (Good)**	**Predictor of overall outcome (Poor)**	**Predictor of outcome of injection (Good)**	**Predictor of outcome of injection (Poor)**	**Predictor of outcome of splinting (Good)**	**Predictor of outcome of splinting (Poor)**	**Predictor of outcome of surgery (Good)**	**Predictor of outcome of surgery (Poor)**
Comorbidities									
Hypothyroidism	T,L		√√						
Diabetes	T,L		√√						√
On dialysis	L								√
Inflammatory conditions / associated arthritis / tendonitis / epicondylitis	T,L,S	√ (1)	√√√ (4)	√ (ra) (5)	√√(oa) (4)				√(oa) (3)
Double crush syndrome	L								√
Thoracic outlet syndrome	L								√
Acromegaly	L		√						
CTS following trauma	T,S		√	√ (1)					
Anxiety and / or depression	T,L,S		√√√ (3)						√√ (2)
Dyssomnia	T,S	√ (3)	√				√ (2)		
Functional disorders	T,L		√√						
Obesity	T,L		√√				√		

Absence of co-morbidity	S	√ (1)						√ (1)	
Any comorbidity	S		√ (4)						
Absence of anxiety and / or depression	S	√ (2)				√ (1)		√ (2)	
Clinical characteristics									
Bilateral symptoms	T,L		√√						
Unilateral symptoms	S	√ (1)				√ (2)			
Affecting dominant hand	L		√						
Well defined distribution of symptoms / clear diagnosis	S	√ (2)		√ (6)				√ (1)	
Vague symptoms / diagnostic uncertainty	T,S		√√ (3)		√ (4)				
Recurrent CTS	T,S		√		√ (3)				
Higher symptom severity	T,L,P,S		√√√√ (5)	√	√√ (2)			√√ (2)	
Lower symptom severity	L,S	√ (5)	√	√		√ (2)			√
Postural symptoms only	S	√ (3)		√ (3)		√ (3)		√ (3)	
Intermittent paraesthesia / symptoms	L,S	√ (3)		√ (3)		√ (2)		√	
Continuous symptoms	T,S		√√ (8)		√		√ (4)		√ (4)
Longer symptom duration	P,L,S		√√√ (8)		√		√ (6)		√ (4)
Shorter symptom duration	L,S	√√ (15)		√ (4)		√(5)		√√ (4)	
Acute onset	S	√ (4)							

Slow, insidious onset	S		√ (2)		√ (2)				
Night / waking symptoms predominate	T,S			√ (4)		√√ (7)		√√ (4)	
Daytime symptoms	S						√ (4)		
Good quality sleep	S	√ (2)							
Multi-site pain	P		√						
Lower functional severity	S	√ (3)							
Functional severity	P		√						
Wasting or weakness of the thenar muscles	T,L,S		√√√ (9)		√√ (5)		√ (6)		√√ (10)
No wasting or weakness of the thenar muscles	S	√ (6)		√ (5)		√(4)		√ (2)	
Positive Phalen's sign	L		√	√ (1)	√				
No or mild NCS changes	L,S		√√ (1)					√	√ (3)
Severe / clearly abnormal NCS changes	L,S	√ (1)			√			√√ (3)	
Less pronounced median nerve swelling / cross sectional area on ultrasound	L			√					
USS evidence of tethering of the median nerve	S								√ (4)
Lower wrist ratio	L		√						
Previous CTS surgery	T,P,S		√√√ (2)		√ (2)		√ (2)		√ (4)
Not treated with surgery	L		√						

Surgical complications	L		√						
Previous response to surgery on contralateral side	S							√ (11)	
Previous response to injection	L			√ (11)				√	
Previous response to injection in another joint	S			√ (3)					
Previous failed response to injection	L,S				√ (15)			√√ (4)	
Previous failed response to injection in another joint	S				√ (3)				
Previous benefit from splint to the other wrist	S					√ (8)			
Previous failure of splint to the other wrist	S						√ (9)		
Previous failure to respond to any treatment	S		√ (2)						
Previous good outcome with CTS	S	√ (1)							
Patients who normally fail to improve no matter what you offer them	S						√ (1)		
Splints uncomfortable / not acceptable to the patient	S						√ (4)		

Injection done at first attendance	S			√ (1)					
Injection accurately cited	S			√ (3)					
Post-operative hand therapy	S							√ (3)	
Poor post-operative care and poor instruction about the post-op period	S								√ (2)
Clinical intuition	T	√		√		√			
Patient choice	T	√		√		√			
Adherence	T					√			
Early treatment intervention	S	√ (2)							
Late treatment intervention	S		√ (2)						
Good patient education / explanation	S	√ (3)		√ (3)		√ (3)			
Poor patient education / explanation	S		√ (3)				√ (3)		
Good compliance with treatment / instructions	S					√ (9)			
Poor compliance with treatment / instructions	S						√ (4)		
Patient request				√ (3)		√ (3)			
Third generation COCP	L		√						
Demographics									

Female gender	T,L,S	√	√√	√					√ (1)
Male gender	L,S							√ (3)	√
Manual / high risk occupation	T,L		√√						√
Successful work role functioning	L							√	
Good work ethic	S	√ (4)		√ (3)		√ (3)		√ (7)	
Supportive employer	T,S	√						√	
Symptoms not related to work	S	√ (3)				√ (2)			
Symptoms related to work	S		√ (3)		√ (1)		√ (2)		√ (3)
Unemployed / on sickness benefit	S		√ (7)		√ (2)		√ (3)		√ (7)
Younger age	T,L	√	√	√					
Middle age	L		√						
Older age	P,L		√√		√				√
Pregnant women	L,S	√		√ (3)		√ (6)			
Perimenopausal	T		√						
Not willing to try treatment / phobia of needles or surgery	S				√(3)				√ (3)
Involved in litigation	L,S		√						√√ (1)
(Realistic) patient expectations	L							√	
Catastrophic thinking	L								√
Poor perceived health scores	L								√
Excess alcohol use	L								√
Smoking	L		√						
Positive approach to surgery	S							√ (4)	

Key

COCP = combined oral contraceptive pill CTS = carpal tunnel syndrome OA = osteoarthritis RA = rheumatoid arthritis

L = literature

P = generic prognostic factor (PROG-RES tool)

S = survey (with sum score)

T = think-tank

E. Summary of trial characteristics

Author (Year) **Country**	**Risk of bias** **Cochrane risk of bias (low / unclear / high)**	**Study population**	**Interventions**	**Primary outcome measure(s) / duration follow - up**	**Summary of trial findings**
Atroshi et al 2013 Sweden	6 / 1 / 0	Setting: orthopaedic department CTS diagnosis: Katz diagnostic criteria Inclusion: primary idiopathic CTS, 18-70 years, classic or probable CTS according to the Katz diagnostic criteria, unsuccessful 2 month treatment with wrist splinting, symptom severity warranting referral for consideration for surgery, NCS showing median nerve neuropathy at the wrist Exclusion: Previous steroid injection, thenar muscle atrophy, sensory loss, diabetes, thyroid disorder, inflammatory	Recruitment & randomisation: Computer-generated randomisation in varying blocks (1:1:1). Sequentially numbered opaque, concealed envelopes containing group assignments prepared. Randomisation was done by the research nurse who opened the envelope containing the group assignment Blinding: The nurse prepared the injection in a covered syringe to mask the surgeon and patient to the substance being used. While the needle was withdrawn, a dressing was pressed over	Change in CTS symptom severity score at 10 weeks [32] Rate of surgery at 1 year Missing data: n=1 (Methylprednisolone, 80mg, 10 wk); n=0 at 1 year	Symptom severity score at 10 weeks (SD)±: Methylprednisolone 80mg vs. Placebo -0.64 (-1.06 to -0.21) *P* = 0.003 Methylprednisolone 40mg vs. Placebo -0.88 (-1.30 to -0.46) *P* <0.001 Methylprednisolone 80mg vs. 40mg 0.24 (-0.20 to 0.69) *P* = 0.29 Rate of surgery at 1 year, *n (%)* Methylprednisolone 80mg vs. Placebo 0.24 (0.06 – 0.95) *P* = 0.042

		disease, polyneuropathy, current pregnancy, previous CTR, surgery on the contralateral side in the past 2m, inability to respond to questionnaires, severe illness, drug or alcohol abuse	the puncture site to conceal the colour in case of leakage. At follow up examinations, the nurse covered the patient's palm with a dressing to conceal a possible surgical scar. Intervention 1: 80mg local methylprednisolone (37 patients) Intervention 2: 40mg local methylprednisolone (37 patients) Intervention 3: Placebo (37 patients)		Methylprednisolone 40mg vs. Placebo 0.38 (0.09 – 1.59) *P* =0.16 Methylprednisolone 80mg vs. 40mg 0.63 (0.21 – 1.89) *P* = 0.41
Celiker et al 2002 Turkey	1 / 4 / 2	Setting: Secondary care CTS diagnosis: Electrophysiological abnormality Inclusion: No previous treatment for CTS Exclusion: Thenar atrophy	Recruitment & randomisation: Consecutive patients recruited on attending clinic for NCS, randomly assigned to one of two groups using sequentially numbered sealed opaque envelopes Intervention 1: wrist splints at night with acemetacine 120mg/day	Visual analogue score Symptom severity scale [32] Motor distal latency (ms) Sensory distal latency (ms) Follow up: 8 weeks Missing data: none	Pre-treatment and post-treatment VAS scores not different between groups (*P* > 0.05) but decreased significantly in both groups (*P* < 0.05) Pre-treatment and post-treatment distal latency scores not different between groups (*P* > 0.05)

			(NSAID) (16 wrists, 11 patients) Intervention 2: 40mg local Methylprednisolone (21 wrists, 12 patients)		but improved significantly in both groups ($P < 0.05$) Difference between groups regarding SSS not reported
Gerritsen et al 2002 The Netherlands	7 / 0 / 0	Setting: Secondary care CTS diagnosis: Clinical diagnosis with electrophysiological confirmation Inclusion: 18 years and older and able to complete written questionnaires Exclusion: previous treatment with splinting or surgery, history of writst trauma or surgery, history suggesting underlying cause (pregnancy, diabetes), clinical signs or symptoms or electrophysiological findings that could mimic CTS, severe thenar muscle atrophy	Recruitment & randomisation: Permuted blocks of 4 patients were formed to ensure near equal distribution of patients over the 2 treatment sites. The random sequence of the permuted blocks was generated by using random number tables. Coded and sealed opaque envelopes containing the treatment allocation and the envelopes used sequentially. Blinding: Patients were requested not to divulge treatment to the research physiotherapists. Wrists were bandaged to conceal any wound. Intervention 1: night splinting for at least six weeks (89 patients)	General improvement Number of nights waking up due to symptoms Severity of symptoms [162] Follow up: 3, 6, 12 & 18 months Missing data: n = 19 (22%) (surgery at 18 months) n = 10 (11%) (splinting at 18 months)	Success rate at 18 months (Differences surgery minus splint in success rate and 95% confidence interval) Surgery vs. splinting 15 (3 - 27) $P = 0.02$ Number of nights waking up due to symptoms at 18 months, mean (SD) Surgery vs. splinting 0.4 (-0.6 - 1.4) $P = 0.44$ Severity of main complaint at 18 months, mean (SD) 1.2 (0.2 - 2.3) $P = 0.02$

			Intervention 2: open carpal tunnel release (87 patients)		
Ly-Pen et al 2004 Spain	1 / 3 / 3	Setting: Secondary care (designed to represent the general population that seeks medical attention from primary care) CTS diagnosis: Clinical diagnosis with electrophysiological confirmation Inclusion:18 years and older, symptoms for at least 3 months, unresponsive to at least 2 weeks of non-steroidal anti-inflammatories and splinting Exclusion: thenar atrophy, previous carpal tunnel release or local steroid injection, pregnancy, diabetes, hypothyroidism, inflammatory arthropathy, polyneuropathy	Recruitment & randomisation: Patients were consecutively referred by primary care physicians. Treatment assignments were randomly generated by computer in blocks of 6 cases. Sealed envelopes containing treatments assignments were provided by the statistician. After enrolment, the envelope containing the assignment for each wrist was opened and the specific treatment assigned Blinding: No blinding took place Intervention 1: local steroid injection (83 wrists) Intervention 2: limited palmer incision carpal tunnel release (80 wrists)	Percentage of wrists that reached ≥ 20% response for nocturnal paraesthesia Follow up: 3 months Missing data: n = 13 (16%) (surgery at 3 months) n = 3 (4%) (injection at 3 months)	≥ 20% response for nocturnal paraesthesia at 3 months Injection vs. surgery 94.0% vs. 75.0% (*P* = 0.001)

F. Internal data request form

Arthritis Research UK Primary Care Centre Keele University Internal data request form

To be completed by the Researcher of proposed study

Proposed Study Title: Predicting better response to either corticosteroid injection or night splinting in primary care patients with carpal tunnel syndrome (Sub-study of PhD entitled "The epidemiology, prognosis and management of carpal tunnel syndrome in primary care")				
Researcher: Dr Claire Burton				
Supervisor of Researcher (where applicable): Dr Linda Chesterton, Dr Ying Chen, Prof Danielle van der Windt				
Co-authors: Dr Linda Chesterton, Dr Ying Chen, Prof Danielle van der Windt				
Is the data required for practicing analysis or demonstration/ teaching only? *If so, please provide further details*	**YES**		**NO**	**x**
Research Question / Objective: *(Not required if data required for practicing analysis or demonstration/teaching only)* Investigate the predictive value of candidate prognostic factors available from a pragmatic randomised clinical trial (INSTinCTS) to predict future change in patient-reported CTS-symptoms following primary care management (corticosteroid injection or night splinting) Explore if a priori defined prognostic factors (potential treatment moderators) predict a better response to either corticosteroid injections or night splinting in primary care patients with CTS				

Outline design of analysis:
(Not required if data required for practicing analysis or demonstration/teaching only)

Objective 1

Study population: the INSTinCTS trial, has recruited around 240 patients (males and females over 18 years of age) with mild-to-moderate CTS consulting in primary care or the primary-secondary care interface. Patients were randomised on an equal basis to either steroid injection or a night splint. Clinical diagnosis was standardized, based on presenting symptoms, routine clinical history and physical tests using criteria developed as part of a consensus survey. The eligibility criteria were designed to select a relatively homogeneous group of patients with idiopathic CTS, suitable for both splinting and local injection and who do not require immediate onward referral for surgery.

Outcome measure: The outcome measure for this analysis will be the absolute score for symptom severity and limitations in hand function using the Boston Carpal Tunnel Questionnaire (BCTQ) at six months follow-up which will be collected as part of the INSTINCTS trial. The BCTQ is a condition-specific patient reported outcome measure, which has been shown to be valid, reliable and responsive when used in patients with CTS in various settings. The scale includes two subscales: the symptom severity scale (SSS: 11 items) and function status scale (FSS: 8 items), both scored on 1-5 scales, with final scores for each dimension calculated as a mean score between 1 and 5. Higher scores denote more severe symptoms and greater functional impairment.

Candidate predictors: Candidate predictors have been previously identified through my MPhil work and have been grouped into different categories (comorbidities, patient or clinical characteristics, patient demographics) and are collected as part of the baseline clinical assessment or baseline patient questionnaire within the INSTINCTS study, as described below.

Statistical analysis: Descriptive statistics will be used to illustrate the course of symptoms of carpal tunnel syndrome in all trial participants, and separately for those in each arm of the study. Next, linear regression analysis will be used to determine the association between candidate predictors and symptom severity and functional disability (BCTQ) at six months follow-up in all participants, adjusting for baseline score and randomly allocated treatment (corticosteroid injection or splint). Multiple linear regression will be used to identify the combination of factors is most strongly associated with the future course of symptoms and function limitation. Given the sample size of the INSTinCTS trial, not all candidate predictors will be introduced in the model at once. A stepwise sequential approach will be used adding blocks of variables to investigate the predictive value of adding more complex prognostic information. For each block backwards manual selection will be used to identify the most important predictors, which will be carried forward to the next step. This approach will ensure that there will be at least 10 subjects per variable introduced into the model, at each step in the analysis.

Objective 2

The results of objective 1 will provide a list of prognostic factors that are most strongly associated with future changes in symptoms and functional limitations in patients with CTS treated with commonly used primary care interventions. For this objective, the extent to which some specific prognostic factors predict a differential response to either injection or splints will be explored, as the identification of potential treatment moderators could support the design of a decision aid to be tested in future research. The INSTinCTS trial is not powered to test treatment moderation (this would require subgroup analysis and testing of treatment-moderator interactions) and there are currently no similar trials with which to pool its data. This analysis will therefore be an exploratory analysis of a small set of priori defined prognostic factors. Study population and outcome measures will be the same as described above.

Candidate treatment moderators: Factors considered to be likely candidates for this analysis will be informed by the results of the analysis of objective 1, and by the opinions and expertise from members of the Research User Group and a clinical advisory group. No more than 3 or 4 factors will be investigated, for which there are plausible reasons that they are associated with a larger improvement of CTS symptoms or function following corticosteroid injection versus six weeks of night splints.

Statistical analysis: will consist of exploratory subgroup analyses providing estimates of mean change in symptom severity and limitation in function for injection versus splints in patient subgroups defined on the basis of the prognostic factor.
Study (or studies) from which data are requested: Data will be required from INSTinCTS – Injection versus Splinting in Carpal Tunnel Syndrome
Study population required *(For quantitative studies please specify if there are **specific groups of participants** required from the study e.g. age range, gender, and for qualitative studies please specify the **demographic or sample frame** and the **number of participants** you require):* Anonymised data from all randomized participants will be required.

Precise data required
*(For quantitative data please be **specific** on survey wave (e.g. baseline data) and list **all variables** required and for qualitative data please detail the **type of data** required (e.g. interview transcripts, diaries etc):*

For all randomised patients I will required the randomization code and the baseline and six month Boston Carpal Tunnel Questionnaire sum scores (pre-treatment questionnaire: C9 – 20; six month questionnaire 2-13). The answer to six month questionnaire F4 (yes / no) will also be required to ascertain whether surgery has taken place. If time in my PhD allows, it may at a later date be of interest to obtain the BCTQ score and surgical outcome, measured at 12 months. The table below details all variables and their questionnaire location, which will be required.

Variable	Outcome measure	Source of outcome measure	Question location and information required
Gender			Pre-Treatment Questionnaire A1 Male / female
Age			Pre-Treatment Questionnaire A2 & A3
Occupation			Pre-Treatment Questionnaire E 1 (yes / no) If yes E3 a-c (free text)
Anxiety and / or depression	During the last month have you been bothered by feeling down, depressed or hopeless? During the last month have you often been bothered by little interest or pleasure in doing things?	Progress brief assessment tool	Baseline questionnaire G6: yes / no G7: yes / no
Sleep quality	Jenkins questions	Jenkins questions	Pre-Treatment Questionnaire D 1-4 Not at all / on some nights / on most nights
Functional disorders	Have you had pain anywhere	Progress brief assessment tool	Pre-Treatment Questionnaire

	else in the last month?		H4: yes / no
Obesity	BMI	Entered into CRF	Randomisation CRF Height / weight
Absence / presence of any associated co-morbidity		Calculated from above variables	Ascertained from negative answer to H1-4
Laterality of symptoms			Pre-Treatment Questionnaire C 1 Right / left / both
If affecting dominant hand			Pre-Treatment Questionnaire C2 Right / left
Recurrent symptoms			Pre-Treatment Questionnaire B1 Yes / no If no, B2 1 /2 / 3 / >3
Symptom severity	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 9 – 19 (i.e. baseline symptom severity score)
Functional severity	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 20 a-h (i.e. baseline function severity score)
Boston Carpal Tunnel sum score	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 9 – 19 C 20 a-h
Symptom duration / time to intervention	How long have you had your current hand or wrist problems for?		Pre-Treatment Questionnaire C 3 < 3months / 3-six months / 6 – 12 months / > 12months

Postural symptoms only	Are your hand or wrist symptoms only present when you hold your wrist in a particular position?	Question created	Pre-Treatment Questionnaire C 5 Yes / no
Constancy of symptoms	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 12 & 13 (scale 1-5)
Symptoms limited to night-time	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 12 If answered 1
Daytime symptoms	Boston Carpal Tunnel Questionnaire	Levine et al	Pre-Treatment Questionnaire C 11 (scale 1-5)
Nature of onset	How did you symptoms start?	Adapted from DwdW BMJ 1998	Pre-Treatment Questionnaire C 4 Suddenly / gradually
Multi-site pain	To include with 'functional disorders'	Progress brief assessment tool *Full symptom checklist likely to be over-burdensome*	Pre-Treatment Questionnaire H4 yes / no H5 <3m / 3-6m / 6-12m / 1-3 years / >3 years
Phalen's sign	Checked at eligibility screening		Eligibility CRF A2 Positive / negative
Previous response of CTS to wrist injection / splint and surgery	Which of the following treatments have you received for your carpal tunnel syndrome in the past? For each treatment you	BeBack	Pre-Treatment Questionnaire If B1 = no, answer to B4 (ticked box) and B5 ticked options: of great help / of some help / of little help / of no help (specific to

	have received in the past detailed in Question 4, please state for each one how useful it has been		each treatment)
Previous response to any treatment	Answer to B5, not specific to treatment	BeBack	Pre-Treatment Questionnaire If B1 = no, answer to B4 (ticked box) and B5 ticked options: of great help / of some help / of little help / of no help (not treatment specific)
Previous response to injection (any site)	Have you ever had a steroid injection into a joint other than your wrist before? Yes / no If yes, How much do you think the treatment helped your problem	BeBack	Pre-Treatment Questionnaire If B6 yes, answer to B7 ticked options: then of great help / of some help / of little help / of no help
Acceptability / preference of treatment	…if you were to have a choice, would you prefer one treatment over the other?		Pre-Treatment Questionnaire F1 I would strongly prefer a wrist injection > I would strongly prefer night splints
Acceptability /	If you were to receive a wrist injection /		Pre-treatment Questionnaire F2 yes / no

expectation of treatment	night splint, would you expect your symptoms to improve within six weeks following treatment?		F3 yes / no
Quality of patient education	Patient education leaflets will be provided and satisfaction measured at six weeks		six week questionnaire G3 0 - 10
Support of employer	How much do you agree or disagree with the following statement… I feel that my welfare is important to my employer	Adapted from Karasek	Pre-Treatment Questionnaire E10 Strongly disagree / disagree / agree / strongly agree
Successful work role functioning	On average to what extent have your hand or wrist problems affected your performance at work over the past month?	Presenteeism scale	Pre-Treatment Questionnaire E 7 (0 – 10)
If symptoms are work related	If you are not doing your usual job, is this because of your hand or wrist problems?	Adapted from Karasek	Pre-Treatment Questionnaire If E5 NOT 'doing my usual job' E 6 Yes / no
If unemployed / receiving social support	Which of the following best describes your current situation?		Pre-Treatment Questionnaire If E1 'no', Unemployed ticked?

