Diagnosis, Causation and Treatment of Carpal Tunnel Syndrome: An Evidence-Based Assessment

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Diagnosis, Causation and Treatment of Carpal Tunnel Syndrome: An Evidence-Based Assessment

A Background Paper prepared for Medical Services
Workers' Compensation Board – Alberta

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EXECUTIVE SUMMARY

Carpal tunnel syndrome (CTS) arises from the intermittent or continuous compression or entrapment of the median nerve as it passes through the carpal tunnel from the wrist to the hand. Increased pressure on the median nerve in the carpal tunnel can result in progressive sensory and motor disturbances in parts of the hand innervated by this nerve, leading to pain and loss of function.

Despite the large number of original research studies on carpal tunnel syndrome, considerable uncertainty and even controversy exists in the medical community about its extent and etiology, the contribution of work and non-work risk factors to its development, the criteria used to diagnose it, the outcomes of various treatment methods, and the appropriate strategies for intervention and prevention.

The intent of this investigation is to establish a current, valid, clinically important and applicable foundation of peer-reviewed scientific evidence that can be used to make evidence-based decisions about the diagnosis, causation and treatment of carpal tunnel syndrome.

Because high quality, clinically relevant research is a small subset of the journal literature and can be difficult to find, the selection of original research studies for consideration in this review was a systematic and deliberate process that involved multiple stages: establishing a research context, executing literature searches, reviewing titles and abstracts, identifying articles for retrieval, and finally selecting, classifying and critically appraising the original research studies that make up the primary evidence base.

FINDINGS ON DIAGNOSIS OF CARPAL TUNNEL SYNDROME

- Diagnosis of CTS is complicated by the lack of agreement upon a "gold standard" or "reference standard" diagnostic method for verifying its presence or absence. A rigorous diagnosis of CTS is essential, however, as it forms the basis of appropriate treatment. The importance of an accurate medical diagnosis cannot be overstated.

- Although there is insufficient evidence to identify a single "best" examination-based clinical test, reliability and accuracy of certain clinical tests support their use as components of a clinical diagnosis of CTS. In our systematic review, the Phalen test was most consistently identified as accurate in high quality studies (greatest "coherence" of evidence). The carpal compression test and the hand symptom diagram also appear to be useful diagnostic tools. Combinations of independent tests (models) likely perform better diagnostically than do single tests. With the exception of thenar wasting, all clinical diagnostic methods rely on subjective input.

- Despite their limitations, electrodiagnostic studies are the most objective test available to demonstrate median nerve deficit, and their accuracy is good when properly performed. If surgery is being contemplated, electrodiagnostic confirmation of the clinical diagnosis is desirable. Use of electrodiagnostic study findings as the sole diagnostic tool is not recommended: they must be correlated with the history and physical examination.

- It may be difficult for a physician to distinguish between CTS and other conditions with similar symptoms (like tendonitis). There is ample evidence that the accuracy of the available diagnostic tools is not very good.

- No studies meeting the inclusion criteria addressed the frequency with which forearm conditions co-exist with CTS, and data on prevalence of those conditions would likely suffer from the same comparative problems for diagnosis as does prevalence data on carpal tunnel syndrome.

FINDINGS ON CAUSATION OF CARPAL TUNNEL SYNDROME

- Carpal tunnel syndrome has an indistinct, multifactorial etiology: often a single cause cannot be identified. A variety of contributing etiological factors and conditions can affect the median nerve in the carpal tunnel.

- Individuals vary in their susceptibility to developing carpal tunnel syndrome based on congenital or acquired anatomic structure, body mass index, gender, age, and psychosocial factors. Genetic predisposition may play a major role in the causation of carpal tunnel syndrome.

- Systemic conditions or pathologies that may cause or contribute to the causation of carpal tunnel syndrome include hormonal disorders, diabetes, pregnancy, thyroid disorders, and inflammatory arthritis.

- The evidence on the role of force, repetition, and/or force combined with repetition as risk factors for carpal tunnel syndrome is mixed and conflicting. While several studies in the evidence base reported risk of carpal tunnel syndrome associated with job tasks that require exposure to forceful repetitive wrist motion, others did not demonstrate that association.

- One study meeting the inclusion criteria provides evidence that vibration associated with job tasks increases the risk for carpal tunnel syndrome, although the study did not quantify the frequency or duration of the vibration.

- Tasks characterized by a high frequency but low force, i.e. computer key pad use, do not appear to be important precipitating factors for carpal tunnel syndrome.

- No studies meeting the inclusion criteria addressed the role of palmar impacting activities, gripping activities, grasping activities, wrist posture, static load, static body posture, local mechanical stresses, manual materials handling, pushing, pulling and carrying, grip type, impact loading, unaccustomed activity, driving, sheet metal work, temperature, use of gloves, or use of tin snips and pliers in the causation of carpal tunnel syndrome.

- The "double crush theory" (which proposes that if a nerve is compressed at two separate places, even though the degree of compression at one or both sites is sub-clinical, the cumulative impairment of conduction could be enough to cause symptoms of motor or sensory impairment) is actively under investigation, but it is experimental and unproven. It has by no means entered the mainstream of medical thought and its applicability to clinical medicine is not clear at this point.

- No studies meeting the inclusion criteria addressed a potential causal relationship between co-existing forearm conditions and CTS.

- Recurrence of CTS is the return of the disease and its symptoms after apparent recovery. Ongoing disease and symptoms constitute continuation. The concepts of recurrence and

continuation rest on the assumption that non-resolution or return of symptoms is not a result of misdiagnosis of another syndrome or condition as CTS.

- We were unable to identify any specific work-related activity that may predispose to bilateral carpal tunnel syndrome. In relation to work-related risk factors, each hand appears to be at independent risk depending on that hand's activity, and it is reasonable to assess each hand individually. Bilateral carpal tunnel syndrome should prompt a review for systemic medical conditions that may cause peripheral neuropathy.

FINDINGS ON TREATMENT OF CARPAL TUNNEL SYNDROME

- Factors that predict good or poor CTS treatment outcomes may not be the same in a workers' compensation population as in a general population. If results of CTS treatment studies are extrapolated from a general population to a workers' compensation population, it should be with caution.

- Two studies meeting our inclusion criteria looked at whether endoscopic or open carpal tunnel release surgery results in better outcomes. Neither study showed a statistical difference in benefit between the two procedures.

- Three studies meeting our inclusion criteria compared the effectiveness of surgical and non-surgical treatment for carpal tunnel syndrome and concluded that surgery resulted in better outcomes than non-surgical treatment, although all three studies were to some degree flawed.

- The evidence suggests that local steroid injection can be effective in providing symptom relief. This relief may be temporary, and limited by the risk of repeated steroid injections into the carpal tunnel. Oral steroids may also provide a measure of symptom relief, though this is a less common approach for most clinicians, and has additional risks.

- The evidence suggests that there is no difference in symptom reduction or functional improvement between night-only and full-time splint wear instructions, no significant differences in efficacy between conservative medical and chiropractic care, and no benefit from neuromagnetic treatment.

- The evidence on the therapeutic benefit of ultrasound, nerve and tendon gliding exercises, and treatment with low-level laser was mixed and conflicting.

- The consensus of medical opinion is that, in the majority of cases, a course of appropriate conservative management of carpal tunnel syndrome should be attempted before advising surgery. Exceptions may be made if there is obvious thenar wasting. In such cases, expedited medical and surgical assessment is required due to the risk of progressive and permanent neurological damage. Surgical consultation should also be made in the initial treatment phase if there is severe sensory disturbance, or a history of acute or traumatic onset.

- Carpal tunnel syndrome that has been appropriately diagnosed and that does not resolve with conservative measures, or carpal tunnel syndrome that is rapidly progressing, may require surgical intervention. In the vast majority of cases, electrophysiological testing

should be performed prior to surgery to confirm the diagnosis. Surgical treatment is usually only offered to electrophysiologically confirmed cases with no underlying reversible disorder.

- In cases of surgical failure, a complete reassessment by the surgeon and clinician is indicated. The patient should undergo a thorough re-examination and repeat electrodiagnostic assessment to rule out other, less common causes of peripheral neuropathy.

- A range of biomedical and non-biomedical variables influence return to work, both directly and indirectly, by influencing symptom relief. Following surgery, most patients can return to light hand use following the removal of sutures, but may not tolerate the use of tools that require a power grip for an average of six to eight weeks.