Locus of control	There is a lot which I can do to control my symptoms What I do, can determine whether my pain problem gets better or worse	Single items from the Illness Perception Questionnaire (taken from the multi-item subscales (dimensions)	Pre-Treatment Questionnaire F4 c&d Strongly disagree / disagree / neither agree nor disagree / agree / strongly agree
Treatment control	Treatment can control my problem	Single items from the Illness Perception Questionnaire (taken from the multi-item subscales (dimensions	Pre-Treatment Questionnaire F4 e Strongly disagree / disagree / neither agree nor disagree / agree / strongly agree
Adherence to treatment	For splint only, …over the past six weeks, on average, how many nights per week have you been wearing your splint?		six week Questionnaire If F1 yes, answer to F3: Every night / 4-6 nights / 1-3 nights / never
Peri-menopause	Age calculated 45 – 55 years		Pre-Treatment Questionnaire Calculated yes / no from A2
Perceived health scores	EQ 5D	EQ 5D	Pre-Treatment Questionnaire Cumulative score from G 1-5
Excess alcohol use	On average how often do you drink alcohol	NORSTOP	Pre-Treatment Questionnaire H6 Daily or most days / Once or twice a week /

			Once or twice a month / Once or twice a year / Never
Smoking	What is your current smoking status?	NORSTOP	Pre-Treatment Questionnaire H7 Never smoked / previously smoked / currently smoking

Is new REC approval required?	**YES**		**NO**	**x**

In order to permit a more complete description of baseline characteristics, additional questions were added to the original trial baseline questionnaire. The addition of these questions was approved on 3rd July 2013 (REC reference 13/NW/0280, amendment 1).

The Patient Information Leaflet includes a paragraph explaining that anonymized data may be used for further research.

"The study information collected about you may be shared with other research teams to answer new research questions in the future. If this is the case, information will be anonymised. Your full name and contact details will not be disclosed."

Further new REC approval is therefore not required.

Into which Centre portfolio and methodology group(s) does this study fit? *(Please tick all that apply)*

OA Trials……		**Quantitative Trials……..**	
Musculoskeletal Trials……...		**Quantitative Epidemiology...**	
OA Epidemiology…….	x	**Qualitative…….**	
Musculoskeletal Epidemiology…		**Behavioural……...**	
Inflammatory Studies……		**User Involvement……..**	
		Education & Training…….	

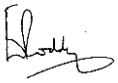
Signature of Supervisor of Researcher requesting the data:

Date:

24/2/17

I confirm that the data specified in this request are required to answer the research question. If there are any queries in relation to the data requested I understand that it is my responsibility to support the researcher to complete an accurate data request form, in line with the needs of the research question

Signature of Principal investigator(s) of study (or studies) from which data are requested:



Date:

24/2/17

Date of data release:

Signature of data custodian upon data release:

NB The data must be stored on your S:drive only in accordance with the Centre's Procedures for data security and management of identifiable and sensitive data relating to research participants and Standard Operating Procedures, and the principles and conditions set out in the Data Protection Act 1998, the Research Governance Framework, and with proper safeguards to ensure confidentiality.

Arthritis Research UK Primary Care Centre

Keele University

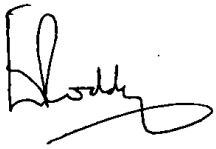
Internal data request form – Amendment

To be completed by the Researcher of the study

Study Title: Predicting better response to either corticosteroid injection or night splinting in primary care patients with carpal tunnel syndrome (Sub-study of PhD entitled "The epidemiology, prognosis and management of carpal tunnel syndrome in primary care")	**DCAP number of original data request*: n/a –** original Internal data request form signed 24/2/17
Researcher: Dr Claire Burton	**Supervisor of Researcher (where applicable):** Prof Danielle van der Windt Dr Ying Chen
Amendment number: 1	
Study (or studies) from which data are requested: INSTinCTS – The clinical and cost-effectiveness of corticosteroid injection versus night splints for carpal tunnel syndrome (INSTinCTS trial): an open-label, parallel group, randomized controlled trial	
Study population required *(e.g. age range, gender):* All participants	
Precise data required *(please be **specific** on survey wave (e.g. baseline data) and list **all variables** required):* I would like to request the six week outcome data (symptom severity score, function status scale and overall BCTQ) for all trial participants, in order to be able to describe more fully the course of symptoms of the trial participants as a cohort. This will allow me to more fully discuss the results of the first objective of my initial data request *(to investigate the predictive value of candidate prognostic factors available from a pragmatic randomised clinical trial (INSTinCTS) to predict future change in patient-reported CTS-symptoms following primary care management (corticosteroid injection or night splinting)*.	

Is the data requested in this amendment to be used to address the stated objectives in the original data request form?	**YES**	**x**	**NO**	

Signature of Supervisor of Researcher requesting the data:  *I confirm that the data variables specified in this request are required to answer the research question. If there are any queries in relation to the data requested I understand that it is my responsibility to support the researcher to complete an accurate data request form, in line with the needs of the research question*	Date: 30/01/2019

Signature of Principal Investigator(s) of study (or studies) from which data are requested: 	Date: 31/01/2019
Date of data release: **Signature of data custodian upon data release:**	
NB The data must be stored on your S:drive only, in accordance with the principles and conditions set out in the Data Protection Act 1998, the Research Governance Framework, and with proper safeguards to ensure confidentiality.	

* - The DCAP number of the original request can be found on the Internal Data Request Repository (P:\data request repositories\internal\ Internal Request Register.xls)

G. Published articles associated with the work presented in this thesis

Claire Burton, Linda S Chesterton and Graham Davenport

Diagnosing and managing carpal tunnel syndrome in primary care

Clinical Question

How can carpal tunnel syndrome be diagnosed and managed in a primary care setting?

CL Burton, MMedSci, MRCGP, NIHR In Practice Fellowship researcher; **LS Chesterton**, PhD, MCSP, FHEA, senior lecturer; **G Davenport**, FRCGP, senior lecturer and clinical champion for musculoskeletal medicine, Keele University and past president of the Primary Care Rheumatology Society, Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele.

Address for correspondence
Claire Burton, Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele, Staffordshire, ST5 5BG.
E-mail: c.burton@keele.ac.uk
Submitted: 22 October 2013; **Editor's response:** 30 October 2013; **final acceptance:** 12 November 2013.

DOI: 10.3399/bjgp14X679903

INTRODUCTION

Carpal tunnel syndrome (CTS) is a symptomatic compression neuropathy of the median nerve at the level of the wrist; characterised by hand pain, numbness, and tingling in the distribution of the median nerve (thumb, index, middle finger, and the radial side of the ring finger) and a reduction in grip strength and hand function. The severity of symptoms can be clinically categorised into mild, moderate, and severe. A figure of 55–65% of CTS cases present bilaterally[1] and the condition can be associated with conditions such as hypothyroidism, diabetes, and rheumatoid arthritis. CTS may present in late pregnancy but is usually transient.

A study from the UK General Practice Research Database in 2000, calculated the incidence in males to be 88 per 100 000 and in females to be 193 per 100 000, with new presentations being most frequent at ages 45–54 years in females and 75–84 years in males.[2] CTS is a recognised work-related musculoskeletal disorder (WMSD) caused by strain and repeated movements (biomechanical overload) and is hence more common in manual workers. Work absence and associated healthcare costs contribute to a significant socioeconomic burden on the UK economy.[3]

Consultations and surgical referrals appear to be increasing and commissioners are engaged in the review of referral protocols, incorporating conservative treatments for mild-to-moderate disease, to help manage surgical demand.

ASSESSMENT

A clear history and targeted examination, which identifies standard features and provocative factors, increases the likelihood of a diagnosis.[4]

Diagnosis can be achieved by use of criteria agreed by GPs with a special interest in musculoskeletal health, from the Primary Care Rheumatology Society. The criteria comprise eight questions (Box 1) followed by a decision tree (Figure 1).[5]

Alternative diagnoses that should be considered include: cervical radiculopathy, peripheral neuropathy, wrist/trapeziometacarpal, arthrosis, wrist tendonitis/tenosynovitis and ulnar neuropathy.[4] Contributing factors such as diabetes, hypothyroidism, and inflammatory conditions should be considered and managed appropriately, although there is no evidence that routine screening should be undertaken.[5]

Electromyography and nerve conduction studies may be considered if the diagnosis is uncertain, if surgery is being considered, or in the case of litigation;[4,6,7] although care pathways and local availability may vary.

MANAGEMENT

CTS may improve spontaneously in up to one-third of patients over a 10–15 month period.[8] Treatment options depend on severity. Non-surgical management (splinting or injection) should be considered in cases of mild to moderate disease, whereby pain and numbness are intermittent and there is no wasting or weakness of the thenar muscles. Referral for surgical management (decompression of the carpal tunnel) should be considered if: symptoms are severe or constant, the motor or sensory deficit is

Box 1. Questions to be asked to a patient presenting with hand or wrist symptoms

1. Do you have numbness or tingling in your wrist, hand, or fingers?
2. Do your symptoms spare your little finger?
3. Are the symptoms worse at night?
4. Do the symptoms wake you up at night?
5. Have you noticed your hand is weak; for example, have you found yourself dropping things?
6. Do you find shaking your hand, holding your hand or running it under warm water improves your symptoms?
7. Are the symptoms made worse by activities such as driving, holding a telephone, using vibrating tools, or typing?
8. Have splints or injections helped with your pain if you have had it in the past?

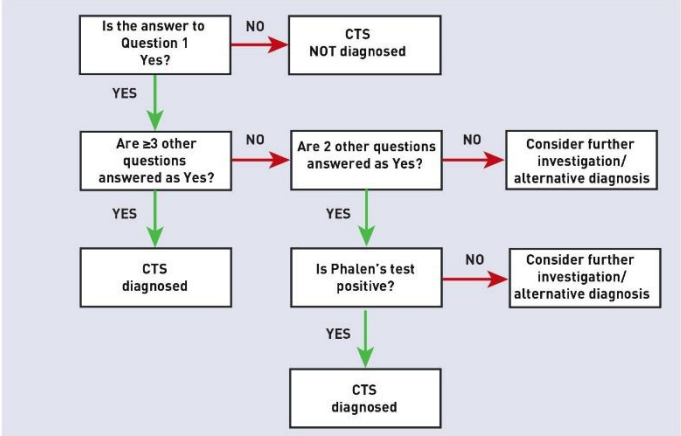


Figure 1. Decision tree to be used in conjunction with the questions in Box 1. © Keele University.

progressive, or there is no improvement within 3 months of conservative treatment.[6]

The use of non-steroidal anti-inflammatory drugs or diuretics should not be routinely recommended. Patients should be advised to minimise activities that exacerbate symptoms but it should be explained that evidence for work place modifications is lacking.[6]

Night splinting holds the wrist in a near neutral position preventing wrist flexion and limiting extension. Splints are inexpensive with no reported serious adverse effects[7] and, although there is limited evidence as to their effectiveness,[9] are recommended as a treatment option in primary care with the proviso that benefits should be apparent within 8 weeks.[6]

Corticosteroid injections are considered a safe and effective treatment option in the management of CTS and are believed to act by decreasing the symptomatic swelling of the flexor synovialis.

Cochrane review evidence exists for the short-term improvement of symptoms following an injection, while longer-term effects beyond 3 months are uncertain.[10] An accepted method for injection is shown in Figure 2; appropriate training is necessary.

CONCLUSION

CTS is a common, disabling, and distressing condition. Wrist splinting and corticosteroid injections are non-surgical treatment options that can be considered in primary care for the management of mild-to-moderate disease.

Patients with severe symptoms or who fail to respond to non-surgical management should be referred for surgical consideration.

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Figure 2. Suggested method for injection of the carpal tunnel

- Equipment: chlorhexidine wipe; 1 ml syringe, 23 gauge (blue) or 25 gauge (orange) needle for injection; corticosteroid without lidocaine; simple dressing.
- Explain and consent the patient for the treatment. Ensure there are no contraindications to a local steroid injection.
- Use a sterile 'no-touch' technique.
- The patient places hand palm up in a neutral or slightly extended wrist position (patient sitting).
- Clean skin following standard local practice.
- Insert needle at proximal skin crease at wrist, avoiding median nerve which lies under palmaris longus.
- Aspirate back into the syringe to avoid intravascular injection.
- Inject. Do not inject against resistance or if severe pain: if this occurs, reposition the needle and inject again.
- Ensure haemostasis and apply dressing.
- Provide patient with leaflet regarding the carpal tunnel steroid injection.
- The patient should be advised to wait in the surgery for 30 minutes following injection or alternatively ensure that they are accompanied by a responsible adult for that time.

Funding

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Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests

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REFERENCES

1. Bland JDP, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991–2001. *J Neurol Neurosurg Psychiatry* 2003; **74(12):** 1674–1679.
2. Latinovic R, Gulliford MC, Hughes RA. Incidence of common compressive neuropathies in primary care. *J Neurol Neurosurg Psychiatry* 2006; **77(2):** 263–265.
3. Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal tunnel syndrome: a review of the recent literature. *Open Orthop J* 2012; **6:** 69–76.
4. American Academy of Orthopaedic Surgeons. *Clinical practice guideline on the diagnosis of carpal tunnel syndrome.* 2007. http://www.aaos.org/Research/guidelines/CTS_guideline.pdf (accessed 11 Apr 2014).
5. Burton C, Chesterton L, Davenport G, *et al.* Developing agreed clinical criteria for the diagnosis of carpal tunnel syndrome in primary care — a clinical consensus exercise. Society of Academic Primary Care Annual Conference: Nottingham, 4 July 2013: 2E.2.
6. National Institute for Health and Care Excellence. *Carpal tunnel syndrome.* NIHR, 2012. http://cks.nice.org.uk/carpal-tunnel-syndrome#!scenariorecommendation:1 (accessed 10 Apr 2014).
7. Bland JD. Carpal tunnel syndrome. *BMJ* 2007; **335(7615):** 343–346.
8. Padua L, Aprile I, Caliandro P, *et al.* Carpal tunnel syndrome in pregnancy: multiperspective follow-up of untreated cases. *Neurology* 2002; **59(10):** 1643–1646.
9. Page MJ, Massy-Westropp N, O'Connor D, Pitt V. Splinting for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2012; **7:** CD010003.
10. Marshall SC, Tardif G, Ashworth NL. Local corticosteroid injection for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2007; **2:** CD001554.

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REVIEW ARTICLE

Clinical Course and Prognostic Factors in Conservatively Managed Carpal Tunnel Syndrome: A Systematic Review

Claire L. Burton, MBChB, MMedSci, Linda S. Chesterton, PhD, Ying Chen, PhD, Daniëlle A. van der Windt, PhD

From the Arthritis Research UK Primary Care Center, Research Institute for Primary Care and Health Sciences, Keele University, Keele, Staffordshire, United Kingdom.

Abstract

Objective: To summarize the available evidence regarding the course of symptoms and prognostic factors in patients with diagnosed carpal tunnel syndrome (CTS) who are treated conservatively.

Data Sources: Computerized databases, reference checking, and experts in the field were used to identify studies for inclusion in the review.

Study Selection: Multiple reviewers were used to identify studies which included adults (aged ≥18y) diagnosed with CTS in either a clinical setting or population setting. The study must have observed the course of CTS over at least a 6-week period in patients receiving no treatment or usual care that included conservative (nonsurgical) treatments. The design was of a longitudinal cohort study with either prospective or retrospective data collection. There were no language restrictions, and none of the research identified was only reported in abstract form.

Data Extraction: Methodological bias was assessed using the Quality in Prognosis Studies tool. A high risk of bias (predominantly relating to study attrition, confounding, and/or statistical analysis and reporting) was judged to be present in 8 studies. Designs showed wide variability with respect to characteristics of the included population, definition of CTS, assessment of prognostic factors, types of interventions provided, and types of outcome measures applied. This prevented pooled estimates from being produced.

Data Synthesis: A negative outcome at 3 years' follow-up of conservatively treated participants ranged from 23% to 89%. Four included studies observed the rate of surgical intervention after initial conservative management and found this to be 57% to 66%. Evidence regarding factors predicting the negative outcome of no treatment or conservative treatment was graded, taking into account the number of studies evaluating the factor, the methodological quality of these studies, and the consistency of the available evidence. There was 100% agreement in at least 3 cohorts with a medium or high risk of bias that symptom duration, a positive Phalen's test, and thenar wasting were associated with a negative outcome of conservative management; however, not all results were statistically significant, and hence the overall judgment remained inconclusive.

Conclusions: Results of this review should be treated with caution because of the heterogeneity of studies and the risks of bias identified. However, the course of CTS appears variable, and poor prognosis may be predicted by a longer symptom duration, a positive Phalen's test, and thenar wasting. Archives of Physical Medicine and Rehabilitation 2015;■:■■■-■■■

Carpal tunnel syndrome (CTS) is a chronic focal compressive neuropathy caused by the entrapment of the median nerve at the level of the carpal tunnel.[1] CTS is the most common of the entrapment neuropathies, accounting for 90% of presentations,[2] and is characterized by numbness, tingling, hand and arm pain, and muscle dysfunction.[3] Between 55% and 65% of CTS cases present bilaterally,[4] and the condition can be associated with hypothyroidism, diabetes, and rheumatoid arthritis, among others. CTS may present in late pregnancy but is usually transient.

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van der Windt is a member of PROGRESS Medical Research Council Prognosis Research Strategy (PROGRESS) Partnership (G0902393/99558).

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Studies in different countries have reported varying results with respect to the incidence of CTS.[5] A survey of the Skåne Health Care Register in Sweden by Atroshi et al[5] was age adjusted to the 2000 U.S. standard population to allow comparison with the results of a U.S.-based survey of the Rochester Epidemiology Project.[6] The estimated incidence of CTS in Sweden was reported as 324 per 100,000 in women compared with 542 per 100,000 in the United States, and in men, 166 per 100,000 in Sweden compared with 303 in the United States.[5,6] The explanation for variation between countries is unknown; however, suggested possibilities include differences in health care–seeking behavior and variation in etiologic factors including occupation, diabetes, and inflammatory joint disease.[5]

The treatment of CTS is often categorized as either surgical or conservative (nonsurgical). Surgical treatment is generally recommended for those with severe CTS (ie, evidence of denervation of the median nerve), while conservative treatments are recommended for the initial management of those who have intermittent or mild symptoms or in whom surgery is contraindicated.[7] The U.S. standardized annual incidence of carpal tunnel release surgery per 100,000 persons was 166 in Sweden compared with 171 in the United States and, among men, 58 in Sweden compared with 96 in the United States.[5,6] Examples of conservative treatment include oral steroids, steroid injections, physical therapy, electrotherapy, night splinting, and workplace alterations.[8] In United Kingdom primary care, steroid injections and night splinting form the mainstay of conservative treatment options, as indicated by national care pathways (eg, National Institute for Health and Care Excellence Clinical Knowledge Summaries).[9,10] Guidelines for the management of CTS by the American Association of Orthopaedic Surgeons[11] conclude that patients with more severe and prolonged CTS may not benefit from extended conservative treatment. However, the authors were unable to recommend in which patients conservative treatments were unlikely to be effective.[11]

Cochrane systematic reviews of conservative treatments for CTS[12] have included the assessment of local corticosteroid injections[13] and splinting.[7] With respect to splinting, the authors conclude that there is limited evidence that night splinting is more effective than no treatment in the short-term. They do, however, suggest that more research is needed on the long-term effects of this intervention.[7] With regard to steroid injections, it was concluded that robust evidence demonstrates clinical improvement up to 1 month compared with placebo, but relief beyond this period has not yet been shown.[13]

With ongoing clinical uncertainty regarding the most effective management strategy for CTS, there is a clear need for a greater understanding of the likely long-term course of CTS symptoms (overall prognosis) of the condition and patient factors that may be associated with outcome (prognostic factors).

Outcomes and predictors of surgical outcome have been well reported in the literature. However, few studies and no systematic reviews have been performed to summarize the evidence for prognosis and prognostic factors in conservatively managed disease—that is, that which can be delivered in a primary care environment. An estimate of average prognosis is required by public health policymakers in order for the population burden of a condition to be assessed. Understanding the future outcomes of patients with a particular condition in relation to current practice and even in the absence of clinical care (the natural history) is crucial because it allows the potential impact of interventions to be more fully assessed.[14] Such information is not only important when considering the potential benefits of interventions, but also in order to inform patients, clinicians, and policymakers of the potential harms, variations (such as underuse, overuse, misuse), and potential impact on health care efficiencies.[14]

This systematic review and narrative synthesis initially focuses on summarizing the prognosis research regarding the general course of CTS. The "start point" of this review will be the point of diagnosis of CTS that is being treated conservatively or with no clinical treatment. The "endpoint" will vary depending on the primary study. This synthesis therefore seeks to describe the course of CTS being managed either with no intervention or with conservative approaches.

The second part of this systematic review aims to identify predictors of long-term outcome (prognostic factors) in CTS. A prognostic factor is "any measure that, among people with a given health condition (start point), is associated with a subsequent clinical outcome (endpoint)."[15(p1)] Prognostic factor research thus seeks to identify the predictive value of such factors.

Research of prognostic factors aims to identify features that could potentially contribute to the development of prognostic models or represent predictors of differential treatment response, which may further contribute to a stratified care approach to a condition. Prognostic factors may also represent modifiable targets for interventions and could hence lead to the development of new management strategies through an improved understanding of disease mechanisms.[15]

List of abbreviations:

CTS carpal tunnel syndrome
QUIPS Quality in Prognosis Studies

Methods

Identification and selection of literature

Details of the protocol for this systematic review were registered on PROSPERO (CRD42013006608) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006608#.VYk_RflVhBc. Eligible publications had to report the course of CTS symptoms (persistence/recovery or severity of pain or other symptoms) and/or the association between a potential prognostic factor and outcome, as well as meeting the following eligibility criteria: (1) The study included adults (aged ≥18y) diagnosed with CTS in either a clinical setting or population setting. Studies in pregnant women and in populations such as specific occupational groups were excluded. (2) The study observed the course of CTS over at least a 6-week period in patients receiving no treatment or usual care that included conservative (nonsurgical) treatments. Studies reporting risk factors for onset of CTS as opposed to predictors of outcome were excluded, as were studies investigating predictors of the effectiveness of a specific treatment (which would ideally require a review of randomized controlled trials and is planned for the future). (3) The design was of a longitudinal cohort study with either prospective or retrospective data collection. (4) There were no language restrictions, and none of the research identified was only reported in abstract form.

A systematic computerized search of the literature was conducted in MEDLINE, Embase, AMED, HMIC, PsycINFO, CINAHL, Cochrane, SCI-EXPANDED, and CPCI-S from their inception until December 2013. The MEDLINE search strategy can be found in supplemental appendix S1 (available online only at http://www.archives-pmr.org/). References of all included full-text articles were hand-searched, and the first 15 pages of Google Scholar results for "carpal tunnel syndrome" and "prognosis" were screened as a further check for relevant hits. Experts were contacted to identify any further studies or publications in the gray literature that had not been identified in the search. The titles were screened by 1 reviewer (C.B.) and abstracts were screened by 2 reviewers (C.B., L.C.), and full articles of potentially eligible studies were retrieved. Such articles were screened by the 2 reviewers independently for eligibility and included in the review if they met the prespecified criteria.

Table 1 Levels of evidence for prognostic factors[17,18]

Level of Evidence	Definition
Strong	Consistent findings (≥75%) in at least 2 cohorts with a low risk of bias
Moderate	Consistent findings (≥75%) in 1 cohort with a low risk of bias and at least 1 cohort with a moderate/high risk of bias
Weak	Findings of 1 cohort with a low risk of bias or consistent findings (≥75%) in at least 3 cohorts with a moderate/high risk of bias
Inconclusive	Inconsistent findings irrespective of study quality, or less than 3 cohorts with a moderate/high risk of bias
No evidence	No data presented

Quality assessment

All selected studies were assessed independently for quality by 2 reviewers (C.B. and L.C.) using the Quality in Prognosis Studies (QUIPS) tool.[16] The QUIPS tool assesses bias in the following 6 domains: (1) study participation; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) study confounding; and (6) statistical analysis and reporting. Judgments of low, moderate, or high risk of bias were made for each applicable domain using descriptors recommended by Hayden et al.[16] Summated scores for overall study quality are not generally recommended; however, assessment of the overall risk of bias is suggested to be useful when synthesizing existing evidence.[16] With the use of suggestions from Hayden,[16] studies were judged to be of low overall risk of bias if all or most of the domains were judged as low risk, and studies in which all or most of the domains were judged as high risk were considered to be of high overall risk of bias. Studies with a moderate risk of bias were those with all or most of the domains being judged as moderate risk. Differences between reviewers were discussed, and a decision was made by agreement. Agreement between reviewers (C.B., L.C.) regarding the judgment of overall risk of bias was presented as a percentage of agreement.

Data extraction

Data were extracted by 1 reviewer (C.B.) and checked by another reviewer (L.C.). Data extraction included details of the study setting, population demographics, diagnostic criteria of CTS used, management approaches used, prognostic factors (type of factors and how measured), outcome measures (definition and instrument used), sample size, rate of attrition, and length of follow-up. With regard to clinical course, the percentage of patients with a negative outcome after conservative treatment or no treatment was recorded. All reported prognostic factors were listed and measures of association with their significance levels recorded.

Analysis

Results regarding the course of symptoms in patients with untreated and conservatively treated CTS were summarized narratively. Pooling of results was not possible because of heterogeneity with regard to study setting, case definition, follow-up periods, and measures of outcome. We summarized findings for the reported prognostic factors by taking into account the number of studies evaluating the factor, the risk of bias of these studies, and the consistency of the available evidence (as defined as significant association with the same direction). A level of evidence was defined for each factor, based on Sackett[17] and Ariens[18] and colleagues, and adapted for use with the QUIPS tool (table 1).

Results

Selection of studies

Figure 1 presents a flow chart of study selection. A total of 15,572 citations were identified (6987 MEDLINE, 6445 Embase, 197 AMED, 19 HMIC, 92 PsycINFO, 707 CINAHL, 755 Cochrane, 370 SCI-EXPANDED and CPCI-S). After the removal of duplicates and a screen of the titles, 146 abstracts were screened and 42 full-text publications retrieved for further eligibility screening. Twenty-six articles were excluded for the following reasons: 1 foreign language duplicate was found; 3 studies reported conditions not specific to CTS (ie, wrist pain or unspecified entrapment neuropathies); 6 studies reported outcomes in a specific population; 4 studies reported the etiology of CTS only; 6 studies reported on outcomes of specific treatments; and 6 studies used a design other than that described in the selection criteria. Sixteen articles (reporting on 16 cohorts) met all eligibility criteria and were included in the review.

Study characteristics

Table 2 summarizes the characteristics of the studies including the QUIPS score, study design and setting, study population, interventions used in the study, the primary outcome measure including the definition of a negative outcome, and the duration of follow-up. The table also presents the percentage of the cohort experiencing a negative outcome (eg, surgery) of conservative or no management.

One study[19] was a retrospective follow-up study of cases identified in the Marshfield Epidemiologic Study Area, a population-based cohort. All other studies were based in secondary or tertiary care, of which 6 were in surgical clinics and 8 in electromyography laboratories. No studies were based in

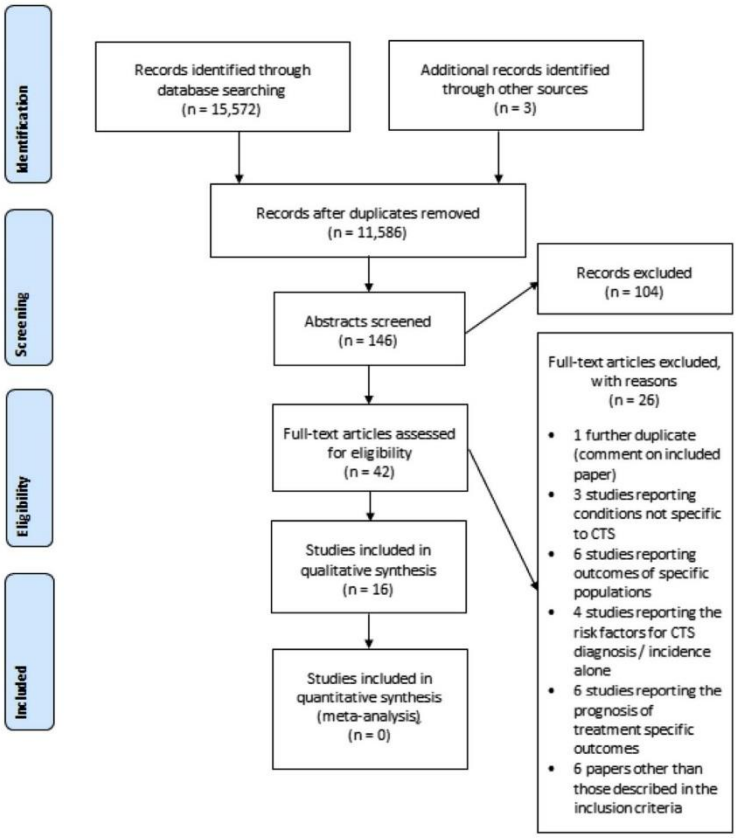

Fig 1 Study selection.

primary care. The case definitions used to identify CTS differed: 6 studies used clinical features only, while the remaining 10 studies required accompanying electrophysiological abnormalities. The combination of clinical characteristics used and the electrophysiological criteria also varied between studies. The interventions used in the studies included wrist splinting (7 studies), nonsteroidal anti-inflammatory drugs (3 studies), other analgesia (2 studies), oral steroids (3 studies), local steroid injections (6 studies), and paraffin treatment (1 study). Three studies provided conservative management without specifying which mode exactly. In 4 studies,[20-23] the course of (clinically) untreated CTS was observed. In some studies, parts of the cohort were treated surgically. Their specific outcomes were not included in this review. A range of outcome measures were used: 3 studies used a surgical episode as a proxy for a negative outcome; 1 study used the shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH) score; 5 used measures of global improvement; 2 used a change in symptom and function severity scores; 1 used the Historic and Objective Scale[24]; 1 used work absence; 2 observed electrophysiological changes; and 1 used absence of clinical contact as an indicator of recovery. The follow-up periods ranged from 12 weeks to 10 years.

Methodological quality

The results of the quality assessment are presented in table 3. In 4 studies that investigated the course of CTS symptoms only, the prognostic factor domain was not assessed. The percentage agreement between the authors (C.B., L.C.) with regard to judgment of the overall risk of bias was 75%, and 100% after discussion. Further adjudication was therefore not required.

Eight studies were judged to have a moderate risk of bias and 8 to have a high risk of bias. The domains that carried a particularly high risk of bias across all studies were study attrition (12 studies), study confounding (10 studies), and statistical analysis and reporting (9 studies). Study attrition tended to be at high risk of bias because the response rates in several studies were low (see table 3), attempts to collect information on participants who dropped out were often lacking, reasons for loss to follow-up were rarely provided, and differences between those lost to follow-up

Table 2 Summary of study characteristics and results regarding the course of symptoms of prognostic cohort studies in CTS

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Treated Populations: Prospective Cohort Studies						
Boyd et al,[33] 2005, Canada	High	Setting: tertiary hand and upper limb center CTS diagnosis: clinical findings and electrophysiological abnormality 68% female Mean age: 49.3y N=25 patients (47 wrists) Dropout: 17%	Splint: all wrists Surgery: 27 (57%) wrists	No surgery vs surgery by 6mo 12wk, with an option to continue follow-up >6mo	Progression to surgery	57% of wrists
Duckworth et al,[34] 2013, Scotland	Moderate	Setting: hand clinic CTS diagnosis: clinical findings and electrophysiological abnormality 67% female Mean age ± SD: males 57±14y; females 54±14y N=275 patients Dropout: 28%	Splint: all patients Injection: 150 (55%) (of whom 38 had surgery) Surgery: 122 (44%) patients No further treatment: 3 (1%) patients	*Quick*DASH score 1y	Progression to surgery	58% of patients
Goodwill,[31] 1965, England	High	Setting: electromyography laboratory CTS diagnosis: paresthesia and pain with electrophysiological abnormality 93% female Age bands: 30–39y: n=7 patients 40–49y: n=19 50–59y: n=39 60–69y: n=18 ≥70y: n=13 N=96 patients (155 wrists) Dropout: 0%	Splint: 98 (63%) wrists Injection: 58 (37%) wrists Surgery: 55 (35%) wrists	Judgment made at follow-up: cured, temporary relief, or no relief 1–3y (average 14mo)	Evidence of symptoms	After steroid injection: 88% of patients After splinting: 89% of patients After surgery: 5% of patients

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Kaplan et al,[27] 1990, United States	High	Setting: hand clinic CTS diagnosis: presence of pain or paresthesia and clinical findings (thenar atrophy, altered sensation, or Phalen's sign) 75% female Mean age: 55y N=229 patients (331 wrists) Dropout: 12%	Splint: "most patients" Nonsteroidal anti-inflammatory drugs: 149 (65.2%) patients Oral steroid: 61 (26.8%) patients Steroid injection: 38 (16.4%) patients	Success of therapy as defined by absence of symptoms for >6mo Minimum of 6mo or until had surgical release (average 15.4mo)	Evidence of symptoms after 6mo Progression to surgery	82% of wrists 66% of wrists
Katz et al,[30] 1998, United States	Moderate	Setting: surgical clinics CTS diagnosis: paresthesia involving at least 2 digits (thumb or index, middle or ring fingers) and symptom duration of at least 1mo 74% female Surgical cohort: >55y mean age ± SD, 68.0±9.1y; <55y compensation nonrecipient mean age ± SD 42.0±7.3y; compensation recipient mean age ± SD, 39.0±8.1y. Nonsurgical cohort >55y mean age ± SD, 64.0±7.0y; compensation nonrecipient mean age ± SD, 41.0±8.9y; compensation recipient mean age ± SD, 37.0±8.8y N=297 patients Dropout: 31%	Nonsurgical cohort: 34 patients received surgery at <3mo and were not included in analyses. By 30mo: Splint: 76 (94%) patients Injection: 36 (44%) patients Physical or occupational therapy: all	Change in status in symptom severity, functional limitations, and health status were recorded over time. Associations were measured for patients crossing between nonsurgical and surgical cohorts after >3mo. Follow-up took place at 6, 18, and 30mo	Would not be happy to live the rest of their lives with symptoms	60% of patients

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Kiylioglu et al,[26] 2009, Turkey	Moderate	Setting: electromyography laboratory CTS diagnosis: clinical findings, supported by electrophysiological abnormality 90% female Diabetic rehabilitation group mean age ± SD, 59.3±7.4y; diabetic untreated group mean age ± SD, 54.6±11.1y; idiopathic rehabilitation group mean age ± SD, 47.8±9.9y; idiopathic surgery group mean age ± SD, 49.2±9.8y N=42 patients (80 wrists) Dropout: 0 (assumed)	Treatment methods not controlled or standardized "Rehabilitation": patients treated with splints, paraffin treatments, and/or oral nonsteroidal anti-inflammatories	Symptom severity score and functional status (Boston questionnaire translated into Turkish) Patients were followed up in the early follow-up period (3–5mo) and late follow-up period (6–12mo).	Percentage improvement in symptom severity scale Percentage improvement in function severity scale	Rehabilitation 82% Surgery 77% Untreated 25% Rehabilitation 73% Surgery 85% Untreated 17%
Treated Populations: Retrospective Cohort Studies						
Kouyoumdjian et al,[32] 2003, Brazil	High	Setting: electromyography laboratory CTS diagnosis: symptoms including hand paresthesia, numbness, and pain mainly at night. 95.8% female Surgical cure group mean age 46y (range, 24–70); unchanged/worse group 44y (range, 39–58y); nonsurgical cure group mean age 61y (range, 48–79y); worse group mean age 50y (range, 30–83y) N=165 patients (222 wrists) Dropout: 69%	Surgery: 147 (66%) wrists Nonsurgical (splint, local injection, medication, and others): 75 (34%) wrists	General patient satisfaction: complete relief; improved "much better"; improved "little"; unchanged; worsened Poorly recorded. Between 5 and 10y (mean, 5.9y after surgery)	Symptoms unchanged or worse	23.7% of wrists

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Lian et al,[25] 2006, Singapore	High	Setting: electromyography laboratory CTS diagnosis: clinical history and examination, confirmed using American Association of Electrodiagnostic Medicine criteria and additional testing if this was normal 81.3% female Mean age: 53.6y N=115 Dropout: 14%	Conservative management: 88 (77%) patients Surgery: 27 (23%) patients	Clinician review of medical records and decision made as to category: resolved; improved; same; worse Follow-up took place at 3 and 6mo (limited data available)	Symptoms unchanged or worse	68.5% of patients
Miranda et al,[35] 2013, United Kingdom	High	Setting: plastic surgery clinic CTS diagnosis: based on clinical symptoms Sex not reported Mean age ± SD: 56±3y N=134 Dropout 10%	Injection: 66 (49%) patients Surgery: 68 (51%) patients	Symptom relief and/or surgery 22.5±0.5mo	Progression to surgery	62% of patients
Muhlau et al,[28] 1984, Germany	Moderate	Setting: electromyography laboratory CTS diagnosis: distal motor latency was >4.7ms Sex and age not reported N=157 (214 wrists) Dropout: 38%	Conservative management: 72 (48%) wrists Surgery: 112 (52%) wrists	An overall categorization was made at follow-up: cured; clear improvement; slight improvement; unchanged findings; further deterioration. These were then dichotomized so that groups 1 and 2 = cured, and 3, 4, and 5 = not cured. Follow-up was at least 2y and defined as when the patient had reached a "steady state."	No evidence of cure	68% of patients

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Treated Populations: Retrospective Follow-Up Study of a Population-Based Case Series						
DeStefano et al,[19] 1997, United States	Moderate	Setting: patients identified from the Marshfield Epidemiologic Study Area CTS diagnosis: ICD-9-CM code 354.0 and evidence of a clinical and/or electrophysiological abnormality in the records. 62% female Mean age: 62y N=425 Dropout: 0%	Analgesia: 143 (34%) patients Nonsteroidal anti-inflammatories: 132 (31%) patients Injection: 6 (1%) patients Splint: 295 (69%) patients Surgery: 198 (47%) patients	No surgery vs surgery and resolution of symptoms Median follow- up 1979–1983: 12.0y (5th and 95th percentiles: 10.0 and 14.8y, respectively). 1984–1988: 7.3y (5.0–9.8y)	Evidence of symptoms	1mo: 75% of patients 2y: 40% 8y: 22%
Treated Populations: Secondary Analysis of Katz et al,[30] 1998						
Katz et al,[29] 1998, United States	Moderate	Setting: surgical clinics CTS diagnosis: paresthesia involving at least 2 digits (thumb or index, middle or ring fingers) and symptom duration of at least 1mo 72% female Mean age ± SD: 43±11y N=253 patients Dropout: 20%	Surgery: 179 (71%) patients	Out of work at 18mo Questionnaires were completed at 6, 18, and 30mo.	Work absence at 18mo due to CTS	23% of patients
Untreated Populations: Prospective Cohort Studies						
Ortiz-Corredor et al,[22] 2008, Columbia	High	Setting: electromyography laboratory CTS diagnosis: as per Rempel et al,[36] 1998 81.1% female Mean age ± SD: 48.8±10.2y N=132 patients Not possible to determine dropout	The course of untreated CTS was observed.	The Historic and Objective Scale was used as the clinical classification. The electrophysiological classification was according to Padua et al,[37] 1997 (mild; moderate A; moderate B; severe; extreme) 24.2±4.2mo	Deterioration in the Historic and Objective Scale	23.4% of patients

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Padua et al,[20] 1998, Italy	Moderate	Setting: electromyography laboratory CTS diagnosis: based on neurophysiological evaluation graded: negative, minimal, mild, moderate, severe, and extreme (Padua et al[20]) 78.8% female Mean age ± SD: 48.8±10.2y N=80 Dropout: 84%	The course of untreated CTS was observed.	Patient-reported global improvement scale: stable, worse, improved Neurophysiological classification: negative, minimal, mild, moderate, severe, extreme 11.6mo (range, 5–23)	Clinical outcome: unchanged Clinical outcome: worse	Neurophysiological classification Negative 50% Minimal 38% Mild 15% Moderate 27.5% Severe 0% Extreme 50% Negative 50% Minimal 31% Mild 58% Moderate 45% Severe 20% Extreme 0%
Padua et al,[21] 2001, Italy	Moderate	Setting: electromyography laboratory CTS diagnosis: based on clinical diagnostic criteria proposed by the American Academy of Neurology and the American Association of Electrodiagnostic Medicine 82% female Mean age ± SD: 52.0±13.4y N=202 (267 wrists) with a further 62 (87 wrists) reevaluated by telephone Dropout: 34%	The course of untreated CTS was observed.	Electrophysiological changes, patient-reported changes, and clinical changes were used to describe if patients had improved, remained stationary, or worsened. 10–15mo	Neurophysiologic class Symptoms Function Historic and Objective Scale Pain	Stationary 57% Worsening 16% Stationary 45% Worsening 21% Stationary 61% Worsening 16% Stationary 46% Worsening 32% Stationary 62% Worsening 12%

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Table 2 (*continued*)

Author, Year, Location	Risk of Bias (QUIPS Score)	Study Population	Interventions Provided to Entire Cohort	Primary Outcome Measure/ Duration of Follow-Up	Measure of Negative Outcome of Conservative Management	Proportion of Patients Treated Conservatively Experiencing Negative Outcome
Untreated Populations: Retrospective Cohort Studies						
Resende et al,[23] 2003, Brazil	High	Setting: electromyography laboratory CTS diagnosis: clinical findings, supported by electrophysiological abnormality N=12 Dropout not possible to determine	The course of untreated CTS was observed.	Clinical and electrophysiological changes were observed. 4–9y	Conduction studies	Marked improvement 25% (of which 100% had improvement in symptoms) Slight improvement 15% (of which 33% had worsening of clinical symptoms) No significant change 50% (of which 50% had worsening of clinical symptoms) Worsening 10% (of which 50% had worsening of clinical symptoms)

NOTE. Compensation recipient and nonrecipient indicates that the patient received compensation or did not receive compensation, respectively, following litigation proceedings.
Abbreviations: ICD-9-CM, *International Classification of Diseases–9th Revision–Clinical Modifications*; QuickDASH, shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire.

Table 3 Results of methodological assessment of prognostic cohort studies on CTS

Author, Year	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Studies Including an Analysis of Prognostic Factors							
Boyd et al,[33] 2005	High	High	Moderate	Moderate	Moderate	High	High
DeStefano et al,[19] 1997	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Duckworth et al,[34] 2013	Moderate	High	Moderate	Moderate	High	Low	Moderate
Goodwill,[31] 1965	High	High	High	High	High	High	High
Kaplan et al,[27] 1990	High	High	High	High	High	High	High
Katz et al,[30] 1998	Low	Moderate	Moderate	Moderate	Low	High	Moderate
Katz et al,[29] 1998	Low	High	Moderate	Low	High	Low	Moderate
Kiylioglu et al,[26] 2009	Moderate	High	Moderate	Moderate	Moderate	High	Moderate
Kouyoumdjian et al,[32] 2003	Moderate	High	Moderate	Moderate	High	High	High
Muhlau et al,[28] 1984	Moderate	High	Low	Moderate	Moderate	Low	Moderate
Padua et al,[21] 2001	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Studies Observing the Course of CTS Only (With No Analysis of Prognostic Factors)							
Lian et al,[25] 2006	High	High	NA	High	High	High	High
Miranda et al,[35] 2013	High	High	NA	High	High	High	High
Ortiz-Corredor et al,[22] 2008	Moderate	Moderate	NA	Low	High	High	High
Padua et al,[20] 1998	High	High	NA	Low	High	Low	Moderate
Resende et al,[23] 2003	High	High	NA	High	High	Moderate	High

Abbreviation: NA, not applicable.

and those actively followed up were not frequently compared. Study confounding was also a frequent finding largely because not all potential confounders were appropriately accounted for, and hence the observed associations of the potential prognostic factors with outcome were likely to be at least partly explained by other (unmeasured) factors. This was particularly true in studies using retrospectively collected data. Statistical analysis and reporting was commonly identified as being of high risk of bias because presentation of the data was frequently insufficient, and in some studies selective reporting of results was evident.

Course of CTS

For each included study, table 2 describes results regarding the course of CTS in conservatively treated or untreated patients by describing the proportion of patients who experience a negative outcome, the definition of which varied between studies (ie, persisting or worsening symptoms, progression to surgery, or work absence because of CTS). Table 4 further summarizes results regarding the course of CTS in terms of the percentage of patients reporting a negative outcome for different follow-up time points.