- None of the studies meeting the inclusion criteria addressed the role of pre- and post-operative electrodiagnostic testing in assessing return to work, recurrence or prognosis, hence we are unable to reach an evidence-based conclusion on these issues.

- There is nothing in the evidence base that suggests that age is a specific demographic variable that predicts a positive or negative outcome after treatment for carpal tunnel syndrome.

BACKGROUND PAPER

I. OVERVIEW

A. Introduction

Carpal tunnel syndrome (CTS) arises from the intermittent or continuous compression or entrapment of the median nerve as it passes through the carpal tunnel from the wrist to the hand. Increased pressure on the median nerve in the carpal tunnel can result in progressive sensory and motor disturbances in parts of the hand innervated by this nerve, leading to pain and loss of function.

Despite the large number of original research studies on carpal tunnel syndrome, controversy persists among physicians about its extent and etiology, the contribution of work and non-work risk factors to its development, the criteria used to diagnose it, the outcomes of various treatment methods, and the appropriate strategies for intervention and prevention (Sluiter 2001). Confusion in the general public is compounded by the dubious quality of the information about carpal tunnel syndrome found in the popular media and on the World Wide Web: as the Internet is a main source of medical information for patients, it is likely many are misinformed about carpal tunnel syndrome (Beredjiklian 2000).[1]

The intent of this investigation is to establish a current, valid, clinically important, and applicable foundation of peer-reviewed scientific evidence that can be used to make evidence-based decisions about the diagnosis, causation, and treatment of carpal tunnel syndrome.

B. Roles and responsibilities

In the spring of 2003 Alberta's Workers' Compensation Board (WCB-Alberta) asked a research team to conduct a comprehensive review of the scientific evidence on the diagnosis, causation and treatment of carpal tunnel syndrome to be used as a foundation for updated,[2] evidence-based Medical Advisory Guidelines for WCB-Alberta's physicians and case managers. Investigators included Bruce Fisher, MD, Master of Science, Fellow of the Royal College of Physicians and Surgeons of Canada; Ron Gorsche, MD, Master of Medical Science (Occupational Health), Certificant of the College of Family Physicians; and Patricia Leake, Master of Public Policy.

WCB-Alberta medical staff members defined the scope of this report and outlined the twenty-four research questions around which it is organized. The research team selected the criteria for retrieving articles and including studies, critically appraised the scientific evidence on the diagnosis, causation and treatment of carpal tunnel syndrome, and formulated evidence-based answers to the research questions. We confined ourselves to the science base and the conclusions that the science could bear: policy considerations were not a part of our mandate and were not addressed in our deliberations. This report is based on information that was collected between January and September, 2003.

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[1] See Appendix A for a summary of Beredjiklian's article.

[2] The previous background paper addressing carpal tunnel syndrome, *Repetitive Strain Injury, Occupational Hand and Wrist Disorders* (Cocchiarella 1995) , was submitted to WCB-Alberta by The Northern Alberta Occupational Health and Safety Resource Center (Edmonton, Alberta). It was last revised October, 1995. More than 90% (36/39) of the articles that met our inclusion criteria (and were therefore included in our primary evidence base) were published after this date.

We gratefully acknowledge the ongoing assistance of WCB Medical Advisors Victoria Cho, David Linklater and Kate Reed. Their thoughtful review of this background paper was much appreciated.

C. Research questions

This background paper systematically evaluates the scope and quality of the available scientific evidence on diagnosis, causation and treatment of carpal tunnel syndrome to answer 24 research questions. Questions 1-6 address diagnosis of carpal tunnel syndrome, questions 7-17 address causation of carpal tunnel syndrome, and questions 18-24 address treatment of carpal tunnel syndrome. The report is correspondingly organized. Together, the 24 research questions (found in Figure 1) define the scope of the background paper. Items not addressed by the research questions are beyond the scope of this document.

D. Guide to the report

Sections I and II of the report provide general and contextual material including an introduction, the respective roles and responsibilities of WCB medical staff members and the research team, the research questions, and background information on CTS.

Section III describes some of the practical and methodological difficulties associated with research on carpal tunnel syndrome and outlines the way in which the scientific evidence was identified and assessed. Sections IV, V, and VI present the research team's findings on the diagnosis, causation and treatment of carpal tunnel syndrome. It is in these sections of the report that the 24 research questions are answered. Section VII concludes the document.

A glossary is found in Appendix M.

Figure 1. Twenty-four Research Questions about Carpal Tunnel Syndrome

Research questions about diagnosis of CTS

Question 1. *How is a clinical diagnosis of carpal tunnel syndrome established?*

Question 2. *What are the respective roles of examination-based clinical diagnosis and of electrodiagnostic studies (EDS) in the diagnosis of carpal tunnel syndrome? Is either necessary? Is either sufficient? When, if ever, are both necessary?*

Question 3. *Are there qualifications and technical limits on the interpretation of electrodiagnostic studies?*

Question 4. *How accurate is examination-based clinical diagnosis? How accurate are electrodiagnostic studies in symptomatic individuals?*

Question 5. *How can a physician distinguish between CTS and other conditions with similar symptoms (e.g. tendonitis)?*

Question 6. *Which forearm conditions co-exist with CTS? With what frequency?*

Research questions about causation of CTS

Question 7. *Which (if any) of the following work-related activities are risk factors for CTS? Palmar impacting activities? Repetitive activities? Gripping activities? Grasping activities? Wrist posture? Are there others?*

Question 8. *Which (if any) of the following tasks increase the risk of CTS and to what degree? Driving? Sheet metal work? Use of tin snips/pliers? Keyboarding?*

Question 9. *Does a static body posture increase the risk of CTS?*

Question 10. *Do the following work environmental factors increase the risk of CTS? Vibration (frequency, duration)? Temperature (what temperature)? Use of gloves? Others?*

Question 11. *What are the systemic conditions that may cause or contribute to CTS? What is the magnitude of the effect?*

Question 12. *What is the relationship of anatomic structure (congenital or acquired, eg., degenerative changes to the wrist) to CTS?*

Question 13. *What individual characteristics (age, gender, body mass, personal habits, psychosocial variables and genetic predispositions) are risk factors for CTS?*

Question 14. *Which co-existing forearm conditions may cause or contribute to CTS?*

Question 15. *Do prior episodes of cervical nerve root irritation pre-dispose to CTS (is there a scientific basis for the "double crush" theory)?*

Question 16. *What constitutes recurrence of CTS and what constitutes continuation of CTS?*

Question 17. *Which work-related activities or conditions may predispose to CTS in both wrists?*

Research questions about treatment of CTS

Question 18. *Which surgical and non-surgical treatments have been shown to be effective in the therapy of CTS?*

Question 19. *Is it possible to identify those cases in which CTS would be best treated with surgery? Non-surgical therapy? Both?*

Question 20. *What indicators suggest that a patient can reasonably be expected to return to work following a course of conservative therapy or surgery? When should this return be expected?*

Question 21. *Is there a role for pre- and post- operative electrodiagnostic testing in assessing work return, recurrence or prognosis?*

Question 22. *Which environmental adaptations have been shown to prevent or help manage CTS? Which ergonomic adaptations? Are safety programs effective?*

Question 23. *What is the appropriate treatment for a "failed" carpal tunnel release?*

Question 24. *Is there a relationship between the patient's age and specific treatment outcomes?*

II. CARPAL TUNNEL SYNDROME IN CONTEXT

A. Definition, classification and characterization of carpal tunnel syndrome

Carpal tunnel syndrome arises from the intermittent or continuous compression or entrapment of the median nerve as it passes through the carpal tunnel from the wrist to the hand. Increased pressure on the median nerve in the carpal tunnel can result in progressive sensory and motor disturbances in parts of the hand innervated by this nerve, leading to pain and loss of function.

In their comprehensive review of the scientific literature on the relationship of work and the workplace to musculoskeletal disorders of the low back and upper extremities, the National Research Council and the Institute of Medicine (NRC&IOM 2001) use the World Health Organization (WHO) definition of work-related disease to characterize carpal tunnel syndrome.

According to the World Health Organization:

> 'multifactorial diseases,' which may frequently be work-related, also occur among the general population, and working conditions and exposures need not be risk factors in each case of any one disease. However, when such diseases affect the worker, they may be work-related in a number of ways: they may be partially caused by adverse working conditions; they may be aggravated, accelerated or exacerbated by workplace exposures; and they may impair working capacity. It is important to remember that personal characteristics, and other environmental and sociocultural factors usually play a role as risk factors for these diseases[3] (WHO 1985).