Table 4 Course of CTS in conservatively treated or untreated patients

		% of Cases Reporting Deterioration Within:				
No. of Studies	Sample Size Range	3mo	6mo	12mo	3y	15y
Untreated cases						
4[20-23]	12–344	NA	NA	32–58	23.4	50
Studies observing cases receiving surgery as a consequence of conservative management failure (% of patients receiving surgery NOT outcome of surgery)						
4[27,33-35]	47–331	NA	57	58	62–66	NA
Studies of conservatively managed patients reporting other definitions of negative outcome						
9[19,25-32]	80–425	68.5–75	82	% improvement of up to 82%*	23–89	22–23.7

NOTE. The percentages shown are not cumulative, since it cannot be assumsed that patients reporting a change in symptoms at 6 months would not have reported something different at an earlier or later date if the study had provided them with such opportunity.
Abbreviation: NA, not applicable.
* Percent change provided in positive direction.[26]

Four studies examined the course of untreated CTS.[20-23] Ortiz-Corredor et al[22] observed that of 132 patients with untreated CTS over a 2-year period, 23.5% showed a deterioration in the Historic and Objective Scale score, but most cases did not show an electrophysiological deterioration (89 remained the same, 33 recovered, and 10 deteriorated). Only 1 patient had both an electrophysiological and clinical deterioration. Padua et al[20] reported whether the clinical outcome was unchanged or worse in groups of patients with different electrophysiological classifications. They found the clinical outcome was worse in 50% of patients with negative electrophysiology, 27.5% with moderate studies, and 50% with extreme studies. Padua et al[21] further observed the electrophysiological, symptomatic, functional, Historic and Objective Scale, and pain changes in patients with CTS. They reported that 16%, 21%, 16%, 32%, and 12% of patients in each of these outcome areas worsened, while 27%, 34%, 23%, 23%, and 26% of patients improved. Resende et al[23] presented the change in electrophysiological measures and accompanying change in symptoms over a 4- to 9-year period and found that 25% of patients had a marked improvement in electrophysiological outcome (100% of whom had improvement in terms of symptoms); 15% showed slight improvement (of whom 33% had worsening of symptoms); 50% showed no significant change (of whom 50% had worsening in terms of symptoms); and 10% had a worsening of electrophysiological measurements (of whom 50% had a worsening of clinical symptoms).

In summary, 32% to 58% of participants receiving no treatment were reported to have a negative outcome at 12 months' follow-up in 2 studies,[20,21] both of which were of moderate risk of bias. The 2 further studies reporting at 3 and 10 years were at high risk of bias and reported a negative outcome in 23.4%[22] and 50%[23] of participants.

In the 9 cohorts receiving conservative treatment, 68.5% to 75% of patients were reported to have a negative outcome within 3 months' follow-up[25,26]; 82% within 6 months[27]; 23% to 89% within 3 years[19,28-31]; and 22% to 24% within 10 years.[28,32] A wide variation in findings was noted according to risk of bias, with studies of a moderate risk of bias appearing to show lower percentages of patients with a negative outcome (eg, 23%–68% at 3y[19,28-30]), compared with studies of high risk of bias (82% at 6mo[27] and 89% at 3y[31]). Four studies[27,33-35] used a surgical episode as a marker of negative outcome of conservative management. A range of 57% to 66% of patients were observed to receive surgery after conservative management over a period of 1 to 3 years.[27,33-35]

In summary, the reported course of conservatively managed CTS is highly variable, but symptoms do improve over time.

Prognostic factors predicting negative outcome of CTS

Eleven of the studies presented data on the association between potential prognostic factors and a negative outcome of conservatively managed CTS. Table 5 presents potential prognostic factors observed in the studies and reported associations. Not all studies presented estimates of associations with confidence intervals. Some presented *P* values only; some simply reported a finding as nonsignificant. Therefore, the number of studies investigating each association, the number of studies of moderate or high risk of bias (none were of low risk), and the number showing an association (direction and significance) are summarized.

In total, 39 potential prognostic factors were identified from the studies. All of these were found to have inconclusive levels of evidence of an association with a negative outcome. This was due to inconsistencies in study findings, nonsignificant results, low numbers of studies investigating each factor, and the moderate to high risk of bias of the studies included.

Discussion

This study is the first systematic review of the prognosis of conservatively managed CTS. A substantial amount of heterogeneity exists in terms of study setting, case definition, follow-up periods, and measures of outcome between the included studies, which prevented a meta-analysis from being conducted. A best-evidence synthesis was therefore presented.

Course of CTS

Four studies[20-23] observed the course of untreated CTS, which is helpful when considering the need for or impact of treatment. These studies suggest that a proportion (28%–62%)[20-23] of patients will recover or not deteriorate further in the absence of treatment, and hence a certain period of "watchful waiting" (not clearly defined by the available evidence) may be considered clinically when discussing treatment options with patients. When considering potential mechanisms for recovery (not including mechanisms of treatment) Padua[20] suggests that certain undefined

Table 5 Prognostic factors and strength of association for an unfavorable outcome of CTS in patients who are conservatively treated or untreated

Prognostic Factor	Direction of Association and Significance	Risk of Bias (No. of Studies)	No. and % of Studies Demonstrating Predictive Association With a Negative Outcome (Statistically Significant)	Level of Evidence
Demographic characteristics				
Female sex	+*,[34]	Moderate (5)	2/6: 33%	Inconclusive
	+[19]	High (1)	(1/6: 17%)	
	0[28-30]			
	0[27]			
Increasing age (group not otherwise specified or >50y)	+*,[21,29]	Moderate (7)	3/10: 30%	Inconclusive
	0[28,30]		(3/10: 30%)	
	−*,[19,26,34]			
	+*,[27]	High (3)		
	−*,[33]			
	−[32]			
Obesity	+[19]	Moderate (2)	1/2: 50%	Inconclusive
	−*,[26]		(0/2: 0%)	
Litigation	+*,[29]	Moderate (3)	1/3: 33%	Inconclusive
	0[28,30]		(1/3: 33%)	
Deprivation quintile	−[34]	Moderate (1)	0/1: 0%	Inconclusive
Vibration tool use	−[34]	Moderate (1)	0/1: 0%	Inconclusive
Occupation status	+*,[29]	Moderate (1)	(1/1: 100%)	Inconclusive
Smoking	+[34]	Moderate (1)	1/1: 100%	Inconclusive
			(0/1: 0%)	
Comorbidity				
Diabetes	+*,[26]	Moderate (1)	(1/1: 100%)	Inconclusive
Diabetes or hypothyroid	+[19]	Moderate (1)	1/1: 100%	Inconclusive
			(0/1: 0%)	
Pregnancy or injury-associated CTS	−[19]	Moderate (1)	0/1: 0%	Inconclusive
Arthritis	+[19]	Moderate (1)	1/1: 100%	Inconclusive
			(0/1: 0%)	
Previous fracture or sprain	0[27]	High (1)	0/1: 0%	Inconclusive
Stenosing flexor tenosynovitis	+*,[27]	High (1)	(1/1: 100%)	Inconclusive
Mental health status	+*,[29]	Moderate (1)	(1/1: 100%)	Inconclusive
Disease characteristics				
Tinel's sign positive	+[34]	Moderate (1)	1/1: 100%	Inconclusive
			(0/1: 0%)	
Phalen's sign positive	+*,[21]	Moderate (2)	3/3: 100%	Inconclusive
	+[34]	High (1)	(2/3: 67%)	
	+*,[27]			
Thenar wasting	+*,[28]	Moderate (2)	3/3: 100%	Inconclusive
	+[34]	High (1)	(2/3: 67%)	
	+*,[27]			
Paresthesia	+*,[27]	High (1)	(1/1: 100%)	Inconclusive
Abnormal 2-point discrimination	0[30]	Moderate (1)	1/2: 50%	Inconclusive
	+*,[27]	High (1)	(1/2: 50%)	
Semmes-Weinstein monofilament testing	0[30]	Moderate	0/1: 0%	Inconclusive
Electrophysiological severity	+[34]	Moderate (3)	2/5: 40%	Inconclusive
	0[26]	High (2)	(0/5: 0%)	
	−*,[21]			
	+[31]			
	−[32]			
Symptom severity	−*,[26]	Moderate (2)	1/3: 33%	Inconclusive
	−*,[21]	High (1)	(1/3: 33%)	
	+*,[33]			

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Table 5 (*continued*)

Prognostic Factor	Direction of Association and Significance	Risk of Bias (No. of Studies)	No. and % of Studies Demonstrating Predictive Association With a Negative Outcome (Statistically Significant)	Level of Evidence
Functional severity	+*,[29] −*,[21,26] 0[33]	Moderate (3) High (1)	1/4: 25% (1/4: 25%)	Inconclusive
CTS category of severity[19]	+*,[19]	Moderate (1)	(1/1: 100%)	Inconclusive
Sensory SF-MPQ	+[34]	Moderate (1)	1/1: 100% (0/1: 0%)	Inconclusive
Affective SF-MPQ	+[34]	Moderate (1)	1/1: 100% (0/1: 0%)	Inconclusive
SF-36	0[33]	High (1)	0/1: 0%	Inconclusive
DASH	0[33]	High (1)	0/1: 0%	Inconclusive
Hi-Ob	−*,[21]	Moderate (1)	0/1: 0%	Inconclusive
Visual analog scale	+[34]	Moderate (1)	1/1: 100% (0/1: 0%)	Inconclusive
Laterality: left only	−[19]	Moderate (1)	0/1: 0%	Inconclusive
Laterality: right only	−*,[19]	Moderate (1)	0/1: 0%	Inconclusive
Laterality: left > right	−[19]	Moderate (1)	0/1: 0%	Inconclusive
Laterality: right > left	−[19]	Moderate (1)	0/1: 0%	Inconclusive
Bilateral	+*,[21] +[34] 0[27]	Moderate (2) High (1)	2/3: 67% (1/3: 33%)	Inconclusive
Grip strength	0[30] −[34]	Moderate (2)	0/2: 0%	Inconclusive
Hand stress	−*,[21]	Moderate (1)	0/1: 0%	Inconclusive
Increasing symptom duration	+*,[28,21] +[26] +*,[27] +[32]	Moderate (3) High (2)	5/5: 100% (3/5: 60%)	Inconclusive

NOTE. 0, not significant and direction not provided; +, predictive of a negative outcome; −, not predictive of a negative outcome.
Abbreviations: DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; Hi-Ob, Historical and Objective Scale; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SF-MPQ, Short-Form McGill Pain Questionnaire.
* Statistically significant.

CTS cases are self-limiting because of a process of neural adaptation, whereby the functional relationship between the nerve and the carpal tunnel adapts over time.

Because of outcomes being measured at discrete time points by each study, it was not possible to provide a cumulative percentage of patients recovering in each period and thus provide clearer information about what is happening to patients with CTS over time. Table 4 does, however, show that a proportion of patients can be observed to have deteriorated from baseline at any point between 3 months and 10 years, suggesting that the course of CTS is likely to be highly variable. It is possible that the studies with longer follow-up periods are representative of patients who improve and relapse over time, but since none of the studies were designed to observe the longitudinal course of CTS (ie, at a week-to-week or month-to-month level), such a symptom course could not be illustrated by this review.

With regard to symptom relapse, only 1 study[31] specifically addressed this issue. Goodwill[31] reported that 85% of patients initially responding to conservative treatment approaches relapsed within 1 to 4 years. The possibility of future relapse therefore puts into question the observations of all studies conducted over a shorter time frame. A further consideration is that a recurrence of symptoms after a conservative treatment that then responds to a further episode of conservative management (if deemed clinically appropriate) may not necessarily represent treatment failure. However, longitudinal data that may describe this phenomenon were not available, again emphasizing the importance of long-term studies with repeated assessment of symptoms in patients with CTS.

The observed between-study variability may be partially explained by substantial differences in study setting, study design, case definitions, interventions (the effectiveness of which cannot be compared between studies), and outcomes used, but possibly also by differences in patient or disease factors (potential prognostic factors) between studies.

Prognostic factors predicting negative outcome of conservatively managed CTS

Because of inconsistencies between study findings and the lack of studies with a low risk of bias, it was not possible to identify conclusive evidence for any of the factors reported by individual studies to predict a negative outcome of conservative management. There was, however, 100% agreement in at least 3 or more

cohorts with a medium or high risk of bias that symptom duration, a positive Phalen's test, and thenar wasting were associated with a negative outcome of conservative management. However, not all results were statistically significant, and hence the overall judgment remained inconclusive.

Because of a lack of robustness in design and conduct of most of the included studies, the overall body of evidence identified was felt to be of moderate and high risk of bias. This limited whether the synthesized evidence could be considered as conclusive, and as such, evidence regarding the prognosis of untreated and conservatively treated CTS remains weak. To improve future research, key recommendations would include identifying patients with CTS at baseline using a robust case definition of the condition. Patients should be followed up for a prolonged period (>3y), preferably at a number of time points using a clinically meaningful, valid, and reliable outcome measure. This would allow a longitudinal picture of CTS to be mapped. Attempts could be made to reduce attrition or better describe the risk of attrition bias by collecting information from nonresponders and to provide a description and reason for any loss to follow-up. Ideally, all potential prognostic factors should be included and measured at baseline using valid and reliable measures.[16]

To capture the start point of the condition and its earliest management, it would be beneficial to set such a study in primary care, where it is likely most patients present initially with their symptoms and commence treatment.

Study limitations

We searched electronic databases considered to be important and relevant to the topic. Titles were screened by 1 person because of the significant number; therefore human error may have led to some titles being missed. Studies not included in databases and not identified through reference checking, Google Scholar, and expert advice may have been overlooked, such as unpublished cohort studies. Because the review did not find strong evidence for any of the prognostic factors, it is unlikely that further unpublished material would have strongly influenced our conclusions. The review focused on studies observing the course of symptoms in patients being treated conservatively for CTS but excluded cohorts being allocated specific treatments. Predictors of differential treatment response (moderators) are best identified by randomized trials, and therefore a further systematic review of these studies is planned.

Results of studies presenting only descriptive results and *P* values were included in the review without any risk estimates. All evidence found could therefore be included, but there is a possibility that the lack of statistical significance was due to small sample sizes and hence represent a lack of evidence for some of the prognostic factors rather than a genuine absence of association. Future prognosis research in the area of CTS should therefore ensure that estimates of associations with outcome are adequately reported and that the study population is of adequate sample size to investigate the hypothesized associations with outcome.

The unit of analysis differed between studies; that is, some analyzed outcomes at the patient level (not necessarily taking into account the laterality of the condition), while others analyzed outcomes at the wrist level (ie, patients with bilateral symptoms may be included as 2 cases, not taking dependence of outcomes within individuals into account). Issues relating to the statistical analysis of bilateral CTS have been discussed at length for clinical trials by Page et al.[38] A unit-of-analysis error, which may give rise to overly narrow confidence intervals and small *P* values, may occur when data are analyzed on the basis of the number of wrists without adjustment for nonindependence.[38] Such an error may also occur in prognosis research, including the reviewed studies, and be a further source of bias. Future prognostic studies should, where possible, take into consideration this risk of bias in their design and analysis plan.

Implications for clinical practice

Patients presenting with CTS can be informed of the possibility of recovery with no treatment or conservative treatment (ie, that they will not require surgery); however, factors that help to predict their likelihood of falling into this group have not been robustly determined. Increasing symptom duration, a positive Phalen's test, and thenar atrophy are likely to be prognostic factors of poor outcome of conservatively managed CTS but need confirmation in further well-designed prognostic studies. The review did not identify electrophysiological severity as a significant predictor of a negative outcome of conservative management. This may have implications for services that ration surgery to patients with more severe results and suggests that other factors should be taken into consideration alongside laboratory investigations.

Conclusions

In this review, we found useful descriptions of both the course of untreated CTS and that of conservatively managed CTS. Although none of the studies were of low risk of bias, studies of moderate and high risk of bias showed a widely ranging course of symptoms, with 23% to 89% of participants reporting a negative outcome at 3 years' follow-up. We found no consistent evidence to support factors that predict future outcome and that help to explain the wide variability in the course of symptoms.

There is likely to be an optimum time by which conservative management should be deemed to have failed and surgical intervention considered in order to prevent long-term harm, although this point has not been clearly determined, nor is it clearly possible to predict which patients may be included in this group.

Keywords

Carpal tunnel syndrome; Disease management; Prognosis; Rehabilitation

Corresponding author

Claire L. Burton, MBChB, MMedSci, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University, Keele, Staffordshire ST5 5BG, UK. *E-mail address:* c.burton@keele.ac.uk.

References

1. Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. Neurol Sci 2010; 31:243-52.

2. Aroori S, Spence RA. Carpal tunnel syndrome. Ulster Med J 2008;77:6-17.
3. Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal tunnel syndrome: a review of the recent literature. Open Orthop J 2012;6:69-76.
4. Bland JD, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991–2001. J Neurol Neurosurg Psychiatry 2003;74:1674-9.
5. Atroshi I, Englund M, Turkiewicz A, Tägil M, Petersson IF. Incidence of physician-diagnosed carpal tunnel syndrome in the general population. Arch Intern Med 2011;171:943-5.
6. Gelfman R, Melton LJ III, Yawn BP, Wollan PC, Amadio PC, Stevens JC. Long-term trends in carpal tunnel syndrome. Neurology 2009;72:33-41.
7. Page MJ, Massy-Westropp N, O'Connor D, Pitt V. Splinting for carpal tunnel syndrome. Cochrane Database Syst Rev 2012;7:CD010003.
8. Huisstede BM, Hoogvliet P, Randsdorp MS, Glerum S, van Middelkoop M, Koes BW. Carpal tunnel syndrome. Part I: effectiveness of nonsurgical treatments—a systematic review. Arch Phys Med Rehabil 2010;91(7):981-1004.
9. National Institute for Health and Care Excellence. Carpal tunnel syndrome. 2012. Available at: http://cks.nice.org.uk/carpal-tunnel-syndrome#!scenariorecommendation:1. Accessed April 10, 2014.
10. NHS: Institute for Innovation and Improvement. Carpal Tunnel Syndrome (CTS) - The Map of Medicine. 2012. Available at: http://app.mapofmedicine.com/mom/127/page.html?department-id=8&specialty-id=1037&pathway-id=3411&page-id=8741&history=clear. Accessed October 25, 2012.
11. American Academy of Orthopaedic Surgeons. AAOS guideline on the treatment of carpal tunnel syndrome: 2011 report for the "re-issue" of the original guideline 2011. Available at: http://www.aaos.org/Research/guidelines/CTS_Treatment_REIssue.pdf. Accessed November 28, 2012.
12. O'Connor D, Marshall SC, Massy-Westropp N, Pitt V. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database Syst Rev 2003;(1):CD003219.
13. Marshall S, Tardif G, Ashworth N. Local corticosteroid injection for carpal tunnel syndrome. Cochrane Database Syst Rev 2007;(2):CD001554.
14. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. BMJ 2013;346:e5595.
15. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis research strategy (PROGRESS) 2: prognostic factor research. PLoS Med 2013;10:e1001380.
16. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280-6.
17. Sackett DL, Straus SE, Richardson WS. Evidence-based medicine. How to practice and teach EMB. Edinburgh: Churchill Livingstone; 2000.
18. Ariens GA, van Mechelen W, Bongers PM, Bouter LM, van der Wal G. Physical risk factors for neck pain. Scand J Work Environ Health 2000;26:7-19.
19. DeStefano F, Nordstrom DL, Vierkant RA. Long-term symptom outcomes of carpal tunnel syndrome and its treatment. J Hand Surg [Am] 1997;22:200-10.
20. Padua L, Padua R, Lo Monaco M, et al. Natural history of carpal tunnel syndrome according to the neurophysiological classification. Ital J Neurol Sci 1998;19:357-61.
21. Padua L, Padua R, Aprile I, Pasqualetti P, Tonali P. Multiperspective follow-up of untreated carpal tunnel syndrome: a multicenter study. Neurology 2001;56:1459-67.
22. Ortiz-Corredor F, Enriquez F, DiazRuiz J, Calambas N. Natural evolution of carpal tunnel syndrome in untreated patients. Clin Neurophysiol 2008;119:1373-8.
23. Resende LA, Tahara A, Fonseca RG, Sardenberg T. The natural history of carpal tunnel syndrome: a study of 20 hands evaluated 4 to 9 years after initial diagnosis. Electromyogr Clin Neurophysiol 2003;43:301-4.
24. Giannini F. Quantitative assessment of historical and objective findings: a new clinical severity scale of CTS. In: Luchetti R, Amadio P, editors. Carpal tunnel syndrome. Berlin, Heidelberg: Springer-Verlag; 2007. p 82-8.
25. Lian BT, Urkude R, Verma KK. Clinical profile, electrodiagnosis and outcome in patients with carpal tunnel syndrome: a Singapore perspective. Singapore Med J 2006;47:1049-52.
26. Kiylioglu N, Bicerol B, Ozkul A, Akyol A. Natural course and treatment efficacy: one-year observation in diabetic and idiopathic carpal tunnel syndrome. J Clin Neurophysiol 2009;26:446-54.
27. Kaplan SJ, Glickel SZ, Eaton RG. Predictive factors in the nonsurgical treatment of carpal tunnel syndrome. J Hand Surg [Br] 1990;15:106-8.
28. Muhlau G, Both R, Kunath H. Carpal tunnel syndrome—course and prognosis. J Neurol 1984;231:83-6.
29. Katz JN, Lew RA, Bessette L, et al. Prevalence and predictors of long-term work disability due to carpal tunnel syndrome. Am J Ind Med 1998;33:543-50.
30. Katz JN, Keller RB, Simmons BP, et al. Maine carpal tunnel study: outcomes of operative and nonoperative therapy for carpal tunnel syndrome in a community-based cohort. J Hand Surg [Am] 1998;23:697-710.
31. Goodwill CJ. The carpal tunnel syndrome. Long-term follow-up showing relation of latency measurements to response to treatment. Ann Phys Med 1965;8:12-21.
32. Kouyoumdjian JA, Morita MP, Molina AF, et al. Long-term outcomes of symptomatic electrodiagnosed carpal tunnel syndrome. Arq Neuropsiquiatr 2003;61(2 A):194-8.
33. Boyd KU, Gan BS, Ross DC, Richards RS, Roth JH, MacDermid JC. Outcomes in carpal tunnel syndrome: symptom severity, conservative management and progression to surgery. Clin Invest Med 2005;28:254-61.
34. Duckworth AD, Jenkins PJ, Roddam P, Watts AC, Ring D, McEachan JE. Pain and carpal tunnel syndrome. J Hand Surg [Am] 2013;38:1540-6.
35. Miranda BH, Asaad K, Cerovac S. Carpal tunnel syndrome study: local corticosteroids, conversion to surgery and NHS implications. J Plast Reconstr Aesthet Surg 2013;66:1432-3.
36. Rempel D, Evanoff B, Amadio PC, et al. Consensus criteria for the classification of carpal tunnel syndrome in epidemiologic studies. Am J Public Health 1998;88:1447-51.
37. 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;18:145-50.
38. Page MJ, O'Connor DA, Pitt V, Massy-Westropp N. Reporting of allocation method and statistical analyses that deal with bilaterally affected wrists in clinical trials for carpal tunnel syndrome. Am J Phys Med Rehabil 2013;92:1012-9.