Underlining a further distinction, the US Department of Health and Human Services Public Health Service Agency for Healthcare Research and Quality recently characterized carpal tunnel syndrome as a "worker-related upper extremity disorder," defining "worker-related" as "a disorder that affects workers, not as a disorder necessarily caused by work" (Chapell 2003).

B. Dimensions of the problem: occurrence and distribution

While carpal tunnel syndrome is believed be a common clinical condition, its prevalence and incidence in general and working populations have not been reliably established by epidemiological studies. There are a number of caveats with respect to the interpretation of epidemiological data on carpal tunnel syndrome. For example:

- Variable diagnostic criteria and lack of agreement on a gold standard for diagnosis of carpal tunnel syndrome have a significant impact on any statistic of prevalence.

- There are no reliable sources of comprehensive national data that capture medically diagnosed carpal tunnel syndrome. Almost all published CTS epidemiological data are

[3] The WHO draws the following distinction between work-related diseases and occupational diseases: "in occupational diseases, there is a direct cause-and-effect relationship between hazard and disease. In work-related diseases, in contrast, the work environment and the performance of work contribute significantly, but as one of a number of factors, to the causation of a multifactorial disease. Occupational diseases therefore stand at one end of the spectrum of work-relatedness, where the relationship to specific causative factors at work has been fully established and the factors concerned can be identified, measured, and eventually controlled. At the other end, diseases may have a weak, inconsistent, unclear relationship to working conditions; in the middle of the spectrum there is a possible causal relationship but the strength and magnitude of it may vary" (WHO 1985).

based on individual self-report in surveys, and CTS prevalence rates are higher when the definition is based on self-reporting (Atroshi 1999).

- It is not feasible to assess the relative contribution of occupational and non-occupational factors to the occurrence of CTS in the general population. General population survey data do not and cannot distinguish cases of carpal tunnel syndrome that may be associated with work from those not likely to be associated with work in the study populations. The data include work and non-work-related cases of carpal tunnel syndrome without distinction. Rates derived from these general population sources cannot be considered in any sense equivalent to rates for background, reference, or unexposed groups. No comprehensive data are available on occupationally unexposed groups, and given the proportion of adults now in the active workforce, any such non-employed group would, by definition, be unrepresentative of the general adult population (NRC 1998, NRC&IOM 2001).

1. Carpal tunnel syndrome in general populations

A general 1997 health survey in southern Sweden found that 354 responders (prevalence 14.4%) reported pain, numbness and or tingling in the median nerve distribution in the hands of the positive responders. Nerve conduction testing showed median neuropathy at the carpal tunnel in 120 symptomatic subjects (prevalence 4.9%). On clinical examination, 94 symptomatic subjects were diagnosed as having clinically certain carpal tunnel syndrome (prevalence 3.8%). Sixty-six symptomatic subjects were found to have clinically and electrophysiologically confirmed CTS (prevalence 2.7%) (Atroshi 1999).

Another study that sought to estimate the incidence rate of CTS in the general population used three different case definitions and medical record review to determine all cases of incident CTS in a defined population in Wisconsin during a 2 year period. The investigators found that newly diagnosed probable or definite CTS (N = 309) occurred at a rate of 3.46 cases per 1000 person years (Nordstrom 1998).

CTS is a condition of middle aged people and is more common in women than in men. A study of the residents of Rochester, Minnesota, found that the mean age at diagnosis was 50 years for men and 51 years for women. Women accounted for 78.5% of the cases. While the prevalence for men generally increases steadily with rising age, for women the prevalence peaks dramatically during middle age (45-55 years of age) and then levels off (Stevens 1992). It has been hypothesized that the higher incidence of CTS in women than in men is due in part to differences in carpal tunnel volume between men and women (Chapell 2003). It has also been suggested that hormonal changes (for example during pregnancy and menopause) influence the onset of CTS in women (Chiang 1993, Ferrero 2001), causing swelling that increases pressure on the median nerve (Wilgis 2002b).

2. Carpal tunnel syndrome in working populations

In 1992, repetitive motion disorders (stresses and strains resulting from free bodily movement with no impact involved) were surveyed by the US Bureau of Labor Statistics.[4] Nearly 90,000 cases resulting in lost time were found. Carpal tunnel syndrome was the most common disabling condition at 36% of the total, and resulted in more lost work (median 32 days per

[4] The Annual Survey of Occupational Injuries and Illnesses conducted by the US Bureau of Labor Statistics is the only routinely published, national source about occupational injuries and illnesses in US workers. No similar routinely published source of Canadian national data on occupational injuries and illnesses was identified.

case) than any other illness or injury reported in 2.3 million cases. The 1994 Bureau of Labor Statistics survey of injuries and illnesses showed that repetitive motion disorders had increased by just 3% over the 1992 figures, but cases of CTS resulting in lost work time had increased by 16% and by then represented more than 41% of all repetitive motion disorders (Atcheson 1998).

The National Institute for Occupational Safety and Health (NIOSH) reported that in 1993, CTS occurred at a rate of 5.2 per 10,000 full time workers, and that this syndrome required the longest recuperation period of all conditions that result in lost work days, with a median of 30 days lost (NIOSH 1996).

Information pertaining to CTS prevalence and incidence in specific occupational groups is found in Table 10, Studies Meeting the Inclusion Criteria: Causation of CTS.

3. Carpal tunnel syndrome and workers' compensation

During the 1970s the first carpal tunnel syndrome claims were submitted to US state workers' compensation systems. Awareness expanded in the mid-1980s with the emergence of hand and wrist disorders as a focus of union activism in meat-packing. Safety concerns, particularly concerns related to carpal tunnel syndrome, became a key issue for management-labor relations. The most prominent and notorious strike occurred from August 1985 to September 1986 at the flagship Hormel plant in Austin, Minnesota. When union organizers chose work-related carpal tunnel syndrome as the focal point of their complaints against the company, the syndrome gained widespread national media attention for the first time (Dembe 1996). Carpal tunnel syndrome has since emerged as a significant and increasing source of claims in workers' compensation systems worldwide.

There is evidence of a marked increase in the number and cost of CTS compensation claims in Canada from the early to mid 1990s. In Nova Scotia, for example, cases of newly reported work-related CTS rose from 56 per annum in 1991 to 207 in 1996. In Alberta, newly reported work-related CTS cases rose from 316 per annum in 1990 to 868 per annum in 1997. The overall costs for CTS claims in Alberta increased 2.9 times (from $1.3 million to $3.8 million) and overall compensation days increased 1.7 times (from 18,013 days to 31,386 days) during the same period. The cost of CTS claims in British Columbia increased significantly from 1993 to 1997: according to WCB-BC, each CTS claim in 1993 cost $8,327 in direct WCB payments, while in 1997 the cost per claim was $11,993 (Li 1999).

More recently, over the period from 1998 to 2002, WCB Alberta accepted a total of almost 4000 CTS claims (roughly 800 per year). Over 90% of these claims were exclusively for CTS ("clean claims"); the rest were for CTS in combination with another illness or injury. Total claims for CTS were almost evenly divided between no time loss (48%) and time loss (52%). Average days lost per accepted time loss claim has fallen steadily for the last five years in Alberta, from 151 in 1998 to 98 in 2002, while carpal tunnel surgeries[5] increased from 37 in 1998 to 233 in 2002 (WCB-Alberta 2003). WCB Alberta currently provides workplace liability and disability insurance to more than 1.3 million workers.

The Washington State Department of Labor and Industries is the sole regulator of workers' compensation coverage in Washington State (like Alberta covering approximately 1.3 million full time workers). In his study of occupational carpal tunnel syndrome in Washington State,

[5] The data represent procedures, not individuals. Individuals with operations on more than one occasion would be counted more than once.

Franklin reported a CTS incidence of 1.74 per 1000 FTEs in Washington between 1984 and 1988. He found that the mean age and female/male ratio in the population of compensated workers differed from those reported in non-occupational CTS studies: while the mean age of CTS onset is 51 years in the general population, it was only 37.4 years among compensated workers in Washington. The female/male ratio was 1.2:1 in the compensated population: the ratio in non-occupational carpal tunnel studies was 3:1 (Franklin 1991).[6] Carpal tunnel syndrome was subsequently reported to have the highest rate of work absence of all work-related disorders in the Washington system, with >20% of those with some work loss being out of work for at least 6 months (Katz 1997).