Supplemental Appendix S1 Medline Search Strategy

1. median neuropathy/ or exp carpal tunnel syndrome/
2. "carpal tunnel syndrome".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. Nerve Compression Syndromes/
4. entrapment neuropath*.ti,ab.
5. exp Median Nerve/
6. nerve entrapment*.ti,ab.
7. Hand/ and Pain/
8. Pain/ and Wrist/
9. (carpal$ adj3 tunnel$).mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Prognosis/
12. exp Disease Progression/
13. prognos*.mp.
14. predict*.mp.
15. factor*.mp.
16. risk*.mp.
17. model*.mp.
18. evolution.mp.
19. history.mp.
20. indicator*.mp.
21. course.mp.
22. rule*.mp.
23. transition*.mp.
24. determinant*.mp.
25. pattern*.mp.
26. subgroup*.mp.
27. sub-group*.mp.
28. screen*.mp.
29. long-term.mp.
30. progress*.mp.
31. modif*.mp.
32. mediat*.mp.
33. or/11-32
34. exp Epidemiologic Studies/
35. cohort*.mp.
36. follow-up.mp.
37. follow-up.mp.
38. ("case control" or "case controlled").mp.
39. retrospective*.mp.
40. prospective*.mp.
41. ((patient* or medical) adj3 (record* or review* or histor*)).mp.
42. longitudinal*.mp.
43. inception.mp.
44. observation*.mp.
45. time series.mp.
46. outcome*.mp.
47. or/34-46
48. 33 and 47
49. 10 and 48

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Trends in the prevalence, incidence and surgical management of carpal tunnel syndrome between 1993 and 2013: an observational analysis of UK primary care records

Claire L Burton, Ying Chen, Linda S Chesterton, Danielle A van der Windt

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Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Staffordshire, UK

Correspondence to
Dr Claire L Burton;
c.burton@keele.ac.uk

ABSTRACT

Objectives To describe the prevalence, incidence and surgical management of carpal tunnel syndrome (CTS), between 1993 and 2013, as recorded in the Clinical Practice Research Datalink (CPRD).

Design We completed a series of cross-sectional epidemiological analyses to observe trends over time.

Setting Primary care data collected between 1993 and 2013, stored in the CPRD.

Population Individuals aged ≥18 years were selected. Prevalent and incident episodes of CTS and episodes of surgical intervention were identified using a list of preidentified Read codes.

Analysis We defined incident episodes as those with no preceding diagnostic code for CTS in the past 2 years of data. Episodes of surgery were expressed as a percentage of the prevalent population during the same calendar year. Joinpoint regression was used to determine significant changes in the underlying trend.

Results The prevalence of CTS increased over the study period, with a particular incline between 2000 and 2004 (annual percentage change 7.81). The female-to-male prevalence ratio reduced over time from 2.74 in 1993 to 1.93 in 2013. The median age of females and males with CTS were noted to increase from 49 and 53 years, respectively in 1993 to 54 and 59 years, respectively in 2013. Incidence was also noted to increase over time. After an initial increase between 1993 and 2007, the percentage of prevalent patients with a coded surgical episode began to decrease after 2007 to 27.41% in 2013 (annual percentage change −1.7).

Conclusion This study has demonstrated that the prevalence and incidence of CTS increased over the study period between 1993 and 2013. Rates of surgery for CTS also increased over the study period; however after 2007, the per cent of patients receiving surgery showed a statistically significant decline back to the rate seen in 2004.

Strengths and limitations of this study

- ► Provides updated epidemiological data about a common and bothersome condition.
- ► Set in primary care, where most cases of carpal tunnel syndrome present.
- ► Uses a large primary care database, generalisable to the UK population.
- ► Relies on the correct coding and capture of episodes of carpal tunnel syndrome and carpal tunnel release surgery.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a chronic focal compressive neuropathy caused by the entrapment of the median nerve at the level of the carpal tunnel in the wrist.[1] CTS is the most common presentation of the entrapment neuropathies[2] and is characterised by symptoms including paraesthesia, dysesthesia, sensory loss and eventually weakness and atrophy of the thenar muscle. Symptoms are usually localised to the hand but can spread proximally to the forearm, upper arm and even shoulder.[3] Despite causing relatively localised symptoms, CTS can have substantial physical, psychological and economic consequences.[4 5] In some cases, there may be associations with certain occupations (such as the care and leisure industry),[6] which involve the overuse of the hand and wrist as well as other physical comorbidities including pregnancy, diabetes, hypothyroidism and obesity.[7]

The diagnosis of CTS is generally accepted to be a clinical one (based on history and examination findings),[8] although electrodiagnostic tests are commonly requested to confirm the diagnosis or differentiate among diagnoses, especially in the presence of thenar atrophy and/or persistent numbness or if surgical management is being considered.[9] The treatment of CTS is usually defined as either surgical or conservative (non-surgical). Local steroid injections and night splinting form the mainstay of primary

care interventions in CTS, as indicated by national care pathways.[10 11] Patients with moderate, severe or deteriorating symptoms following conservative treatment or sudden and severe symptoms are recommended to be referred for consideration of surgery.[12] Carpal tunnel release surgery (CTR) is routinely carried out under local anaesthetic as day surgery. Open and endoscopic approaches are used to release the flexor retinaculum.[13] Previous studies have sought to estimate the prevalence and/or incidence of CTS. Such epidemiological studies have been diverse in their approach to the populations studied and case definitions applied.[14] The reported estimates for annual prevalence range from 3720 to 5700 per 100 000 per year[15–17] and the reported incidence from 72 to 8200 per 100 000 per year.[6 14 18–23] CTS is generally accepted to be more common in women; the female-to-male ratio ranges between 0.78 and 9.66.[14 15] A number of previous studies have observed the trends of prevalence or incidence over time and identified an increase,[19 20 24] with 2005 being the latest data collection point. The most recent primary care-based study in the UK used data between 1992 and 2000.[18]

Episodes of CTR have also been shown to have increased, with audit data from one major tertiary UK Hand Centre suggesting that referral for CTR increased over a 10-year period from 59.7 to 112 per 100 000 population per year between 1989–1999 and 2000–2001.[25] Using Hospital Episode Statistics (HES) between 1998 and 2011, Bebbington and Furniss also observed an increase in the absolute number of patients with CTS and episodes of CTR; however, they also noted a decrease in the use of surgery post-2008.[26]

Previous studies have used a range of methods to classify episodes of CTS and have been conducted in a number of population settings. CTS is essentially a clinical diagnosis, and in the UK, the majority of patients will first present to and be managed within primary care. Only a proportion of these patients will be referred into more specialised services and since not all surgical episodes will take place in secondary care (hospitals), as community clinics are now receiving referrals, primary care records should capture the majority of episodes. Data from a high-quality source, representative of the UK population is necessary to support the planning and commissioning of services.

The aim of this study is therefore to provide updated estimates of the prevalence, incidence and surgical management of CTS and describe trends over a 20-year period, using data from a large national primary care database (Clinical Practice Research Datalink (CPRD)).

METHODS

This was an observational study using the CPRD to estimate the prevalence, incidence and surgical management of CTS from 1993 to 2013. CPRD is a live, primary care database of anonymised medical records from general practices. It holds information of over 11.3 million patients from 674 practices in the UK since 1987; 4.4 million active (alive and currently registered) patients are currently contributing information to the datalink, which equates to 6.9% of the UK population.[27] The CPRD is broadly representative of the UK general population in terms of age, gender and ethnicity.[27] The CPRD has National Research Ethics Committee approval for observational research using primary care data and as such no further permissions were required. The Independent Scientific Advisory Committee study protocol 14_167 was approved in September 2014.

Table 1 Read codes used to define a prevalent or incident episode of carpal tunnel syndrome

Term	Read code
Carpal tunnel syndrome	F340
Injection of carpal tunnel	85BE.00
Carpal tunnel release	70560
Endoscopic carpal tunnel release	7056011
Carpal tunnel decompression	70564

During clinical interactions, Read codes are used to record signs and symptoms, treatments and therapies, investigations, occupations, diagnoses and appliances. Read codes make up a hierarchical 'thesaurus' stored by the computer. Clinical information is hence stored in a retrievable and analysable format.[28]

The study population consisted of men and women over 18 years of age. Data was used from practices which met a data quality standard based on continuity of recorded data, and from patients who had a record including at least their registration status, age and gender. These quality standards were required to have been met for at least 2 years prior to an incident episode and at the point of diagnosis for a prevalent episode.[27]

Prevalent and incident patients were identified by a consultation recorded using one of the Read codes listed in table 1. Some treatment codes and in the case of in injections, linked prescription data, were included as evidence of diagnosis as per previous studies.[18] Pilot work using a local primary care database (Consultations in Primary Care Archive (CiPCA)[29]) had noted that 30% of CTS cases with a treatment code (ie, CTR or a coded carpal tunnel injection) had not initially received a diagnosis code. This means that at presentation, patients may have been attributed a more generic term such as 'hand pain' and later gone on to receive condition-specific treatment. Hence, treatment codes were used to capture such cases, which would be missed when using diagnostic codes only.

The prevalence of individuals consulting with CTS was calculated per annum. The numerator for prevalence was the number of patients with a record of a CTS diagnosis or evidence of an episode of CTR or a carpal tunnel injection (CTI), in each calendar year. In order to determine annual incidence, the numerator was the

number of patients with a record of CTS or evidence of CTR or CTI, without a prior record of these codes during a run-in period of 2 years. This 2-year run-in period was based on expert consensus with the aim of estimating the period of time during which a new episode of CTS may develop. It was felt unlikely that a patient with ongoing bothersome symptoms would not have presented in primary care within this 2-year period. This however is an assumption made in order to define incident cases in this data set. It remains possible that patients had CTS in the community and did not present, presented in an alternative setting or indeed had a misdiagnosis/uncoded diagnosis made. CTS could present as a new episode in the contralateral wrist sometime after the initial presentation, hence it was not felt possible to define this criterion as 'no previous recorded episode'. All incidence patients were therefore required to have complete registration for this two calendar years prior to the event date. Pilot work in CiPCA had shown that over 9 years observed, 4% of potential incident cases were lost due to the lack of 2 years registration data required to define an incident episode.

The denominator population for calculation of prevalence was the total up-to-standard person-years contributed to CPRD by patients over the age of 18 years, for each annual period between 1993 and 2013. In order to apply the same criteria to both the numerator and denominator populations, the denominator populations for calculating incidence were also required to have registration at the mid-point of the year, two calendar years before the index year.

Episodes of CTR were identified using Read codes as shown in table 2. In addition, codes used to define 'rerelease of carpal tunnel' and 'revision of carpal tunnel release' were included as a surgical episode (if first recorded). These terms were not included in the definition of CTS for the estimation of prevalence and incidence as they may not have indicated an episode of 'idiopathic' CTS but rather iatrogenic symptoms following previous (unsuccessful) surgery. Of note, revision codes contributed 1.00% of the total surgical codes used. Results were expressed as the percentage of patients with a prevalent episode of CTS having a code of CTR in the same calendar year. Percentages were calculated based on the number of prevalent cases as opposed to incident cases as it was felt likely that patients would receive surgery in the annual period following their index consultation.

Table 2 Read codes used to define a surgical episode

Term	Read code
Carpal tunnel release	817
Rerelease of carpal tunnel	16896
Endoscopic carpal tunnel release	39335
Revision of carpal tunnel release	97195
Carpal tunnel decompression	19249

Statistical methods

Age-specific and sex-specific annual prevalence and incidence were determined for each calendar year, between 1993 and 2013 and presented as n/10 000 person-years. For CI calculation a Poisson distribution was used. As a sensitivity analysis, age-standardised and sex-standardised annual figures of CTS prevalence and incidence for each year were also calculated, using population estimates provided by the website of the Office of National Statistics.[30] Unstandardised and standardised rates were very similar, hence we report unstandardised rates as the primary outcome. The age-standardised and sex-standardised estimates of the annual prevalence and incidence of CTS are shown in online supplementary table 1.

Episodes of CTR were identified and the frequency in each calendar year expressed as a percentage of the prevalent population for the same time period. Emerging trends were described. Joinpoint regression was used to determine mean annual percentage change (APC) and assess when significant changes ('Joinpoints') occurred in the underlying trend for incidence, prevalence and surgery. This method assists the exploration of the potential influence of changes in practice, although such potential associations cannot be proven.[31 32] Models were fitted using the Joinpoint Regression Program (V.4.3.1.0) and the best fitting model chosen (up to five Joinpoints).

Patient and public involvement

Patients were not directly involved in the design of this study; however, the results will be used to inform discussions regarding further research in this field with our local Research User Group.

RESULTS

Trends in prevalence

Table 3 presents the prevalence (crude estimates) of patients presenting in primary care with CTS between 1993 and 2013 and the demographics of the population. The denominator population for prevalence increased from 1 117 433 person-years in 1993 to 3 473 094 person-years in 2013. The total prevalence in 1993 was 26.03 per 10 000 person-years (95% CI 25.10 to 27.00), and for 2013, 36.08 per 10 000 person-years (95% CI 35.45 to 36.72). As shown in figure 1 and corresponding table 4, prevalence appeared to decrease between 1993 and 2000 (APC=−0.8%, 95% CI −2.6 to 1.0). It then increased between 2000 and 2004 (APC=7.8%, 95% CI 3.1 to 12.7) and then increased at a slower rate between 2004 and 2013 (APC=1.1%, 95% CI 0.4 to 1.8). The female-to-male ratio reduced over time from 2.74 in 1993 to 1.93 in 2013. The median age of female and male patients with CTS increased from 49 and 53 years, respectively in 1993 to 54 and 59 years, respectively in 2013 (see online supplementary table 2). Online supplementary table 3 and

Table 3 Crude prevalence of carpal tunnel syndrome (n/10 000 person-years) per calendar year, as presented in UK primary care (Clinical Practice Research Datalink)

Year	Number of person-years	Prevalent individuals	Total crude prevalence per 10 000 person-years, (95% CI)	Female prevalence per 10 000 person-years, (95% CI)	Male prevalence per 10 000 person-years, (95% CI)	Female:male
1993	1 117 443	2909	26.03 (25.10 to 27.00)	37.52 (35.96 to 39.13)	13.69 (12.72 to 14.71)	2.74
1994	1 198 256	3188	26.61 (25.69 to 27.55)	37.23 (35.73 to 38.79)	15.21 (14.23 to 16.25)	2.45
1995	1 286 800	3343	25.98 (25.11 to 26.88)	36.64 (35.20 to 38.12)	14.58 (13.65 to 15.56)	2.51
1996	1 437 567	3706	25.78 (24.96 to 26.62)	36.75 (35.38 to 38.16)	14.09 (13.23 to 15.00)	2.61
1997	1 681 756	4190	24.91 (24.17 to 25.68)	34.87 (33.64 to 36.14)	14.34 (13.53 to 15.18)	2.43
1998	1 899 393	4884	25.71 (25.00 to 26.45)	36.57 (35.38 to 37.79)	14.22 (13.46 to 15.01)	2.57
1999	2 289 158	5696	24.88 (24.24 to 25.54)	35.21 (34.14 to 36.30)	14.01 (13.32 to 14.72)	2.52
2000	2 787 457	6998	25.11 (24.52 to 25.70)	34.82 (33.86 to 35.81)	14.90 (14.26 to 15.57)	2.34
2001	3 057 458	8137	26.61 (26.04 to 27.20)	36.46 (35.52 to 37.42)	16.31 (15.67 to 16.98)	2.23
2002	3 385 511	9722	28.72 (28.15 to 29.29)	39.33 (38.40 to 40.28)	17.64 (17.00 to 18.29)	2.23
2003	3 552 908	11 124	31.31 (30.73 to 31.90)	43.61 (42.66 to 44.59)	18.53 (17.90 to 19.18)	2.35
2004	3 712 172	12 622	34.00 (33.41 to 34.60)	47.20 (46.23 to 48.19)	20.33 (19.68 to 20.99)	2.32
2005	3 808 183	12 741	33.46 (32.88 to 34.04)	46.37 (45.42 to 47.34)	20.09 (19.45 to 20.74)	2.31
2006	3 857 487	12 718	32.97 (32.40 to 33.55)	45.82 (44.88 to 46.78)	19.69 (19.07 to 20.33)	2.33
2007	3 904 068	13 222	33.87 (33.29 to 34.45)	46.35 (45.41 to 47.31)	20.99 (20.35 to 21.65)	2.21
2008	3 897 624	14 030	36.00 (35.40 to 36.60)	49.12 (48.15 to 50.11)	22.46 (21.79 to 23.14)	2.19
2009	3 894 989	14 500	37.23 (36.60 to 37.81)	50.68 (49.69 to 51.68)	23.35 (22.68 to 24.05)	2.17
2010	3 842 773	14 166	36.86 (36.26 to 37.48)	49.75 (48.76 to 50.75)	23.57 (22.88 to 24.27)	2.11
2011	3 769 676	13 529	35.89 (35.29 to 36.50)	47.98 (47.00 to 48.97)	23.36 (22.67 to 24.07)	2.05
2012	3 714 877	13 388	36.04 (35.43 to 36.66)	47.57 (46.59 to 48.56)	24.05 (23.35 to 24.78)	1.98
2013	3 473 094	12 532	36.08 (35.45 to 36.72)	47.19 (46.18 to 48.21)	24.49 (23.75 to 25.25)	1.93

supplementary figures 1 and 2 further illustrate the crude prevalence of CTS over time by age and gender. The prevalence of CTS appears to increase with age in the male population, whereas the prevalence in women peaks in the 50–59 years age group, dips in the 60–69 years age group and then peaks once more in the 70+ years age group.

Trends in incidence

Table 5 presents the annual incidence (crude estimates) for patients presenting in UK primary care with carpal tunnel syndrome between 1993 and 2013 and the demographics of the population. The denominator population for incidence, which is dependent on patients having 2 years up to standard data prior to the mid-point of the year in question, increased from 783 330 person-years in 1993 to 3 015 670 person-years in 2013. The crude incidence in 1993 was 20.22 per 10 000 person-years (95% CI 19.24 to 21.24), and for 2013, 27.68 per 10 000 person-years (95% CI 27.09 to 28.28). As shown in figure 2 and table 6, the results of the best fitting Joinpoint regression suggest the incidence increased between 1993 and 2000 (APC=0.3, 95% CI −2.3 to 2.9). It then increased more quickly between 2000 and 2004 (APC=6.9, 95% CI 0.5 to 13.7), before slowing between 2004 and 2013 (APC=0.7. 95% CI −0.2 to 1.6). The female-to-male ratio reduced over time from 2.57 in 1993 to 1.88 in 2013. The median age of female and male patients were noted to increase from 50 and 51 years, respectively in 1993 to 55 and 59 years, respectively in 2013 (see online supplementary table 4). See online supplementary table 5 and supplementary figures 3 and 4 further illustrate the incidence of CTS over time by age and gender. As with prevalence, the incidence of CTS appears to increase with age in the male population, whereas the prevalence in women peaks in the 50–59 years age group, dip in the 60–69 years age group and then peak once more in the 70+ years age group.

Trends in the percentage of patients with carpal tunnel syndrome receiving surgical management

Table 7 presents the percentage of prevalent patients with a recorded episode of CTR in each calendar year between 1993 and 2013 and the demographics of this sample. The percentage of all patients with a recorded episode of CTR in 1993 was 19.35%, and for 2013, 27.41%. As shown in figure 3 and corresponding table 8, the percentage of patients with a coded episode of CTR increased between 1993 and 2007 (APC=2.6, 95% CI 1.9 to 3.2). It then appeared to decrease between 2007 and 2013 (APC=−1.7, 95% CI −3.3 to −0.3). The median age of females and males receiving CTR were noted to increase from 53 and

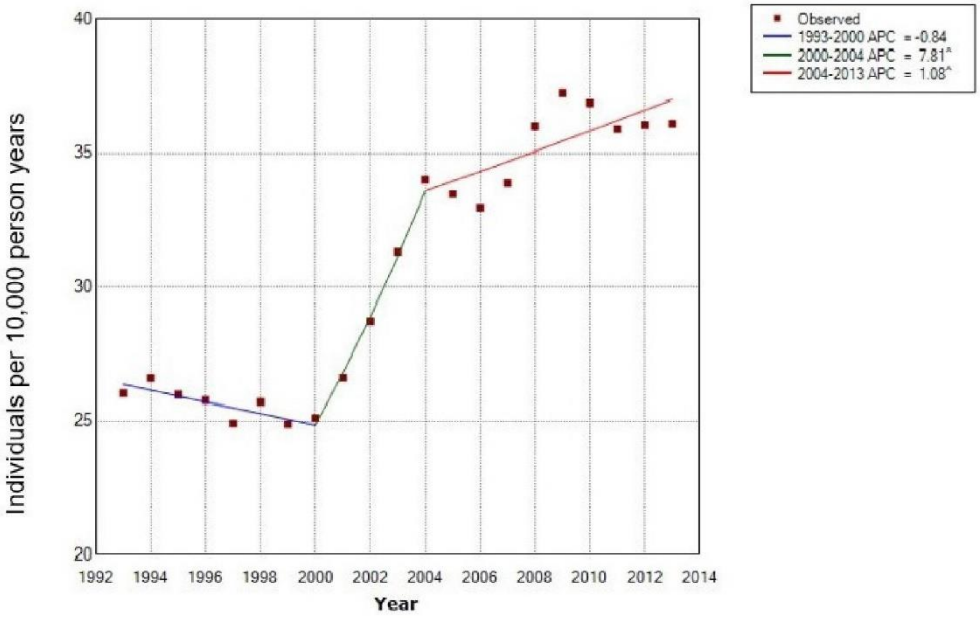

Figure 1 Joinpoint analysis of the crude prevalence of carpal tunnel syndrome between 1993 and 2013. ^, reflects significance at the 0.05 level; APC, annual percentage change.

55 years, respectively in 1993 to 57 and 62 years, respectively in 2013.

DISCUSSION

While the prevalence and incidence of CTS have increased over the study period 1993–2013, results show that episodes of surgery, increased until 2007 and declined thereafter.

Online supplementary tables 6 and 7 summarise estimates of the prevalence, incidence and sex ratios of CTS from a previous scoping review of literature pertaining to the general population, demonstrating the substantial variation in results between studies, which may partly be the results of differences in definition of CTS applied and population observed. Studies which also used primary care data showed a similar estimate of the incidence of CTS in a UK primary care population[18] and similarly reported an increase in incidence over time, although in a Dutch primary care population.[21] As described in previous studies, CTS shows a peak in prevalence and incidence in women of middle age (50–59 years age group, likely due to hormonal changes around the time of the menopause),[18] while in the male population, the prevalence and incidence of CTS increased with age. Gelfman *et al* also commented that an increasing number of older people presenting with CTS had been noted over the course of their study.[20] The increase in the prevalence and incidence of CTS in the older-aged male groups, may partially account for the observed decrease in the female-to-male ratio, over time.

The variability in the case definition of CTS was highlighted by Descatha *et al*,[33] who identified seven case definitions of CTS proposed for use in population-based studies. Definitions included variations of symptoms

Table 4 Joinpoint analysis of crude prevalence

Segment	Lower end point	Upper end point	Annual percentage change	Lower 95th CI	Upper 95th CI	Test statistic (t)	Prob > |t|
1	1993	2000	−0.8	−2.6	1.0	−1.0	0.3
2	2000	2004	7.8*	3.1	12.7	3.7	0.0
3	2004	2013	1.1*	0.4	1.8	3.4	0.0

*Reflects significance at the 0.05 level.

Table 5 Crude incidence of carpal tunnel syndrome (n/10 000 person-years) per calendar year, as presented in UK primary care (Clinical Practice Research Datalink)

Year	Number of person-years	Incident individuals	Total crude incidence per 10 000 person-years (95% CI)	Female incidence per 10 000 person-years (95% CI)	Male incidence per 10 000 person-years (95% CI)	Female:male
1993	783 330	1584	20.22 (19.24 to 21.24)	28.72 (27.09 to 30.42)	11.17 (10.14 to 12.29)	2.57
1994	868 616	1797	20.69 (19.74 to 21.67)	28.52 (26.97 to 30.13)	12.38 (11.34 to 13.69)	2.30
1995	1 003 593	1963	19.56 (18.70 to 20.45)	27.53 (26.12 to 29.00)	11.12 (10.20 to 12.10)	2.48
1996	1 065 068	2142	20.11 (19.27 to 20.98)	28.39 (27.00 to 29.84)	11.37 (10.47 to 12.33)	2.50
1997	1 150 299	2306	20.05 (19.24 to 20.88)	28.39 (27.05 to 29.79)	11.25 (10.39 to 12.16)	2.52
1998	1 300 074	2696	20.74 (19.95 to 21.52)	29.65 (28.57 to 31.22)	11.37 (10.56 to 12.23)	2.61
1999	1 497 673	3030	20.23 (19.52 to 20.10)	28.53 (27.35 to 29.75)	11.54 (10.77 to 12.34)	2.47
2000	1 682 027	3462	20.58 (19.90 to 21.28)	28.66 (27.54 to 29.81)	12.15 (11.41 to 12.93)	2.36
2001	2 019 596	4391	21.74 (21.10 to 22.40)	29.72 (28.68 to 30.79)	13.46 (12.74 to 14.20)	2.21
2002	2 456 761	5718	23.27 (22.68 to 31.78)	31.78 (30.78 to 32.79)	14.47 (13.80 to 15.17)	2.20
2003	2 669 111	6772	25.37 (24.77 to 25.98)	35.13 (34.14 to 36.14)	15.33 (14.67 to 16.02)	2.29
2004	2 779 821	7868	28.30 (27.68 to 28.94)	39.22 (38.19 to 40.27)	17.10 (16.42 to 17.81)	2.29
2005	3 164 506	8113	25.64 (25.08 to 26.20)	35.55 (34.63 to 36.48)	15.49 (14.88 to 16.12)	2.30
2006	3 307 051	8337	25.21 (24.67 to 25.76)	34.91 (34.02 to 35.82)	15.27 (14.68 to 15.89)	2.29
2007	3 343 009	8865	26.52 (25.97 to 27.08)	35.76 (34.86 to 36.67)	17.07 (16.45 to 17.71)	2.09
2008	3 341 299	9437	28.24 (27.68 to 28.82)	38.23 (37.30 to 39.17)	18.06 (17.42 to 18.72)	2.12
2009	3 383 196	9918	29.32 (28.74 to 29.90)	39.73 (38.79 to 50.68)	18.69 (18.04 to 19.36)	2.13
2010	3 357 338	9634	28.70 (28.13 to 29.27)	38.70 (37.77 to 39.64)	18.46 (17.82 to 19.13)	2.10
2011	3 269 296	9083	27.78 (27.21 to 28.36)	37.11 (36.19 to 38.05)	18.20 (17.54 to 18.87)	2.04
2012	3 222 880	9011	27.96 (27.39 to 28.54)	36.44 (35.52 to 37.88)	19.23 (18.56 to 19.93)	1.89
2013	3 015 670	8346	27.68 (27.09 to 28.28)	35.95 (35.01 to 36.92)	19.12 (18.43 to 19.84)	1.88

only; symptoms and examination findings; symptoms and either physical examination or electrodiagnostic results and symptoms and electrodiagnostic results. This study showed a range in the population prevalence of CTS from 2.5% to 11%, with studies using less specific case definitions yielding higher prevalence rates.[33] Misclassification ranged between 1% and 10%. The prevalence of CTS in any given population is likely therefore to depend on the definition of CTS applied. The case definition in our study is derived from general practitioner (GP)-recorded diagnosis and treatment codes, which may have been based on clinical findings alone; those who have had further investigations and those who have received definitive condition-specific treatment. Hence, it uses a pragmatic approach, across a large population that will include all patients presenting to their GP with symptoms. Our study methods do however assume that patients with symptoms will be presenting in primary care or be receiving definitive coded treatment. The study will not capture patients with chronic symptoms who are not presenting in primary care or who had a coded episode of surgery or injection.

Although Joinpoint analysis does not provide evidence for the cause of a change in observed outcomes, it highlights when a significant change in trend has taken place. Our results suggest that the annual percentage change in prevalence and incidence was highest between 2000 and 2004. A possible reason for this may be the publication of the UK Government's information technology strategy for the NHS in 1998,[34] which proposed that by 2005, the person-based electronic health record (HER), would have been fully implemented.[35] Although no direct evidence for this was found, it may be possible that with the increasing use of IT systems in primary care and attention to providing Read codes for each consultation, episodes of CTS were more frequently and accurately recorded. This would not however explain the continuing increase of the incidence in CTS post-2005.

Between 2000 and 2004, the Government implemented the second phase of its 'War on Waiting', that is, the reduction of waiting times. For example, the maximum wait for a day-case procedure (eg, a CTR) was reduced from 18 months to 6 months.[36] The peak in prevalence of CTS (with our definition partly based also on treatment codes, which in 2013 constituted 29.36% of prevalent patients) observed in 2004 may therefore be partly explained by the fact that patients requiring surgery were 'accumulating' between 2000 and 2004 and subsequently received definitive treatment. This effect would however not be expected to impact so heavily on the incidence, which

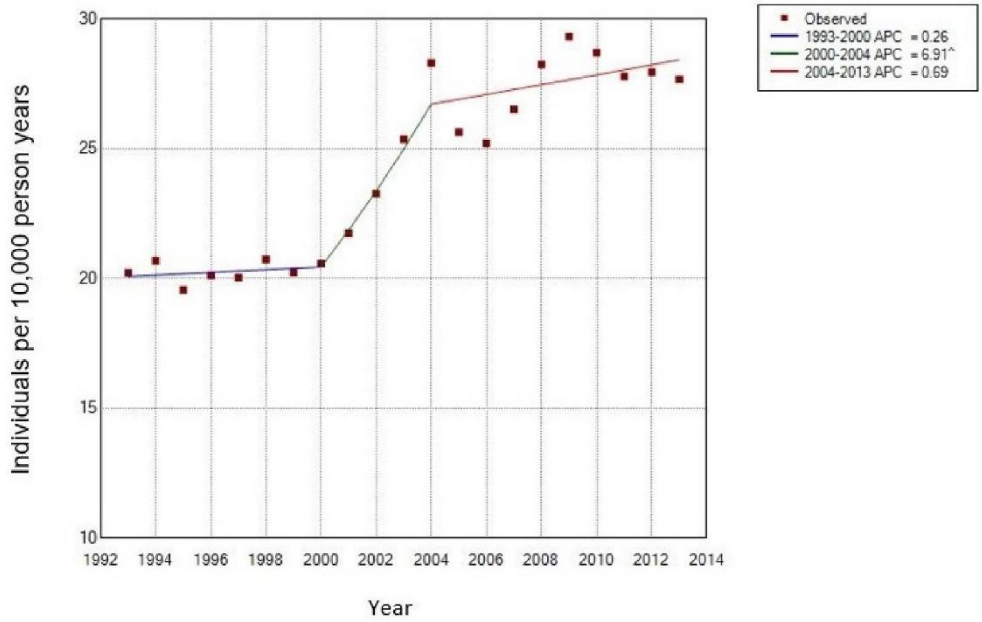

Figure 2 Joinpoint analysis of the crude incidence of carpal tunnel syndrome between 1993 and 2013. ^, reflects significance at the 0.05 level; APC, annual percentage change.

disregards repeat patient presentations in subsequent annual periods, unless patients with a less specific code received treatment and appeared as an incident case. The introduction of the 18-week target of time from referral to treatment in 2008 did not seem to have a similar impact on estimates of prevalence or incidence of CTS, which makes it less certain to what extent these policy changes may have influenced our results. There are likely to be further reasons behind the observed changes.

The change in trends of 2004 may also represent a change in service. The introduction of the Quality and Outcome Framework (QOF) occurred with the advent of the General Medical Services contract in 2004. Although there has never been a musculoskeletal health domain, the importance of coding to maintain registers and evidence of outcomes in line with QOF may have influenced coding behaviour.

At the same time as QOF, Primary Care Trusts (PCTs) were given a role in commissioning services. The ability of PCTs to commission new services heralded the development of the Musculoskeletal Interface Clinics (MIC), which act as a 'one stop shop' for patients with musculoskeletal problems. A referral to this clinic from primary care may also be a reason prevalent patients with persisting symptoms stopped presenting in primary care.

These three factors (improved coding, service redevelopment and a reduction in waiting times) may all partly explain the change in incidence and prevalence of CTS between 2000 and 2004 but are unlikely to fully explain the observed trends. Further factors of potential influence may include the increasing rates of risk factors of CTS such as diabetes and obesity.[37 38] While standardising the prevalence and incidence by age and gender did not change the overall picture of the changing trends, online

Table 6 Joinpoint analysis of crude incidence

Segment	Lower end point	Upper end point	Annual percentage change	Lower 95th CI	Upper 95th CI	Test statistic (t)	Prob > |t|
1	1993	2000	0.3	−2.3	2.9	0.2	0.8
2	2000	2004	6.9*	0.5	13.7	2.3	0.0
3	2004	2013	0.7	−0.2	1.6	1.7	0.1

*Reflects significance at the 0.05 level.

Table 7 Percentage of patients with carpal tunnel syndrome with a recorded episode of carpal tunnel release surgery per calendar year, as presented in UK primary care (Clinical Practice Research Datalink)

Year	Episodes per 10000 person-years	% prevalent individuals having surgery	% prevalent females having surgery	% prevalent males having surgery	Female median age (25%–75% IQR)	Male median age (25%–75% IQR)
1993	5.04	19.35	18.78	21.03	53 (43–64)	55 (44–69)
1994	5.70	21.42	20.62	23.52	53 (43–68)	58 (45–70)
1995	6.19	23.81	23.40	24.92	53 (42–67)	55 (44–70)
1996	5.41	20.99	20.48	22.43	53 (44–65)	52 (40–65)
1997	5.70	22.89	22.14	24.81	53 (45–67)	56 (42–69)
1998	5.73	22.28	21.28	25.00	53 (44–65)	53 (44–65)
1999	6.24	25.09	24.60	26.38	54 (44–67)	56 (46–70)
2000	6.41	25.54	24.84	27.23	54 (44–68)	56 (45–69)
2001	6.88	25.87	25.95	25.68	55 (45–68)	58 (46–71)
2002	7.02	24.46	24.19	25.09	57 (46–71)	55 (45–68)
2003	8.26	26.39	25.88	27.66	56 (45–67)	57 (46–71)
2004	9.34	27.48	27.38	27.74	56 (46–67)	57 (47–68)
2005	9.70	29.00	28.31	30.65	57 (47–68)	58 (46–71)
2006	9.36	28.40	28.31	28.61	57 (47–68)	60 (48–72)
2007	9.71	28.66	28.26	29.59	56 (46–69)	59 (48–71)
2008	10.53	29.25	29.00	29.82	56 (46–68)	60 (49–72)
2009	10.92	29.32	28.73	30.66	56 (46–70)	61 (49–72)
2010	10.40	28.22	27.57	29.62	57 (47–71)	61 (48–73)
2011	9.47	26.37	26.11	26.93	57 (47–70)	61 (49–73)
2012	9.48	26.31	25.89	27.19	57 (47–71)	60 (49–73)
2013	9.89	27.41	26.47	29.30	57 (48–70)	62 (51–74)

supplementary figure 1 suggests that the prevalence of CTS increased most obviously in the male and female over 70 years age groups.

The Joinpoint analysis suggested an increase in surgical management of CTS between 1993 and 2007 (APC=2.55), followed by a reducing trend between 2007 (95% CI 2004 to 2009) and the end of the study in 2013 (APC=−1.72).

Previous studies have described the epidemiology and the rates of CTR in the UK. This study provides updated data observing the presenting primary care population. Using data from the General Practice Research Database (GPRD) (forerunner to CPRD), Latinovic *et al* reported that 31% of patients with CTS had surgery in 2000,[18] which is similar to the 25.5% found in our study at the same time point. The small difference between the estimates may be the result of a difference in the calculation used to derive the denominator population. Audit data from one tertiary hand centre, Wildin *et al* also showed that the rate of referrals for CTR surgery had increased over the 10 years between 1989–1999 and 2000–2001.[25] Furthermore, Bebbington and Furniss observed demographic population shifts in hand conditions including CTS within HES, which record diagnoses and procedures performed within the National Health Service (NHS) Hospitals in England. They used linear regression to predict future trends in hand surgery, showing that while absolute numbers of CTS diagnoses and CTR procedures increased between 1998 and 2011, the pre-2008 increase in CTR was significantly steeper than the post-2008 slope ($p<0.001$).[26] This is suggestive of a decrease in the surgical management of CTS in terms of the proportion of patients with CTS having an operation, but not necessarily in the numbers of surgical episodes in absolute terms, which Bebbington and Furniss predict will have increased by 99% (95% CI 65 to 132) in 2030 compared with 2011.[26] The data from CPRD however, suggested a reduction in both real-term episodes of CTR as well as the proportion of the (increasing) prevalent population receiving surgical treatment.

We may speculate regarding potential reasons for the initial increase in surgical management of CTS, for example, increased access to specialist services (eg, community-based MIC), increased litigation leading to more definitive treatments being sought and increased patient expectations and demand, but we have no evidence for such explanations.

The decreasing trend in the use of CTR post-2007 is likely to be multifactorial; however, the changing structure of the NHS and its funding streams may have influenced the observed trend. Around 2007–2008, practice-based

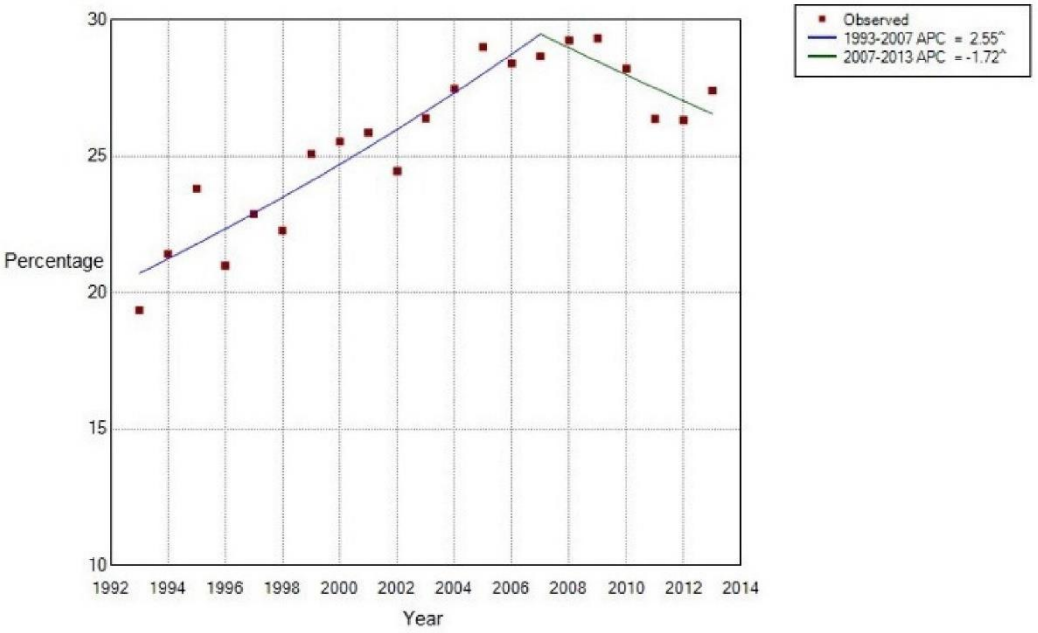

Figure 3 Joinpoint analysis of the percentage of prevalent patients with a recorded episode of carpal tunnel release, in each calendar year syndrome, between 1993 and 2013. ^, reflects significance at the 0.05 level; APC, annual percentage change.

commissioning was being introduced. This gave primary care notional budgets with which to purchase care for their patients with the aim of aligning clinical and financial responsibility. Restricting access to certain procedures including CTR, by implementing prespecified criteria, was one way to help achieve this, which may have resulted in a reduction in the use of CTR.

There are a number of limitations associated with the data in this study. The accuracy of consultation data is dependent on the validity of the computerised information it uses. In a review of 212 publications which aimed to validate diagnoses recorded in GPRD data, Herrett *et al* reported that the median proportion of cases with a confirmed diagnosis was 89% (range 24%–100%), but the majority of publications did not present the sensitivity of a coded diagnosis, which means that information regarding the proportion of missed cases is lacking. Potential misclassification; non-attendance in primary care; variation in between GP coding and a lack of coding may all lead to an unmeasured shortfall in observed cases.[27 39] This study relies on the diagnosis of CTS to be correct and the subsequent coding to be precise. While CTS diagnoses have not been validated, in a study comparing musculoskeletal diagnoses in four different databases, Jordan *et al* suggested that musculoskeletal coding in GPRD was less reliable than in its other healthcare datasets including CiPCA.[40] We took measures to reduce the effect of miscoding (eg, including surgery and injection codes in prevalence measures, if diagnostic codes had not been used), but it is possible that results will not be entirely representative of the true prevalence and incidence of CTS.

Given the lack of clarity in the accuracy of coding and the likelihood that associated clinical encounters following a CTR were coded using a surgical code, only the first surgical code could reliably be used to indicate an

Table 8 Joinpoint analysis of the use of surgery

Segment	Lower end point	Upper end point	Annual percentage change	Lower 95th CI	Upper 95thCI	Test statistic (t)	Prob > |t|
1	1993	2007	2.6*	1.9	3.2	8.2	0.0
2	2007	2013	−1.7*	−3.1	−0.3	−2.6	0.0

*Reflects significance at the 0.05 level.

episode of surgery. This is likely to have led to an underestimation of surgical episodes being identified as episodes on the contralateral hand will have been automatically discounted as they were undistinguishable. Furthermore, prevalence and incidence were similarly likely to have been underestimated as repeat presentations for the ipsilateral hand are indistinguishable from presentations in the contralateral hand.

While CPRD provides a large generalisable sample, which has substantial benefits when estimating epidemiological trends, it cannot directly measure patient-reported outcomes. Furthermore, surgery can be seen as a 'gold standard' treatment, but it does not necessarily signify cure. A review of the surgical treatment of CTS reported that 70%–90% of patients undergoing a CTR have a good outcome (definitions varied).[41] In a retrospective cohort study over a mean follow-up of 13 years postsurgery, 88% of patients were either completely satisfied or very satisfied with surgery. Seventy-four per cent reported their symptoms had completely resolved; 1.8% (113 patients) had undergone repeat surgery.[42] There is little evidence however that CTR is an appropriate initial management option for patients presenting to primary care with mild-to-moderate symptoms, especially in the absence of high-quality trial evidence that conservative management is ineffective.[43 44]

Future research in this field could describe the characteristics of patients presenting with CTS in greater detail, and observe course and prognosis of CTS in primary care. It may then be possible to identify predictors of the outcome of primary care management, and potentially identify patients requiring surgery.

CONCLUSION

An increase in the incidence and prevalence of CTS is likely to lead to an increased demand on services and cost to the healthcare economy.[26] This study has demonstrated an increase in the prevalence and incidence of physician diagnosed CTS over the study period between 1993 and 2013. Rates of referral for CTS and surgical intervention have also increased over the study period; however in the later years of the study, the per cent of patients receiving surgery has begun to decline .