The epidemiological transition from acute, unequivocal injuries to slow onset, multifactorial disorders like carpal tunnel syndrome has emerged as one of the fundamental challenges to North American workers' compensation systems (Sullivan 2000b).

4. Carpal tunnel syndrome and the changing nature of the Canadian workforce

The average age of the Canadian workforce is increasing, with individuals in the large baby boom population[7] now entering their fifties. In addition, thanks to improvements in health technology as well as healthier lifestyles, both men and women are living longer.[8] This increase in life expectancy, coupled with the aging of baby boomers, means that in the future substantially larger portions of the population will be in the older age brackets, and older workers will be responsible for an increasing fraction of total compensation claims. Older workers are more prone to conditions that are age-related, and work-related conditions with long latency periods may become manifest. This could increase claim costs, while longer life expectancy could increase the duration of claims (Gunderson 2000b).

At the same time, the workforce of the future will continue to reflect the increasing labor force participation of women, and the injuries, conditions and diseases women experience may constitute an increasing proportion of workers' compensation claims (Chung 2000).

Together, these two demographic trends have potentially profound implications for Canadian workers' compensation systems, as conditions like carpal tunnel syndrome that are more common among women and older people become increasingly prominent.

C. Anatomical review

1. Anatomy of the carpal tunnel

The carpal tunnel is a fibro-osseous U-shaped canal with a bony floor and walls and a roof of fibrous flexor retinaculum. The median nerve and nine flexor tendons (four flexor digitorum

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[6] A caveat with respect to interpretation of WCB generated data is that the epidemiological information on injury and disease is based on accepted claims. WCB data are limited by the criteria governing the acceptance of claims, the extent to which employers are registered with the WCB, and the extent to which workers report their injuries to the WCB. Although claims acceptance rates are obviously related to underlying disease and injury rates, the claims acceptance process is an administrative and policy filter that limits the extent to which these data can be generalized to characterize an entire at-risk population (Ostry 2000).

[7] People born between 1946 and 1966.

[8] The life expectancy of Canadian women is projected to increase from 78.2 years in 1992 to 86.9 years by 2010. Similarly, Canadian male life expectancy, which was 72.1 years in 1992, is expected to increase to 80.3 years by 2010 (Gunderson 2000b).

superficialis, four flexor digitorum profundus tendons, and the flexor pollicis longus tendon) run through the carpal tunnel (Patry 1998).

2. The median nerve

The median nerve is a mixed sensory and motor nerve that enters the hand on the palmar side of the wrist, through a narrow, rigid, fibro-osseous passageway (the carpal tunnel) bordered on three sides by the carpal bones and on the other by the flexor retinaculum (or transverse carpal ligament).

The nerve is the softest and most sensitive element in the carpal tunnel. Anything that decreases the size of the tunnel or increases the size of its contents can result in compression of the median nerve. Examples include space occupying lesions, arthritis, trauma, edema, and dislocation of the lunate bone (Chapell 2003).

a. Sensory innervation

The median nerve usually arises principally from the C6, C7, and T1 nerve roots. Its sensory fibers innervate the palmar aspect of the thumb, index finger, middle finger and radial half of the ring finger, and the dorsal aspect of the tip of these fingers. The pad of the index and middle fingers constitutes its selective sensory field (Patry 1998).

b. Motor innervation

The motor branches of the median nerve innervate three muscles in the thenar eminence (the abductor pollicis brevis, opponens pollicis, and flexor pollicis brevis) and the lumbricals of the index and middle finger. Because variant innervation patterns are common, the most reliable indicator of motor disorders of the median nerve is weakness of the abductor pollicis brevis (Patry 1998).

D. Pathogenesis and pathophysiology

Carpal tunnel syndrome is the symptomatic presentation of median nerve entrapment at the wrist. The median nerve is damaged within the rigid confines of the carpal tunnel. CTS occurs as a result of an increase in pressure transmitted to the median nerve in the canal. Two theories have been proposed to explain the effect that this increase in pressure has upon the median nerve: transient ischemic episodes linked to microvascular disorders, or median nerve compression as a result of a reduction in tunnel volume or an increase in the volume of tunnel contents. Both theories attempt to explain the nerve's response to pressure, but not the cause (Patry 1998).

Intrinsic abnormalities of the median nerve itself may act to lower the threshold for symptomatic compression. Pressures within the carpal canal that might not otherwise cause symptoms of carpal tunnel syndrome may do so if the nerve is rendered particularly sensitive to pressure by some other disease or condition. A common example of this is diabetes mellitus, which frequently affects peripheral nerve function. Peripheral nerves, including the median nerve, are a target of diabetes and in individuals with this condition, carpal tunnel syndrome may occur even where the pressure in the carpal canal is insufficient to cause these symptoms in a non-diabetic individual. In this case, diabetes may be considered a pre-existing condition that predisposes the median nerve to symptoms of compression under circumstances where this might not otherwise occur (Graham 2001).

The signs and symptoms of carpal tunnel syndrome appear suddenly or progressively in the median nerve's innervation field in the hand. Most commonly, a median nerve disorder is progressive. The acute form appears more frequently in the working population, with sudden intense symptoms usually resulting from trauma or unusual exertion involving the wrist.

Especially in its acute form, idiopathic CTS results from an ischemia-reperfusion injury to the median nerve. The final common pathway begins with intermittent increases in interstitial fluid pressure, leading to degenerative changes in the flexor tenosynovium and fibrotic changes in the perineural tissue. Sud et al reported a significant increase in synovial absorption rate compared to controls in a prospective controlled study of 27 CTS subjects (Sud 2002). A study by Freeland reported a significant increase in biologic markers such as malondialdehyde (MDA, a known marker for cellular reperfusion distress and damage), interleukin 6 and prostaglandin PGE2, but not inflammatory markers compared to controls (Freeland 2002). These two studies help us understand why CTS is not an "itis" but may be an "osis" (Freeland 2002; Gross 1995).

Pregnancy, obesity, hypothyroidism and changes in hormone levels could all contribute to an increase in interstitial fluid pressure. Anatomical factors such as incursion of the lumbrical muscles during flexion and space occupying lesions have also been shown to increase intracarpal canal pressures. (Keir 2000, Szabo 1998, Seigal 1995, Seradge 1995, Hamanaka 1995).

E. The three stages in the evolution of the progressive form of CTS

1. Stage 1 carpal tunnel syndrome

In Stage 1 carpal tunnel syndrome, transient epineural ischemic episodes cause intermittent pain and paresthesia in the median nerve's field in the hand. These symptoms typically occur at night, or following specific activities such as driving a car or holding a book or newspaper, and suggest the presence of nerve transmission disorders (Szabo 1992).

2. Stage 2 carpal tunnel syndrome

In Stage 2 carpal tunnel syndrome, there is constant paresthesia and tingling, corresponding to disturbed intraneural and epineural microcirculation concomitant with intrafascicular edema. Electrodiagnostic tests usually reveal abnormal sensory conduction (Szabo 1992).

3. Stage 3 carpal tunnel syndrome

In Stage 3 carpal tunnel syndrome, sensory and motor function are permanently damaged, and there is atrophy of the thenar eminence. Electrodiagnostic tests are abnormal, and demyelinisation and axonal degeneration secondary to prolonged endoneural edema may be present (Szabo 1992).

III. ASSESSING THE EVIDENCE

A. Research on carpal tunnel syndrome: methodological and practical challenges

There is a vast medical literature on the diagnosis, causation and treatment of carpal tunnel syndrome. It includes a wide variety of research designs, assessment instruments, and methods of analysis, and is characterized by research studies of heterogeneous methodological quality and inconsistent results. Some of the practical and methodological challenges encountered by researchers, as well as by those conducting a critical appraisal of CTS research, are summarized below.

1. Lack of a diagnostic gold standard

The evaluation of diagnostic tests for carpal tunnel syndrome is greatly complicated by the absence of an agreed upon independent "gold standard." No single test absolutely confirms the diagnosis of CTS. Neither the validity nor the reliability of existing diagnostic tests is fully established (Rempel 1998). Determinations of who has and who does not have CTS are imperfect (for example, persons who do not have CTS may have symptoms of another condition that mimics CTS), so it is very difficult for studies to reach accurate conclusions on how well a particular diagnostic test performs.

There are wide variations in the diagnostic criteria used by investigators to determine the independent effect of the workplace as a cause of carpal tunnel syndrome. Different diagnostic criteria and different case definitions used by different researchers in their studies of possible work-related risk factors contributes to many of the controversies surrounding the causation of carpal tunnel syndrome. The manner in which carpal tunnel syndrome is diagnosed varies so much from study to study that comparison of studies is difficult and sometimes impossible. In some studies, for example, the fact that the patient had surgery for carpal tunnel syndrome is taken as the comparative standard for diagnosis of carpal tunnel syndrome, with no consideration of whether or not the surgery was appropriate (Szabo 1999).

2. Potential for spectrum bias

The definitions of the groups being compared in a study can affect results by introducing spectrum effects into the study population. Most CTS diagnostic trials compare groups of patients with known or suspected CTS and groups of healthy normal controls. There are a number of difficulties with such studies:

- Potential spectrum bias because the controls are required to be asymptomatic, and subjects with unrelated upper extremity disorders are excluded. In routine practice, the spectrum of negative cases is likely to include patients with abnormalities that mimic carpal tunnel syndrome, thereby reducing test specificity and positive predictive value (Chapell 2003).

- Potential spectrum bias when severe or clear-cut cases are selected as subjects, and patients with mild carpal tunnel syndrome (that would be harder to diagnose) are excluded. This would be the case, for example, if subjects were patients presenting to a hand surgeon: patients who reach a hand surgeon may present late in their disease, especially if the surgeon's clinic is very busy (Massy-Westropp 2000). In routine practice, the spectrum of patients with CTS is likely to include mild cases that may not be detected by diagnostic tests, thereby reducing sensitivity and negative predictive value (Chapell 2003).

- The converse of the spectrum bias described above, where inclusion criteria are designed to study patients with mild carpal tunnel syndrome. Studies of only patients with mild disorders will underestimate test performance (Chapell 2003). Results of a study performed by occupational health physicians on site in a vocational setting, for example, would be based on a population of subjects who would tend to present early (Massy-Westropp 2000).

- Potential age bias arising from selection of young hospital or laboratory workers as controls rather than persons of the same age as CTS sufferers (Chapell 2003).

- Potential sex bias arising from different sex distributions in the patient group and the control group (Chapell 2003).

Together, these spectrum effects amplify the differences that are found in research studies of diagnostic techniques, and the results may not be applicable to the population most likely to get a test in routine practice: persons in high risk groups or with ambiguous symptoms (Chapell 2003).

The sensitivity of a diagnostic test could change at each of the various stages of CTS. Some of these difficulties would be resolved if research studies routinely broke CTS down into stages (Stage 1, 2, and 3) but this rare (Massy-Westropp 2000).[9]

3. Potential for surveillance bias

In cohort studies on causation of CTS, ascertainment of outcome is a key issue. One possible explanation for some of the increased risk reported in these studies might be that physicians, aware of a possible risk, search more diligently and therefore detect disease that might otherwise go unnoticed or detect disease at an earlier point in time. This could result in the exposed cohort having an apparent, but spurious, increase in risk, a situation referred to as surveillance bias (Levine 2003).

4. Shortcomings of the available epidemiological data

Much of the epidemiological data on CTS is derived from self-report. These data are not based on medical diagnoses of CTS made by physicians, but on individuals' assessment of their symptoms, their "self-diagnoses," or their knowledge of a physician's diagnosis. The problem stems in part from the difficulty associated with diagnosis of CTS: even in some physicians' evaluations, CTS diagnosis is based largely on subjective information provided by patients. Prevalence rates of carpal tunnel syndrome are higher when the definition is based on self reporting (Atroshi 1999).

No databases provide rates of CTS in an "unexposed" population, since the exposures of interest are so widespread. High workforce participation rates complicate identification of non-working populations: it is difficult to distinguish work exposures from other life exposures that lead to carpal tunnel syndrome because 80% of the population works. As the data derived from general population estimates are not linked to data that would allow discrimination or apportionment among work and nonwork-related exposures, that data's usefulness is limited (Chapell 2003).

[9] Information on the stages of CTS is found in section II.E.

5. Difficulty of meaningful measurement of workplace exposure

Attributions of occupational causality are also problematic because meaningful measure of workplace exposure is difficult.[10] Exposure measurements range from very crude measures (e.g. occupation title) to complex analytical techniques (e.g. spectral analysis of electrogoniometer measurements of joint motions).

Exposure assessment related to the identification of work-related risk factors for carpal tunnel syndrome is frequently subjective and lacks standardization (Moore 1995). Some studies rely on self-assessment of physical workload by study subjects, and the accuracy of such self assessment is debatable (Bernard 1997). Many studies make no attempt whatsoever to quantify workplace exposure.

In part because of the ease of access to administrative data sets, there is a vast literature in which job title is accepted as the surrogate measure of exposure, despite the fact that the variable "job category" is acknowledged to be a poor surrogate for actual ergonomically hazardous exposures encountered by working people (Gerr 1999).

There are significant differences between work styles - the manner and intensity in which an individual meets the demands of a particular work task. Work styles are complex, multidimensional responses to work demands and arise from the interaction of physiological, behavioral and cognitive factors (Feuerstein 1996). Workers are unique individuals, a "job" includes many discrete tasks, and tasks vary. Even the impact of apparently highly stereotypical tasks may vary enormously due to individual differences in body type, performance, and job expectations.

6. Failure to control for confounding risk factors

Studies of the relationship of CTS causation to the content of tasks must consider other known risk factors that modify the likelihood that the disorder will occur. For example, the frequency of carpal tunnel syndrome is a function of age, so age needs to be taken into account before attributing CTS to a work exposure. Obesity and diabetes mellitus are examples of possible confounders that are not always controlled for. With the exception of gender and age very few associations are routinely considered in the design or analysis of research studies on the causation of carpal tunnel syndrome. Inability or failure to control for confounding risk factors means that plausible but unmeasured risk factors could explain some or all of the observed differences in rates of CTS in these studies. Incorrectly attributing the etiology of CTS to the wrong risk factor results in inappropriate causal conclusions (NRC&IOM 2001).

Some factors that have been identified in the pathogenesis of carpal tunnel syndrome are rarely considered as possible confounders in epidemiological studies, if they are considered at all. Psychosocial determinants of carpal tunnel syndrome, for example, are seldom controlled for. Although the pathways are unclear, a significant body of literature has accumulated that implicates psychosocial factors in the causal path and underlines the potential for interaction between psychosocial and biophysical factors in the occurrence of work-related carpal tunnel

[10] One method proposed to analyze jobs for risk of musculoskeletal injuries to the hands and forearm is the Moore-Garg Strain Index. The six variables in the strain index are intensity of exertion, duration of force per cycle, efforts per minute, wrist posture, speed of exertion, and duration of task per day. A job is divided into tasks, and for each task and each hand, the six job risk factors are assessed and rated. The strain index is the product of the six ratings and using this total, the job is classified as safe or hazardous (Moore 1995). More information on the strain index is found in Table 10, Studies Meeting the Inclusion Criteria: Causation of CTS (Rucker 2002), and in Appendix B.

syndrome (Moon 1996). High job stress and high job demands, for example, are work-related factors that are consistently associated with the occurrence of symptoms and disorders in the upper extremities (Chapell 2003).[11]

7. Simultaneous measurement of exposure and outcome

Temporality is an absolute prerequisite for causality: if the exposure did not precede the outcome, the relationship between exposure and outcome cannot have been causal.

A longitudinal study design can address temporality in a substantive fashion, and is an excellent study design for inferring causation. Longitudinal studies examining the occupational causation of carpal tunnel syndrome are scarce. These studies are difficult to perform due to the lengthy follow-up time required (length of interval between exposure and outcome/latency period), workers changing jobs or dropping out of the study, changes in the nature of the jobs or tasks of interest and financial limitations.

Most of the epidemiological studies of CTS are prevalence studies in which exposures were measured at the same time that disease status was established. In a cross-sectional study, the prevalence of disease among the exposed is compared to that of the unexposed. Cross-sectional studies, which examine associations at one point in time, have a weak ability to provide evidence of causation (NRC&IOM 2001).

It is difficult to assess current exposure, but it is even more difficult to assess cumulative past exposure retrospectively. Accurate retrospective data are usually not available; thus the exposure assessment is often based on self-reports, and the assessment may incur information bias (Bernard 1997).

B. An evidence-based approach

Research that is poorly designed and executed provides weak evidence.[12] In contrast, the evidence from a few well-conceived and well-executed studies can strongly outweigh the "noise" created by a large number of mediocre ones. Accordingly, what follows is an evidence-based approach.