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REFERENCES

1. Alfonso C, Jann S, Massa R, *et al*. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. *Neurol Sci* 2010;31:243–52.
2. Aroori S, Spence RA. Carpal tunnel syndrome. *Ulster Med J* 2008;77:6–17.
3. Padua L, Padua R, Lo Monaco M, *et al*. Multiperspective assessment of carpal tunnel syndrome: a multicenter study. Italian CTS Study Group. *Neurology* 1999;53:1654–9.
4. Foley M, Silverstein B, Polissar N. The economic burden of carpal tunnel syndrome: long-term earnings of CTS claimants in Washington State. *Am J Ind Med* 2007;50:155–72.
5. Atroshi I, Gummesson C, Johnsson R, *et al*. Symptoms, disability, and quality of life in patients with carpal tunnel syndrome. *J Hand Surg Am* 1999;24:398–404.
6. Jenkins PJ, Srikantharajah D, Duckworth AD, *et al*. Carpal tunnel syndrome: the association with occupation at a population level. *Journal of Hand Surgery* 2013;38:67–72.
7. Middleton SD, Anakwe RE. Carpal tunnel syndrome. *BMJ* 2014;349:g6437.
8. Padua L, Coraci D, Erra C, *et al*. Carpal tunnel syndrome: clinical features, diagnosis, and management. *Lancet Neurol* 2016;15:1273–84.
9. American Academy of Orthopaedic Surgeons. Clinical practice guideline on the diagnosis of carpal tunnel syndrome. 2007.
10. Carpal tunnel syndrome. http://cks.nice.org.uk/carpal-tunnel-syndrome#!scenariorecommendation:1 (accessed 14 May 2013).
11. Carpal Tunnel Syndrome (CTS) - the map of medicine. http://app.mapofmedicine.com/mom/127/page.html?department-id=8&specialty-id=1037&pathway-id=3411&page-id=8741&history=clear (accessed 25 Oct 2012).
12. Royal College of Surgeons. Commissioning guide: treatment of carpal tunnel syndrome. 2016.
13. Middleton SD, Anakwe RE. Carpal tunnel syndrome: evidence-based medicine. *BMJ* 2014;349.
14. Ferry S, Pritchard T, Keenan J, *et al*. Estimating the prevalence of delayed median nerve conduction in the general population. *Br J Rheumatol* 1998;37:630–5.
15. de Krom MC, Knipschild PG, Kester AD, *et al*. Carpal tunnel syndrome: prevalence in the general population. *J Clin Epidemiol* 1992;45:373–6.
16. Atroshi I. Carpal tunnel syndrome-prevalence, electrodiagnosis and outcome instruments. *Acta Orthop Scand* 1999;70:70–1.
17. Papanicolaou GD, McCabe SJ, Firrell J. The prevalence and characteristics of nerve compression symptoms in the general population. *J Hand Surg Am* 2001;26:460–6.
18. Latinovic R, Gulliford MC, Hughes RA. Incidence of common compressive neuropathies in primary care. *J Neurol Neurosurg Psychiatry* 2006;77:263–5.
19. Bland JDP, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991-2001. *J Neurol, Neurosurg & Psyc* 2003;74:1674–9.
20. Gelfman R, Melton LJ, Yawn BP, *et al*Long-term trends in carpal tunnel syndrome. *Neurology* 2009;72:33–41.
21. Bongers FJ, Schellevis FG, van den Bosch WJ, *et al*. Carpal tunnel syndrome in general practice (1987 and 2001): incidence and the role of occupational and non-occupational factors. *Br J Gen Pract* 2007;57:36–9.
22. Atroshi I, Englund M, Turkiewicz A, *et al*. Incidence of physician-diagnosed carpal tunnel syndrome in the general population. *Arch Intern Med* 2011;171:941–5.

23. Jenkins PJ, Watts AC, Duckworth AD, *et al*. Socioeconomic deprivation and the epidemiology of carpal tunnel syndrome. *J Hand Surg Eur Vol* 2012;37:123–9.
24. Nordstrom DL, DeStefano F, Vierkant RA, *et al*. Incidence of diagnosed carpal tunnel syndrome in a general population. *Epidemiology* 1998;9:342–5.
25. Wildin C, Dias JJ, Heras-Palou C, *et al*. Trends in elective hand surgery referrals from primary care. *Ann R Coll Surg Engl* 2006;88:543–6.
26. Bebbington E, Furniss D. Linear regression analysis of hospital episode statistics predicts a large increase in demand for elective hand surgery in England. *J Plast Reconstr Aesthet Surg* 2015;68:243–51.
27. Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
28. Chisholm J. The read clinical classification. *BMJ* 1990;300:1092.
29. Jordan K, Porcheret M, Croft P. Quality of morbidity coding in general practice computerized medical records: a systematic review. *Fam Pract* 2004;21:396–412.
30. Population estimates. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates (accessed 16 Feb 2017).
31. National Cancer Institute. Joinpoint Regression Program - Surveillance Research Program. 2017.
32. Bedson J, Chen Y, Hayward RA, *et al*. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. *Pain* 2016;157:1525–31.
33. Descatha A, Dale AM, Franzblau A, *et al*. Comparison of research case definitions for carpal tunnel syndrome. *Scand J Work Environ Health* 2011;37:298–306.
34. NHS Executive. Information for health: an information strategy for the modern NHS 1998–2005. A national strategy for local implementation. 1998.
35. Porcheret M, Hughes R, Evans D, *et al*. Data quality of general practice electronic health records: the impact of a program of assessments, feedback, and training. *J Am Med Inform Assoc* 2004;11:78–86.
36. Lewis R, Appleby J. Can the english NHS meet the 18-week waiting list target? *J R Soc Med* 2006;99:10–13.
37. Pourmemari MH, Shiri R. Diabetes as a risk factor for carpal tunnel syndrome: a systematic review and meta-analysis. *Diabet Med* 2016;33:10–16.
38. Shiri R, Pourmemari MH, Falah-Hassani K, *et al*. The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies. *Obes Rev* 2015;16:1094–104.
39. Herrett E, Thomas SL, Schoonen WM, *et al*. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14.
40. Jordan K, Clarke AM, Symmons DP, *et al*. Measuring disease prevalence: a comparison of musculoskeletal disease using four general practice consultation databases. *Br J Gen Pract* 2007;57:7–14.
41. Turner A, Kimble F, Gulyás K, *et al*. Can the outcome of open carpal tunnel release be predicted?: a review of the literature. *ANZ J Surg* 2010;80:50–4.
42. Louie DL, Earp BE, Collins JE, *et al*. Outcomes of open carpal tunnel release at a minimum of ten years. *J Bone Joint Surg Am* 2013;95:1067–73.
43. Marshall SC, Tardif G, Ashworth NL. Cochrane Neuromuscular Group. Local corticosteroid injection for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2007;29:001554.
44. Page MJ, Massy-Westropp N, O'Connor D, *et al*. Splinting for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2012:CD010003.

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ORIGINAL RESEARCH

Predicting surgical intervention in patients presenting with carpal tunnel syndrome in primary care

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Claire L Burton
Linda S Chesterton
Ying Chen
Danielle A van der Windt

Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, UK

Purpose: Carpal tunnel syndrome (CTS) is a symptomatic compression neuropathy of the median nerve. This study investigated the value of candidate prognostic factors (PFs) in predicting carpal tunnel release surgery.

Patients and methods: This is a retrospective cohort study set in the Clinical Practice Research Datalink. Patients ≥18 years presenting with an incident episode of CTS were identified between 1989 and 2013. Candidate PF's defined in coded electronic patient records were identified following literature review and consultation with clinicians. Time to first carpal tunnel release surgery was the primary end point. A manual backward stepwise selection procedure was used to obtain an optimal prediction model, which included all the significant PFs.

Results: In total, 91,412 patients were included in the cohort. The following PFs were included in an optimal model (C-statistic: 0.588 [95% CI 0.584–0.592]) for predicting surgical intervention: geographical region; deprivation status; age hazard ratio (HR 1.02 per year, 95% CI 1.01–1.02); obesity (HR 1.23, 95% CI 1.19–1.27); alcohol drinker (HR 1.05, 95% CI 1.00–1.10); smoker (HR 1.06, 95% 1.03–1.10); inflammatory condition (HR 1.13, 95% CI 0.98–1.29); neck condition (HR 1.13, 95% CI 1.03–1.23); and multisite pain (HR 1.10, 95% CI 1.05–1.15). Although not included in the multivariable model, pregnancy (if gender female) within 1 year of the index consultation, reduced the risk of surgery (HR 0.24, 95% CI 0.21–0.28).

Conclusion: This study shows that patients who are older and who have comorbidities including other pain conditions are more likely to have surgery, whereas patients presenting with CTS during or within a year of pregnancy are less likely to have surgery. This information can help to inform clinicians and patients about the likely outcome of treatment and to be aware of which patients may be less responsive to primary care interventions.

Keywords: carpal tunnel syndrome, prognosis, epidemiology, primary care

Introduction

Carpal tunnel syndrome (CTS) is a chronic focal compressive neuropathy caused by the entrapment of the median nerve at the level of the carpal tunnel in the wrist.[1] CTS is the most common entrapment neuropathy[2] and is characterized by symptoms of paresthesia, dysesthesia, sensory loss, and in severe cases, weakness, and atrophy of the thenar muscle. Symptoms are usually localized to the hand but can spread proximally to the forearm, upper arm, and even shoulder.[3] Despite usually causing relatively localized symptoms, CTS can have substantial physical, psychological, and economic consequences.[4,5] Previous studies have sought to estimate the prevalence and/or incidence of CTS. Such epidemiological studies have been diverse in their approach to the populations studied and case definitions applied.[6] The reported estimates for

Correspondence: Claire Burton
Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire ST5 5BG, UK
Tel +44 178 273 3891
Fax +44 1 782 73 4719
Email c.burton@keele.ac.uk

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annual prevalence range from 3,720 to 5,700 per 100,000 per year[7–9] and the reported incidence from 72 to 8,200 per 100,000 per year.[6,10–16] CTS is generally accepted to be more common in females; the female to male ratio ranges between 0.78 and 9.66.[6,7] A number of previous studies have observed the trends of prevalence or incidence over time and identified an increase.[11,12,17]

The diagnosis of CTS is generally determined by clinical history and examination findings,[18] although electrodiagnostic tests are requested to confirm the diagnosis or differentiate among diagnoses.[19] The treatment of CTS is usually defined as either surgical or conservative (nonsurgical). Local steroid injections and night splinting form the mainstay of conservative primary care interventions in CTS, as indicated by national care pathways.[20,21] Patients with moderate or deteriorating symptoms following conservative treatment or sudden and severe symptoms should be referred for consideration of surgery.[22] Carpal tunnel release surgery (CTR) is routinely carried out under local anesthetic as day surgery. Open and endoscopic approaches are used to release the flexor retinaculum. Adjuncts to the release include a tenosynovectomy, neurolysis of the median nerve, or lengthening or reconstruction of the flexor retinaculum.[23] A review of the surgical treatment of CTS reported that 70%–90% of patients undergoing a CTR have a good outcome (definitions varied).[24] In a retrospective cohort study over a mean follow-up of 13 years post surgery, 88% of patients were either completely satisfied or very satisfied with surgical outcome; 74% reported their symptoms had completely resolved and 1.8% (113 patients) had undergone repeat surgery.[25] There is little evidence, however, that CTR is an appropriate initial management option for patients with mild to moderate symptoms, especially in the absence of high-quality trial evidence that conservative management is unlikely to be effective.

Episodes of CTR appear to be on the increase, with audit data from one major tertiary UK Hand Centre suggesting that referral for CTR increased over a 10-year period from 59.7 to 112 per 100,000 population per year between 1989–1999 and 2000–2011.[26] Using Hospital Episode Statistics (HES) between 1998 and 2011, Bebbington and Furniss also observed an increase in the absolute number of patients with CTS and episodes of CTR; however, they noted a decrease in the use of surgery per diagnosis, post 2008.[27] The increasing prevalence of the etiological factors are cited as contributing to the observed and predicted increase in the prevalence of the condition.[27] In the UK, CTR has been labeled by some Clinical Commissioning Groups (member organizations who determine how National Health Service (NHS) funds are spent in a particular locality) as a "procedure of limited clinical value" leading to variable patient access to the procedure.[28] The Royal College of Surgeons expressed their concern on the potential impact on patient health and well-being.[29]

The general course of CTS, prior to surgical management, is variable.[30] We conducted a systematic review of studies summarizing evidence regarding the course and prognosis of CTS; four studies[31–34] investigated the rate of surgery in patients initially treated with conservative management, reporting a range of 57%–66% of patients receiving surgery during follow-up of between 1 and 3 years. Studies published since the review have reported lower rates of surgery following local corticosteroid injection (15%–41% with follow-up between 1 and 8 years).[35–37] Evidence is therefore equivocal. A narrative synthesis of the 16 studies included in the review failed to identify consistent evidence of factors predicting poor outcome (including CTR), following conservative treatment.[30] Limitations of previous research identified by the review included a lack of studies conducted in a primary care setting, where most conservative management takes place. Design of the studies also showed wide variability with respect to characteristics of the included population, definition of CTS, assessment of prognostic factors, types of interventions provided, and types of outcome measures applied.

This study therefore aims to investigate the predictive value of candidate prognostic factors, identified through both review of the literature and discussion with clinicians, available in primary care consultation data, to predict (the first occurrence of) CTR surgery as an indicator of poor outcome of conservative management deliverable in primary care. Such evidence would be of benefit to patients, clinicians, and policy makers to inform planning of health care resources and decision-making regarding the management of CTS.

Methods

Setting

This was a retrospective cohort set in the Clinical Practice Research Datalink (CPRD). CPRD is a live primary care database of anonymized medical records, holding information of over 11.3 million patients from 674 practices in the UK since 1987. 4.4 million active (alive and currently registered) patients are currently contributing information to the datalink, which equates to 6.9% of the UK population.[38] CPRD is broadly representative of the UK general population in terms of age, gender, and ethnicity.[38] During clinical interactions, patients' signs and symptoms, treatments and therapies, investigations, occupations, diagnoses, and appliances are assigned Read Codes, which are stored

in the electronic primary care records in a retrievable and analyzable format,[39] although in practice, these can also be recorded in free text and as such are not always retrievable. The CPRD has National Research Ethics Committee approval for observational research using primary care data, and as such no further permissions were required. The Independent Scientific Advisory Committee study protocol 14_167 was approved in September 2014.

Study population (start point)

Individuals >18 years of age with evidence of an incident diagnosis of CTS and at least 2 years of acceptable data preceding the diagnosis were identified between 1989 and 2013, using the diagnostic Read code for CTS (F340). Patients were required to have up to standard (practice level) research quality (patient level) data in CPRD, for 2 years prior to an incident episode. The "up to standard" metric is based on continuity of recording and recording of deaths and set at the latest date at which practices met the quality criteria. The acceptable patient metric is based on registration status, the patient record itself, and a valid entry of age and gender.[38]

In order to attempt avoiding crossover between diagnosis and treatment (potentially bilaterally or a recurrent episode), only the first incident CTS episode was included, and thus, no patient with CTS was knowingly included more than once. It remained possible that a patient could be included more than once if they moved to another practice contributing to CPRD during the follow-up period, and consulted with a second episode of incident CTS after 2 years of registration, but this was considered to be unlikely. Only patients with an incident episode identified with a surgical (treatment) code were excluded, as it was not possible to identify a start point and baseline presentation for such patients.

End point

The maximum length of follow-up was set to 3 years. Surgery occurring >3 years after the baseline diagnosis was felt unlikely to be related to the observed episode. Three years was chosen to include the presumed maximum period of 2 years, during which an episode was considered to be ongoing, plus 1 year for further referrals, investigation, and surgery. CPRD is not able to discriminate between handedness and since around 50% of patients with CTS experience bilateral symptoms, it was felt using more than a 3-year follow-up would increase the risk of including events in the contralateral hand.

Candidate prognostic factors

Seventeen candidate prognostic factors were identified based on an appraisal of the available literature and clinical consensus work with a group of general practitioners and physiotherapists with a specialist interest in musculoskeletal health. Only those variables identifiable by Read code were included. Read code lists were either taken from an Institutional store or developed by the author (Read code lists available on request). The prognostic factors were subdivided into patient demographics (age, gender, geographical region, and deprivation score); lifestyle factors (evidence of obesity, smoking history, alcohol history, and pregnancy within 1 year of the index diagnosis of CTS); and comorbidities (affective disorders, hypothyroidism, diabetes, inflammatory conditions, neck conditions, multisite pain [including osteoarthritis], tendonitis/epicondylitis, and previous wrist trauma). Year of diagnosis was included in the unadjusted univariable analysis but not included in the multivariable model as this would have, by definition, prevented the model being used contemporaneously. Pregnancy was also not included in the multivariable model as it would limit its applicability to the presenting population.

For the multivariable prediction model, age was analyzed as a continuous variable, but the association with time to surgery was also presented in 10-year age categories for descriptive purposes. Body mass index (BMI) was dichotomized into obese and nonobese categories as it was considered clinically important to distinguish between these two subgroups. Smoking and drinking were identified in CPRD as cigarettes per day and alcohol units per week but entries were more frequently observed in the additional CPRD dataset which provided a "yes / no / unknown" outcome to "smoker" and "alcohol drinker". These binary variables were selected as there were fewer missing data and they were considered to be clinically meaningful.

Statistical methods

Cox proportional hazards modeling was used to determine the association between candidate prognostic factors and the first episode of surgical intervention. This time to event analysis included the censoring of patients when they received CTR, were recorded as deceased, left the practice, or the practice no longer contributed to CPRD. Proportional hazards assumptions were checked using Schoenfeld residual testing.

Univariable (unadjusted) analysis was performed to describe the crude association of each prognostic factor with outcome. All candidate factors were then entered in a

multivariable model, and a backward selection procedure was used to determine the prognostic factors for the final prediction model. Prognostic factors with a *P*-value >0.1 were omitted at each step, using a conservative significance level of 0.1 to reduce the risk of missing prognostic factors with potential clinical importance.[40] Prognostic factors eliminated were reentered in the final multivariable model with adjustment for the remaining prognostic factors to assess if they were of predictive value in the presence of other combinations of factors. The predictive performance (discrimination) of the final multivariable model was assessed using concordance statistics (C-statistics).[41]

Not all practices contribute deprivation data to CPRD, and in some cases, data were missing for lifestyle variables including BMI, alcohol use, and smoking history. Missing data were accounted for by adding a "missing" category to predictor variables. Missing data were not imputed as such data were likely to be "missing not at random" (MNAR; i.e., a patient with obesity was more likely to have a BMI recorded that someone who was not obese). Imputing data that are MNAR increases the risk of bias,[42] and we therefore used a sensitivity analysis using complete cases only to examine the potential effects of missing data.

The number of events (cases with CTR) within the CPRD cohort was sufficiently large to allow reliable estimation of all 46 predictor parameters in the full model when considering an event per predictor parameter ratio of at least 10[43] or even 20.[44,45]

Results

In total, 91,412 patients were included in the cohort. Out of this, 18,500 (20.2%) had surgery in the 3-year period following the index presentation (absolute CPRD population rate: 1.52 episodes of surgery per 100 person-years). The median time to surgery was 221 days interquartile range (IQR 111–409). Table 1 describes the demographic and clinical characteristics of all eligible patients at baseline with an incident CTS diagnosis code and of those without any data missing from collected prognostic factors (n = 44,522). A total of 2,967 patients had a preceding incident episode coded only with a surgical code for CTR and were not included in the analysis. Similarly, 253 patients with a diagnostic code attributed on the same day as a CTR code, and 8 patients diagnosed on their "end date" had no follow-up period to observe and were not included in the analyses.

Table 2 describes the unadjusted univariable associations of each candidate prognostic factor with time to surgery. The prognostic factor with the largest effect size was pregnancy, suggesting that patients presenting within a year of their coded antenatal period, were less likely to require surgery than other females (this analysis was completed in female patients only). Diabetes, inflammatory conditions, and multisite pain appeared to be predictors of surgery on univariable analysis.

Following the manual stepwise process of selecting candidate prognostic factors, the final multivariable model was derived, as shown in Table 3. Variables included in the final model are geographical region; deprivation status; age hazard ratio (HR 1.02 per year, 95% CI 1.01–1.02); obesity (HR, 1.23, 95% CI 1.19–1.27); alcohol drinker (HR 1.05, 95% CI 1.00–1.10); smoker (HR 1.06, 95% 1.03–1.10); inflammatory condition (HR 1.13, 95% CI 0.98–1.29); neck condition (HR 1.13, 95% CI 1.03–1.23); and multisite pain (HR 1.10, 95% CI 1.05–1.15). The Harrell's C concordance statistic for this model is 0.588 (95% CI 0.584–0.592). All variables except age, region, and deprivation met the Cox proportional hazards assumption. For these variables, the model considers the average effect over the 3-year follow-up period.

The results of the sensitivity analysis, using data only from patients who had complete predictor data (i.e., entries for deprivation, BMI, smoking, and alcohol status), are shown in Table 4. Deprivation status, alcohol status, smoking status, and neck conditions were lost from this model, suggesting these factors, particularly the lifestyle factors, may not be

Table 1 Description of cohort and cohort without missing data

	All patients	Patients without missing data
Participants, n	91,412	44,522
Patients with a coded episode of surgery n (%)	18,500 (20.24)	8,971 (20.15)
Practice	685 practices contributed	383 practices contributed
Year of baseline diagnosis, median (IQR)	2006 (2002–2010)	2007 (2003–2010)
Year of surgery, median (IQR)	2007 (2004–2011)	2008 (2004–2011)
Time to surgery in days, median (IQR)	221 (111–409) max 3 years	249 (118–559) max 3 years
Follow-up time in days, median (IQR)	1,095.75 (385–1,095.75)	1,095.75 (370–1,095.75)

(*Continued*)

Table 1 (*Continued*)

	All patients		Patients without missing data
Demographics			
Age at diagnosis, median (IQR)	53.00 (42.00–66.00)		53.96 (43.20–66.31)
Age group, n (%)			
18–29	4,713 (5.16)		1,810 (4.07)
30–39	13,741 (15.03)		6,504 (14.61)
40–49	19,366 (21.18)		9,504 (21.35)
50–59	21,597 (23.63)		10,825 (24.31)
60–69	13,964 (15.28)		69,333 (15.57)
>70	18,032 (19.73)		8,946 (20.09)
Female, n (%)	63,194 (69.13)		32,030 (71.94)
Geographical region, n (%)			
North East	1,460 (1.6)		929 (2.09)
North West	9,637 (19.59)		5,928 (13.31)
Yorkshire and The Humber	3,984 (10.54)		2,248 (5.05)
East Midlands	3,583 (3.92)		1,613 (3.62)
West Midlands	8,281 (9.06)		5,193 (11.66)
East of England	10,191 (11.15)		6,230 (13.99)
South West	8,841 (11.15)		5,931 (13.32)
South Central	10,832 (11.85)		5,876 (13.20)
London	8,270 (9.05)		5,232 (11.75)
South East Coast	9,483 (10.37)		5,342 (12.00)
Northern Ireland	2,371 (2.59)		–
Scotland	6,366 (6.96)		–
Wales	8,113 (8.88)		–
Deprivation score			
1 (least)	13,878 (15.18)	23.82[d]	10,631 (23.88)
2	14,041 (15.36)	24.10[d]	10,507 (23.60)
3	11,800 (12.91)	20.25[d]	8,981 (20.17)
4	10,594 (11.59)	18.18[d]	8,241 (18.51)
5 (most)	7,950 (8.70)	13.65[d]	61,362 (13.84)
Unknown	33,149 (36.26)	–	–
Lifestyle factors			
Body mass index[a] (Kg/m^2), median (IQR)	27.2 (23.9–31.2)		27.1 (24–31.2)
<30	54,209 (59.30)	67.24[d]	30,480 (68.46)
≥30	26,410 (28.89)	32.76[d]	14,042 (31.54)
Unknown	10,793 (11.81)	–	–
Ever drinker, n (%)			
No	10,968 (12.00)	13.94[d]	6,034 (13.55)
Yes	67,736 (74.10)	86.06[d]	38,488 (86.45)
Unknown	12,708 (13.90)	–	–
Ever smoker, n (%)			
No	50,924 (55.71)	62.95[d]	28,432 (63.86)
Yes	29,967 (32.78)	37.05[d]	16,090 (36.14)
Unknown	10,521 (11.51)	–	–
Pregnancy (in female patients)[b], n (%)	3,869 (4.23)		1,908 (5.96)
Comorbidities			
Affective disorder[c], n (%)	4,576 (5.01)		2,244 (5.04)
Hypothyroidism[c], n (%)	1,904 (2.08)		951 (2.14)
Diabetes[c], n (%)	1,795 (1.96)		1,012 (2.27)
Inflammatory condition[c], n (%)	851 (0.93)		426 (0.96)
Neck condition[c], n (%)	2,371 (2.59)		1,113 (2.50)
Multisite pain (including osteoarthritis)[c], n (%)	7,799 (8.53)		3,854 (8.66)
Tendonitis/epicondylitis[c], n (%)	850 (0.93)		421 (0.95)
Wrist trauma[c], n (%)	615 (0.67)		294 (0.66)

Notes: [a]Closest recorded value preceding the baseline diagnosis. [b]Identified between 1 year prior to baseline and baseline. [c]Identified between 2 years prior to baseline and baseline. [d]Percentage of patients, excluding the "unknown" category. [e]Censored at the episode of surgery.
Abbreviations: IQR, interquartile range.