Evidence-based medicine is the conscientious, explicit and judicious use of the best current scientific evidence by medical decision makers.[13] External evidence from high quality original research invalidates previously accepted medical principles and replaces them with new ones that are more powerful, more efficacious and safer (Sackett 1996). Because of the limitations of anecdote, uncontrolled experience and unsystematic clinical observations, today it is expected that medical decision-making will be grounded in high quality scientific evidence.

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[11] Considering psychosocial and biomechanical factors to be separate kinds of exposures is a somewhat artificial distinction, as the two classes of stressors are strongly linked. Both result from core aspects of the organization: its technology, culture and work organization. Biomechanical and psychosocial risk factors both result from the way work is organized, the technology and sector of the company, and the organizational policies and culture that drive work organization. Thus the two classes of stressor are generally highly correlated in a workplace (Fed.Reg. 2000).

[12] To the extent that the quality of the evidence is poor, any subsequent inference (and the clinical decision it generates) will be weakened (Guyatt 1993&1994).

[13] Composed of physicians, epidemiologists, bio-statisticians and others, the Evidence-Based Medicine Working Group was established at McMaster University Health Sciences Center in Hamilton, Ontario and started publishing articles in the Journal of the American Medical Association in 1992. A list of members of the Evidence-Based Medicine Working Group appears in *Users' guides to the medical literature. I. How to get started* (Oxman 1993). Appendix N includes a list of evidence-based medicine resources.

The concept of a "hierarchy of evidence" is fundamental to evidence-based medicine. A "hierarchy of evidence" is a schema for grading the scientific evidence (original research studies) based on the tenet that different grades of evidence (study designs[14]) vary in their predictive ability.[15]

Not all studies using the same design are equally valid, however. Potentially useful evidence must be always be critically appraised and its scientific validity, clinical importance and applicability to the person or population under consideration must be determined.

C. Methodology

Evaluation of the best available scientific evidence on the diagnosis, causation and treatment of worker-related carpal tunnel syndrome required a systematic and comprehensive review of the medical literature. Because high quality, clinically relevant research is a small subset of the journal literature and can be difficult to find, the selection of original research studies for consideration in this review was a careful and deliberate process that involved multiple stages: establishing a research context, executing literature searches, reviewing titles and abstracts, identifying articles for retrieval, and finally selecting, classifying, and critically appraising the original research studies that make up the primary evidence base.

1. Establishment of a research context

Four recently published reports address the diagnosis, causation and/or treatment of carpal tunnel syndrome in workers. Each of these reports was prepared by a deliberative group of medical and scientific experts, and together, these four reports provided a background and context for the task of assessing the original clinical research.[16] They are listed below in descending chronological order.

- *Diagnosis and Treatment of Worker-Related Musculoskeletal Disorders of the Upper Extremity. Evidence Report/Technology Assessment Number 62. Agency for Healthcare Research and Quality, US Department of Health and Human Services. May 2003. Chapell R, Turkelson CM, Coates V.* This report includes a comprehensive review of the literature on the diagnosis and treatment of carpal tunnel syndrome.

- *National Research Council and Institute of Medicine. Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities. Panel on Musculoskeletal Disorders and the Workplace. National Academy Press. 2001.* This report includes a comprehensive review of the literature on the causation of carpal tunnel syndrome.

- *Work-Related Musculoskeletal Disorders: A Review of the Evidence. National Research Council. National Academy Press, Washington DC. 1998.* This report includes a comprehensive review of the literature on the causation of carpal tunnel syndrome.

- *Musculoskeletal Disorders and Workplace Factors. A Critical Review of the Epidemiologic Evidence for Work-Related Musculoskeletal Disorders of the Neck, Upper Extremity, and Low Back. National Institute for Occupational Safety and Health (NIOSH). July 1997.*

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[14] Appendix C includes a brief discussion of study designs.
[15] See Levels of Evidence Summary for Therapy, Harm or Causation (Appendix D).
[16] Additional information on these reports is found in Appendix E.

Bruce Bernard, Editor. This report includes a comprehensive review of the literature on the causation of carpal tunnel syndrome.

2. Execution of literature searches

We executed three separate, consecutive series of searches of the published, peer-reviewed literature: one focused on diagnosis of CTS, one on causation of CTS and one on treatment of CTS.[17] We designed and constructed the search strategies with the assistance of medical reference librarians at the J. W. Scott Health Sciences Library, University of Alberta, Edmonton, Alberta.

We searched computerized bibliographic databases without language restriction from 1966 (or the earliest year available, depending on the database searched) through September 2003. Databases searched through the OVID online system included Index Medicus (MEDLINE), Excerpta Medica (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club, and Database of Abstracts of Reviews of Effectiveness (DARE). Terms were consistently "exploded." Quality filters or "hedges" (standardized search strategies tailored to domain and research design) were used to select from the medical literature those articles whose results were most likely to be valid, credible and clinically useful.

The searches generated a total of 487 titles (diagnosis search), 2009 titles (causation search) and 946 titles (treatment search).

3. Review of titles and abstracts; selection of articles for retrieval

Titles and abstracts were screened and assessed independently by members of the research team. Articles that were obviously not relevant to the research questions, did not meet the retrieval criteria, and were in languages other than French and English were excluded at this stage.

To ensure comprehensive retrieval, we retrieved an article whenever there was uncertainty about its relevance. We also retrieved an article when an abstract was not present in the search results, but when the title of the article suggested that the article could be relevant.

We retrieved full texts of 82 potentially relevant diagnosis articles, 205 potentially relevant causation articles, and 48 potentially relevant treatment articles for detailed consideration. The bibliographies and reference lists of the full text articles were subsequently examined to identify additional pertinent articles for retrieval.

4. Selection of original research studies

Next we classified the full text articles. Articles that reported on findings of original research studies were retained.

Seven diagnosis articles, 51 causation articles and 10 treatment articles that did not report on original research (for example, reviews articles, editorials, commentaries and articles that

[17] Additional information on the three searches, including temporal constraints, search terms, and search syntax, is found in Appendix F. Note that search syntax varies by subject and by database.

proposed models or algorithms) were classified as background references and set aside for separate evaluation.

5. Evaluation of original research studies

To be included in the primary evidence base of this report, an original research study had to meet a set of rigorous inclusion criteria. These inclusion criteria were based on:

- the diagnostic method used in the study;
- elements specific to each domain (diagnosis, causation, treatment);
- study design; and
- study relevance.

Differences of opinion between reviewers about whether or not these criteria were met were discussed and resolved by consensus.

a. Inclusion criteria based on diagnostic method

Because there is no gold standard diagnosis for CTS (Rempel 1998) we paid particular attention to the specific techniques that investigators used to diagnose CTS in their study population. Therefore, for studies addressing diagnosis, causation or treatment of carpal tunnel syndrome, the following were considered necessary conditions for a study's inclusion into the primary evidence base of this report:

- the study population had symptoms that could be attributable to carpal tunnel syndrome; and
- a diagnosis of carpal tunnel syndrome was confirmed by an electrodiagnostic study or by a trained clinician using well described, well recognized reproducible diagnostic methods.

b. Domain-specific inclusion criteria

To be included in the primary evidence base of this report, a study had to satisfy domain-specific inclusion criteria, that is, it had to address one or more of the 24 research questions on diagnosis, causation or treatment of CTS outlined earlier in this document.[18] Studies that did not address one of the research questions on diagnosis, causation or treatment of CTS were excluded.

c. Inclusion criteria based on study design

To be included in the primary evidence base of this report, both observational and experimental studies had to satisfy inclusion criteria based on study design. The investigators had to ask and answer a question in a systematic way, apply the scientific method (posit and evaluate hypotheses using rational, unbiased, objective observation or experimentation), adhere to the study protocol, and provide an analysis consistent with study design. Studies with serious design flaws that precluded interpretation of the results were excluded.

[18] The research questions are found in Figure 1 and in sections IV.C., V.C., and VI.C.

d. Inclusion criteria based on clinical relevance

To be included in the primary evidence base of this report, a study had to address issues, procedures and technologies clinically relevant to established medical practice in Alberta. Novel, atypical or experimental diagnostic tests, for example, were excluded.

6. Critical appraisal of original research studies that met the inclusion criteria

The 39 studies (8 diagnosis studies, 14 causation studies and 17 treatment studies) that met the inclusion criteria detailed above form the primary evidence base of this document.