Table 2 Unadjusted univariable associations of each candidate prognostic factor with time to surgery (all patients)

Candidate prognostic factors	Hazard ratio	95% CI
Age at diagnosis[a]	1.01	1.01–1.02
Age group[a]		
18–29	1	
30–39	1.72	1.59–1.92
40–49	2.28	2.05–2.52
50–59	2.67	2.41–2.95
60–69	2.70	2.43–3.00
>70	3.33	3.00–3.68
Gender (female)[a]	0.97	0.94–1.00
Year of diagnosis[a]	1.02	1.01–1.02
Geographical region[a]		
London	1	
North East	1.20	1.05–1.36
North West	1.30	1.21–1.39
Yorkshire and The Humber	1.23	1.13–1.35
East Midlands	1.62	1.48–1.76
West Midlands	1.43	1.34–1.54
East of England	1.11	1.04–1.19
South West	1.21	1.12–1.29
South Central	1.31	1.23–1.41
South East Coast	1.23	1.15–1.32
Northern Ireland	1.11	1.00–1.24
Scotland	1.69	1.57–1.82
Wales	1.28	1.19–1.37
Deprivation score[a]		
1 (least)	1	
2	0.96	0.912–1.01
3	0.99	0.94–1.05
4	0.92	0.87–0.98
5 (most)	0.96	0.90–1.02
Not known	1.00	0.96–1.04
Obesity		
Not obese (BMI <30)	1	
Obese (BMI ≥30)	1.21	1.17–1.25
Not known	0.87	0.83–0.91
Ever alcohol drinker		
No	1	
Yes	1.06	1.01–1.11
Not known	0.94	0.88–0.99
Ever smoker		
No	1	
Yes	0.97	0.94–1.01
Not known	0.99	0.94–1.03
Pregnancy (if gender = female)[a]	0.24	0.21–0.28
Affective disorder	0.96	0.90–1.03
Hypothyroidism	1.06	0.96–1.17
Diabetes	1.26	1.14–1.39
Inflammatory condition	1.26	1.10–1.45
Neck condition	1.15	1.06–1.25
Multisite pain (including osteoarthritis)	1.22	1.16–1.27
Tendonitis/epicondylitis	1.02	0.88–1.18
Wrist trauma	1.04	0.87–1.24

Notes: *P*-value obtained from each group compared to the referent group. [a]Variable does not fit the proportional hazard assumption and therefore presents the average effect over the follow-up period.
Abbreviation: BMI, body mass index.

Table 3 Final multivariable prediction model of prognostic factors associated with time to surgery (all patients)

Prognostic factors	Hazard ratio	95% CI
Age at diagnosis[a]	1.02	1.01–1.02
Geographical region[a]		
London	1	
North East	1.20	1.05–1.36
North West	1.30	1.22–1.40
Yorkshire and The Humber	1.26	1.15–1.38
East Midlands	1.65	1.52–1.80
West Midlands	1.43	1.33–1.53
East of England	1.09	1.02–1.18
South West	1.16	1.08–1.25
South Central	1.31	1.22–1.40
South East Coast	1.20	1.12–1.29
Northern Ireland	1.18	1.06–1.33
Scotland	1.78	1.65–1.93
Wales	1.32	1.22–1.43
Deprivation[a]		
1 (least deprived)	1	
2	0.96	0.91–1.01
3	1.00	0.95–1.06
4	0.94	0.89–1.00
5 (most deprived)	0.98	0.92–1.04
Unknown	0.92	0.87–0.96
Obesity		
Not obese	1	
Obese	1.23	1.19–1.27
Unknown	0.89	0.84–0.94
Ever alcohol drinker		
Never drinker	1	
Ever drinker	1.05	1.00–1.10
Unknown	1.08	1.01–1.15
Ever smoker		
Never smoked	1	
Ever smoked	1.06	1.03–1.10
Unknown	1.01	0.97–1.07
Inflammatory condition	1.13	0.98–1.29
Neck condition	1.13	1.03–1.23
Multisite pain	1.10	1.05–1.15

Notes: *P*-value obtained from each group compared to the referent group. [a]Variable does not fit the proportional hazard assumption and therefore presents the average effect over the follow-up period.

predictors of surgery. The Harrell's C concordance statistic for this model was 0.587 (95% CI 0.581–0.593).

Discussion

Course of CTS in the observed cohort

This is a contemporary study in a large database detailing the current outcome of patients being diagnosed with CTS in a primary care setting. Twenty percent of the cohort required surgery in the 3-year period following their incident consultation, over the course of the study period from 1989 to 2013. Our recent systematic review[30] showed widely varying

Table 4 Sensitivity analyses: final multivariable prediction model of prognostic factors associated with time to surgery, only including patients without missing data

Prognostic factors	Hazard ratio	95% CI (lower)
Age at diagnosis[a]	1.02	1.01–1.02
Geographical region[a]		
London	1	
North East	1.39	1.27–1.52
North West	1.19	1.06–1.34
Yorkshire and The Humber	1.80	1.60–2.03
East Midlands	1.45	1.32–1.58
West Midlands	1.21	1.11–1.32
East of England	1.25	1.14–1.36
South West	1.35	1.24–1.48
South Central	1.30	1.19–1.42
South East Coast	1.28	1.09–1.50
Obesity		
Not obese	1	
Obese	1.21	1.16–1.26
Inflammatory condition	1.37	1.14–1.64
Multisite pain	1.08	1.00–1.15

Note: [a]Variable does not fit the proportional hazard assumption and therefore presents the average effect over the follow-up period.

estimates for the outcome of conservatively treated CTS between included cohort studies. Such a variability was likely to be due to differences between the populations observed and the definition of outcome applied (i.e., patient-recorded outcome or surgical intervention). The range (57%–66%) of patients observed to receive surgery following conservative management over a period of between 1 and 3 years[31–34] was substantially higher than the figure reported in this cohort study. All four of the studies included in the review were set in secondary or tertiary hand clinics. Such populations have, in effect, already been selected due to the severity of their symptoms and/or lack of response to conservative management. This CPRD-derived cohort is likely to be more representative of the UK general practice population than cohorts observed in specialized care settings. Studies published since this review, focusing more specifically on local corticosteroid injection, have reported slightly lower rates of surgery,[35–37] possibly suggesting the use of surgery post conservative management is in decline. If this is the case, understanding the prognosis of conservative management would become all the more important.

It is possible that the occurrence of surgery this study observed was underestimated by the methods applied. We included patients with a diagnostic code for CTS and had to exclude cases where the episode was recorded only using a code for surgery, as it was not possible to observe such patients from their start point (baseline) to surgery or alternative end point. Consequently, findings from this study will represent a conservative and likely underestimated proportion of the CPRD population who required surgery. Furthermore, the observed period following the index incident episode was limited to 3 years as it was felt likely that a surgical outcome after this period was unlikely to be associated with the index presentation, and possibly related to a contralateral or recurrent episode. Finally, an episode of surgery was taken to indicate that the patient's symptoms or functional deficit had not responded to conservative treatment, or had been severe enough to warrant direct surgical consideration. This does not mean, however, that the patient without a surgical episode was necessarily symptom-free and functionally well at the end of the follow-up; consultation data are unable to provide such a level of detail.

Predicting the risk of having a recorded episode of surgery

Despite a number of candidate prognostic factors showing a significant association with surgery, the resulting multivariable model predicts a surgical outcome only moderately better than chance, with a C-statistic of 0.588 (where perfect prediction is 1).

Univariable analysis suggests that increasing age, year of diagnosis (removed from final model as would require contemporaneous data), geographical region, obesity, a record of alcohol consumption, diabetes, inflammatory conditions, neck conditions, and multisite pain, all increase the risk of having surgery. However, on multivariable analysis, diabetes, for example, does not retain significance and the final model itself does not perform well. Although some previous studies have suggested the prognostic value of these candidate predictors, evidence regarding these prognostic factors from the systematic review was not consistent,[30] which is in keeping with the results of this study.

On univariable analysis, the prognostic factor with the largest effect size was pregnancy (HR 0.24, 95% CI 0.21–0.28, measured in the female population). While not included in the final model (doing so would limit the application of the model to a female population), this suggests that patients presenting with CTS in pregnancy are less likely to require surgery than other nonpregnant patients. This is in keeping with a systematic review by Padua et al, which concludes that given the high rates of resolution of CTS following delivery, surgery should be reserved for cases in which conservative management fails or where functional impairment is severe or debilitating.[46]

Within the final model, factors with the largest effect size included certain geographical regions (in particular Scotland

and the East Midlands) and obesity. Region is likely to be a predictor of surgery due to the variability in local care pathways and access to surgery. The inclusion of region in the model acts to control for this, as much as possible. As shown by a recent meta-analysis of 58 studies, obesity is not only a risk factor for the onset of CTS, but also a predictor of CTR (adjusted OR=2.02, 95% CI 1.92–2.13). Obesity, as both a pathogenic cause of CTS and a predictor of severity, is likely to be due to the shape of the wrist exerting excess pressure on the median nerve.[47] The findings from our study further suggest that obesity is associated with surgical intervention in people presenting with CTS in primary care.

Limitations

The nature of using electronic consultation data meant that not all patients had complete datasets, for example, not all patients had a recorded BMI or smoking status. As deprivation linkage was available in practices in England only and not the whole of the UK, this again limited the number of patients with complete data substantially (by 46,890 patients, or 51% of the original cohort). The sensitivity analysis performed using only patients with complete data suggests deprivation, alcohol use, and smoking history may not be significant predictors of surgery; however, these results may be biased due to selective missing data (MNAR). Patients with evidence of such Read codes, in particular related to lifestyle variables, are likely to be a selected sample rather than representative of the total presenting population; for example, a patient who is obese is more likely to have a documented BMI than a patient who is not obese.

The quality of research is dependent on the completeness and accuracy of the data it utilizes. While validation studies of the CPRD have shown a high positive predictive value for some diagnoses,[38] the sensitivity and specificity of diagnoses are largely unreported.[48] It remains possible that the coding of a diagnosis of CTS, and indeed some prognostic factors, was inaccurate or absent. For example, a patient with a history of neck pain may not have received a Read code and hence not have been identified by the study. Patients with chronic conditions, such as diabetes, due to the regular structured follow-up they receive in primary care, may have been more likely to receive a clinical code than someone with a pain-related problem. Such underreporting may contribute to the limited performance of the final predictive model.

The study was also reliant on any surgical episode being captured by clinical coding in the database. As procedures now routinely take place outside of the secondary care environment (from circa. 2008 when the "any willing provider" concept was introduced), it was felt that HES would underestimate the episodes recorded, and hence primary care documentation was used. This relies again on the accurate and precise coding of correspondence into primary care.

Other factors may explain the poor predictive performance of the model. The most probable reason is that potentially important prognostic factors for future surgery could not be measured in CPRD, which include symptom duration and clinical tests such as a positive Phalen's test and thenar atrophy.[30] While Read codes do exist for Phalen's test and thenar atrophy, pilot work demonstrated that they were seldom used and therefore unlikely to provide reliable data when extracted from CPRD. Although geographical region was incorporated into the model as a proxy for the local variability in access to CTR, this will not fully reflect decisions at the level of commissioning health care. Also, the data cannot take into account patient preference and practitioners' referral and management behavior, which may be further possible reasons for the low predictive performance (C-statistic) of the model.

Implications for clinical practice

The aim of this study was to use consultation data to predict the risk of an episode of surgery in patients presenting in primary care with CTS, by developing a prognostic model. In order for a prognostic model to have good clinical utility, it should be generalisable to populations that have similar ranges of predictor variables, use unambiguous definitions of predictors and outcomes reproducible in clinical practice, and be tested in impact studies in order to estimate the effect of using the model on physicians' behavior (treatment decision-making) and the clinical and cost-effectiveness compared to care without the use of the model.[49] While CPRD is generalizable to the UK primary care population[38] and utilizes Read codes, which represent the language used in clinical practice, this model needs to be further developed to improve its predictive performance, using data from high-quality prospective cohort studies with sufficient information regarding potential prognostic factors, and subsequently tested for generalizability and clinical impact. The model, however, does confirm the potential predictive value of several prognostic factors, including obesity, lifestyle factors, other musculoskeletal pain, and comorbidity in a large representative primary care population.

Conclusion

Predicting the course and outcome of CTS presenting in primary care remains challenging. It was not possible to derive

a prognostic model with strong predictive performance using data from routinely collected electronic health care data. Future research needs to include more detailed information regarding the clinical history and physical examination findings in patients with CTS to improve predictive performance.

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Author contributions

CB produced the initial draft and LC, YC, and DvdW all contributed to subsequent revisions. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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References

1. Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. *Neurol Sci*. 2010;31(3):243–252.
2. Aroori S, Spence RA. Carpal tunnel syndrome. *Ulster Med J*. 2008;77(1):6–17.
3. Padua L, Padua R, Lo Monaco M, Aprile I, Tonali P. Multiperspective assessment of carpal tunnel syndrome: a multicenter study. *Neurology*. 1999;53(8):1654–1659.
4. Foley M, Silverstein B, Polissar N. The economic burden of carpal tunnel syndrome: long-term earnings of CTS claimants in Washington State. *Am J Ind Med*. 2007;50(3):155–172.
5. Atroshi I, Gummesson C, Johnsson R, Sprinchorn A. Symptoms, disability, and quality of life in patients with carpal tunnel syndrome. *J Hand Surg Am*. 1999;24(2):398–404.
6. Ferry S, Pritchard T, Keenan J, Croft P, Silman AJ. Estimating the prevalence of delayed median nerve conduction in the general population. *Br J Rheumatol*. 1998;37(6):630–635.
7. de Krom MC, Knipschild PG, Kester AD, Thijs CT, Boekkooi PF, Spaans F. Carpal tunnel syndrome: prevalence in the general population. *J Clin Epidemiol*. 1992;45(4):373–376.
8. Atroshi I. Carpal tunnel syndrome--prevalence, electrodiagnosis and outcome instruments. *Acta Orthop Scand*. 1999;70(6):70–71.
9. Papanicolaou GD, McCabe SJ, Firrell J. The prevalence and characteristics of nerve compression symptoms in the general population. *J Hand Surg Am*. 2001;26(3):460–466.
10. Latinovic R, Gulliford MC, Hughes RA. Incidence of common compressive neuropathies in primary care. *J Neurol Neurosurg Psychiatry*. 2006;77(2):263–265.
11. Bland JDP, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991–2001. *J Neurol Neurosurg Psychiatry*. 2003;74(12):1674–1679.
12. Gelfman R, Melton LJ, 3rd, Yawn BP, Wollan PC, Amadio PC, Stevens JC. Long-term trends in carpal tunnel syndrome. *Neurology*. 2009;72(1):33–41
13. Bongers FJ, Schellevis FG, van den Bosch WJ, van der Zee J. Carpal tunnel syndrome in general practice (1987 and 2001): incidence and the role of occupational and non-occupational factors. *Br J Gen Pract*. 2007;57(534):36–39.
14. Atroshi I, Englund M, Turkiewicz A, Tägil M, Petersson IF. Incidence of physician-diagnosed carpal tunnel syndrome in the general population. *Arch Intern Med*. 2011;171(10):943–945.
15. Jenkins PJ, Watts AC, Duckworth AD, McEachan JE. Socioeconomic deprivation and the epidemiology of carpal tunnel syndrome. *J Hand Surg Eur Vol*. 2012;37E(2):123–129.
16. Jenkins PJ, Srikantharajah D, Duckworth AD, Watts AC, McEachan JE. Carpal tunnel syndrome: the association with occupation at a population level. *J Hand Surg Eur Vol*. 2013;38E(1):67–72.
17. Nordstrom DL, DeStefano F, Vierkant RA, Layde PM. Incidence of diagnosed carpal tunnel syndrome in a general population. *Epidemiology*. 1998;9(3):342–345.
18. Padua L, Coraci D, Erra C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. *Lancet Neurol*. 2016;15(12):1273–1284.
19. American Academy of Orthopaedic Surgeons. *Clinical Practice Guideline on the Diagnosis of Carpal Tunnel Syndrome*. Rosemont, IL, USA. 2007.
20. National Institute for Health and Care Excellence. Carpal Tunnel Syndrome. Available from: http://cks.nice.org.uk/carpal-tunnel-syndrome#!scenariorecommendation:1. Accessed May 14, 2013.
21. NHS: Institute for Innovation and Improvement. Carpal Tunnel Syndrome (CTS) - The Map of Medicine. 2012. Available from: http://app.mapofmedicine.com/mom/127/page.html?department-id=8&specialty-id=1037&pathway-id=3411&page-id=8741&history=clear. Accessed October 25, 2012.
22. Royal College of Surgeons. *Commissioning Guide: Treatment of Carpal Tunnel Syndrome*. London. 2016.
23. Middleton SD, Anakwe RE. Carpal tunnel syndrome. *BMJ*. 2014;349.
24. Turner A, Kimble F, Gulyás K, Ball J. Can the outcome of open carpal tunnel release be predicted?: a review of the literature. *ANZ J Surg*. 2010;80(1–2):50–54.
25. Louie DL, Earp BE, Collins JE, et al. Outcomes of open carpal tunnel release at a minimum of ten years. *J Bone Joint Surg*. 2013;95(12):1067–1073.
26. Wildin C, Dias JJ, Heras-Palou C, Bradley MJ, Burke FD. Trends in elective hand surgery referrals from primary care. *Ann R Coll Surg Engl*. 2006;88(6):543–546.
27. Bebbington E, Furniss D. Linear regression analysis of Hospital Episode Statistics predicts a large increase in demand for elective hand surgery in England. *J Plast Reconstr Aesthet Surg*. 2015;68(2):243–251.
28. Ryan D, Shaw A, Graham S, Mason W. Variation in CCG policies for the treatment of carpal tunnel syndrome. Bulletin. 2017;99(1):28–31.
29. Royal College of Surgeons of England. *Procedures of Limited Clinical Value*. 2011.
30. Burton CL, Chesterton LS, Chen Y, van der Windt DA. Clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: a systematic review. *Arch Phys Med Rehabil*. 2016;97(5):836–852.e1.
31. Boyd KU, Gan BS, Ross DC, Richards RS, Roth JH, MacDermid JC. Outcomes in carpal tunnel syndrome: symptom severity, conservative management and progression to surgery. *Clin Invest Med*. 2005;28(5):254–261.
32. Duckworth AD, Jenkins PJ, Roddam P, Watts AC, Ring D, McEachan JE. Pain and carpal tunnel syndrome. *J Hand Surg Am*. 2013;38(8):1540–1546.
33. Kaplan SJ, Glickel SZ, Eaton RG. Predictive factors in the non-surgical treatment of carpal tunnel syndrome. *J Hand Surg Br*. 1990;15(1):106–108.

34. Miranda BH, Asaad K, Cerovac S. Carpal tunnel syndrome study: local corticosteroids, conversion to surgery and NHS implications. *J Plast Reconstr Aesthet Surg*. 2013;66(10):1432–1433.
35. Jenkins PJ, Duckworth AD, Watts AC, McEachan JE. Corticosteroid injection for carpal tunnel syndrome: a 5-year survivorship analysis. *Hand (New York, N.Y.)*. 2012;7(2):151–156.
36. Evers S, Bryan AJ, Sanders TL, Gunderson T, Gelfman R, Amadio PC. Corticosteroid injections for carpal tunnel syndrome: long-term follow-up in a population-based. *Cohort Plast Reconstr Surg*. 2017;140(2):338–347.
37. Hameso A, Bland JDP. Prevalence of decompression surgery in patients with carpal tunnel syndrome 8 years after initial treatment with a local corticosteroid injection. *J Hand Surg Eur Vol*. 2017;42(3):275–280.
38. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827–836.
39. Chisholm J. The read clinical classification. *BMJ*. 1990;300(6732):1092.
40. Royston P, Moons KGM, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *BMJ*. 2009;338:b604.
41. Harrell FE, Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361–387.
42. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
43. Peduzzi DH, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373–1379.
44. Ogundimu EO, Altman DG, Collins GS. Adequate sample size for developing prediction models is not simply related to events per variable. *J Clin Epidemiol*. 2016;76:175–182.
45. Austin PC, Steyerberg EW. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat Methods Med Res*. 2014;26(2):796–808.
46. Padua L, Di Pasquale A, Pazzaglia C, Liotta GA, Librante A, Mondelli M. Systematic review of pregnancy-related carpal tunnel syndrome. *Muscle Nerve*. 2010;42(5):697–702.
47. Shiri R, Pourmemari MH, Falah-Hassani K, Viikari-Juntura E. The effect of excess body mass on the risk of carpal tunnel syndrome: a meta-analysis of 58 studies. *Obes Rev*. 2015;16(12):1094–1104.
48. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2009;69(1):4–14.
49. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ*. 2009;338:b606.