The research studies selected for inclusion in the primary evidence base were critically appraised using templates we constructed specifically for this project, based on templates in the University of Alberta's Evidence Based Medicine Toolkit.[19] Level of evidence, validity of results, clinical importance and applicability were evaluated for each study based on study type and study characteristics.

The primary evidence base is made up of the studies that provide the best evidence currently available to answer the research questions, so not all the included evidence is of equal quality.

For studies on diagnosis and treatment of carpal tunnel syndrome, level of evidence was rated on a 1 (high level or strong evidence) to 5 (low level or weak evidence) scale.[20] Studies that provided level 1, 2 or 3 evidence were included. Studies that provided level 4 or 5 evidence were not.

Causation studies were not assigned a numeric level of evidence. Given the heterogeneity and the relatively poor quality of the available evidence on causation of carpal tunnel syndrome, we chose to focus instead on the relative strengths and weakness of the studies that met the inclusion criteria, and evaluated the evidence they provide using criteria we developed specifically for this purpose.[21]

Evidence-based findings on the diagnosis, causation and treatment of carpal tunnel syndrome appear in Tables 6, 7, 8, 9, 10 and 11, and in the answers to the 24 research questions.

Figures 2, 3 and 4 summarize the process we used to establish the evidence base on the diagnosis, causation and treatment of carpal tunnel syndrome.[22]

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[19] http://www.med.ualberta.ca/ebm/ebm.htm. The reference documents in the toolkit include Worksheet for Using an Article About Assessing Diagnostic Tests, Worksheet for Using an Article about Causation or Harm, and Worksheet for Using an Article About Therapy or Prevention. The templates developed for this project based on the EBM Toolkit reference document are found in Appendix G, H, and I.

[20] Appendix D outlines the evidence rating system used in this document for studies on diagnosis and therapy.

[21] The Causation Evidence Appraisal Guide is found in Appendix H.

[22] Some of the studies excluded from the evidence base were subsequently identified for use as references for specific pieces of information about CTS anatomy, pathophysiology, comorbidities, etc.

FIGURE 2. Establishing the Evidence Base on Diagnosis of Carpal Tunnel Syndrome

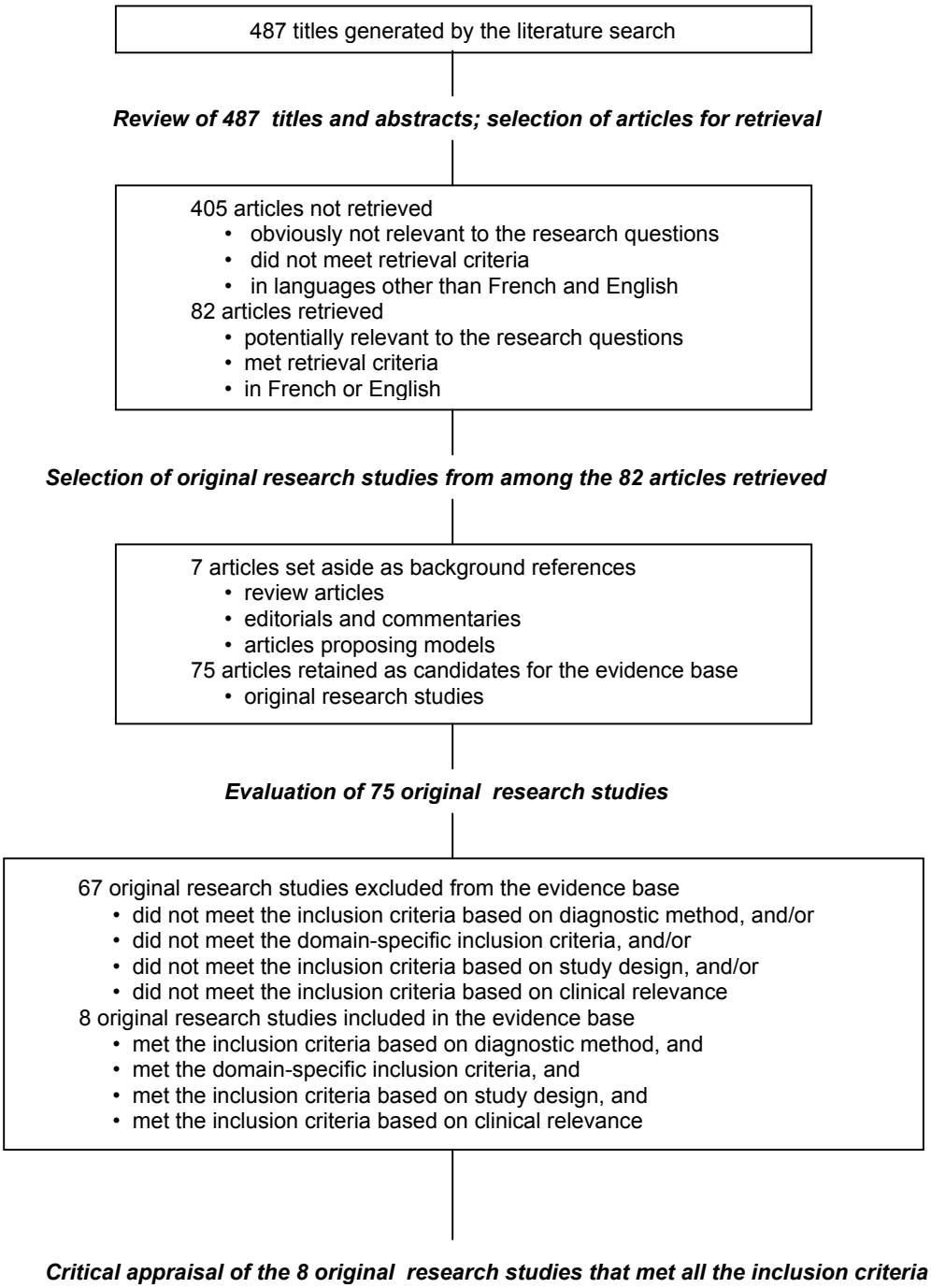


FIGURE 3: Establishing the Evidence Base on Causation of Carpal Tunnel Syndrome

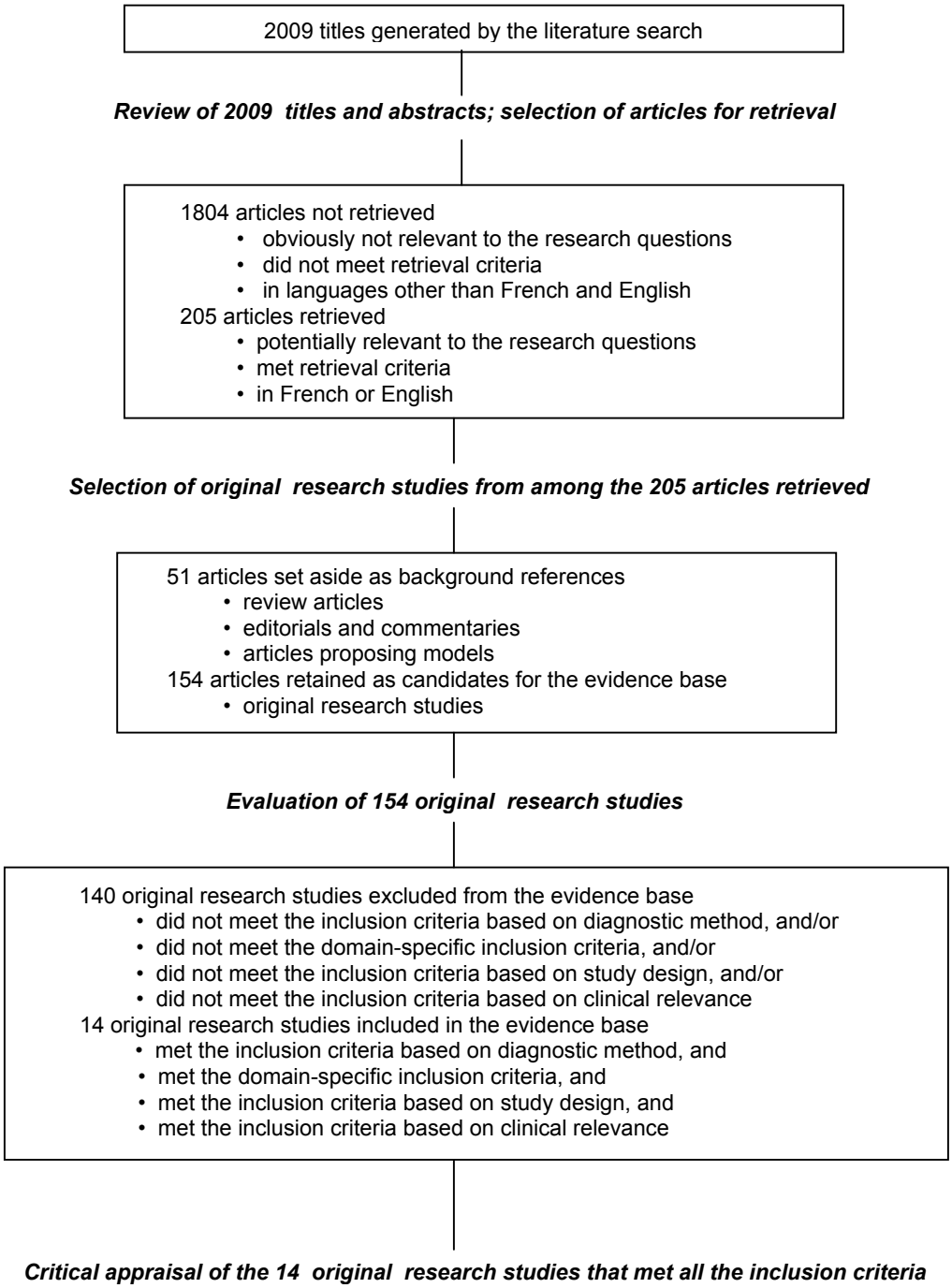
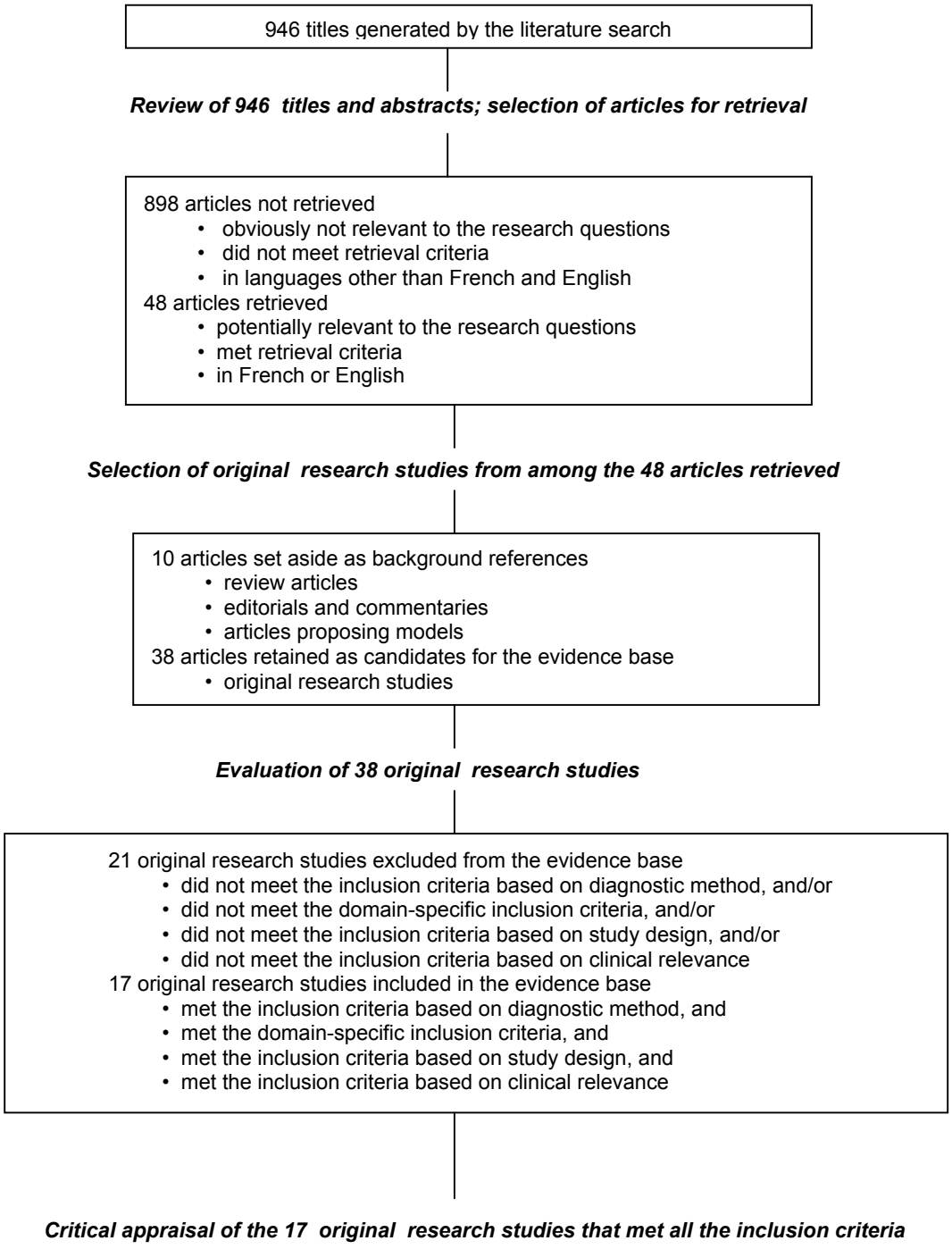


FIGURE 4: Establishing the Evidence Base on Treatment of Carpal Tunnel Syndrome



IV. DIAGNOSIS OF CARPAL TUNNEL SYNDROME

A. Relevant background information

Diagnosis of carpal tunnel syndrome is complicated by the lack of agreement on a "gold standard" or "reference standard" diagnostic method for verifying its presence or absence (Rempel 1998). The diagnosis of CTS is often made according to highly variable criteria: a large number of internal medicine, surgical and primary care specialties treat the condition, and some of the variation appears to be specialty-specific (Graham 2002).

When attempting to diagnose carpal tunnel syndrome, physicians consider symptoms, provocative clinical tests, sensory tests, electrodiagnostic tests, and imaging tests. There are dozens of diagnostic methods currently in use. None is considered definitive and there is evidence of diagnostic accuracy only for a small subset. The relative importance of clinical diagnosis and electrodiagnostic testing is particularly controversial.

Despite these obstacles, a rigorous diagnosis of CTS is essential: it forms the basis of appropriate treatment. Unsatisfactory post-treatment outcomes are often linked to an inaccurate initial diagnosis (Graham 2002), and the costs of misdiagnosing CTS - in both financial and in human terms - are staggering. The importance of an accurate medical diagnosis cannot be overstated.

1. Symptoms

Symptoms of CTS include numbness (anesthesia) and tingling (paresthesia) in the anatomic distribution of the median nerve (the area including the thumb, index finger, long finger, and radial half of the ring finger) (Stevens 1999). A nocturnal symptom of sensory disturbance is considered a classic manifestation of carpal tunnel syndrome. Patients frequently complain of pain in the wrist or hand at night or after frequent use of the hands or fingers, commonly relieved by "shaking it out" (Hennessey 1997).

Symptoms may also include diminished or altered sensation (hypoesthesia or dysesthesia) in the affected area of the hand. In more advanced cases, patients may complain about thumb or index finger weakness, impairment of motor function, loss of the ability to grip or grasp or report dropping items. Symptoms may be intermittent or continuous and associated with certain activities. They may also be accompanied by an aching sensation over the ventral aspect of the wrist. The pain can radiate distally to the palm and fingers or, more commonly, extend proximally along the ventral forearm. In about 1% of cases, permanent nerve damage results, leading to impaired use of the hand. Continued denervation can lead to atrophy of the innervated muscle (Chapell 2003).

Katz proposed a Hand Symptom Diagram (HSD) as a way to use a patient's hand symptoms as a structured diagnostic tool and devised a rating system to classify hand symptom diagrams into four categories: classic, probable, possible or unlikely carpal tunnel syndrome (Katz 1990a).[23]

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[23] Classic: tingling, numbness, or decreased sensation with or without pain in at least 2 of digits 1,2, or 3. Palm and dorsum of the hand excluded; wrist pain or radiation proximal to the wrist allowed.
Probable: same as for classic, except palmar symptoms allowed unless confined solely to ulnar aspect.

Some of the symptoms associated with carpal tunnel syndrome appear below. The presence of these symptoms cannot be considered diagnostic of carpal tunnel syndrome as other disorders may cause identical symptoms.

TABLE 1. SYMPTOMS OF CARPAL TUNNEL SYNDROME[24]

Numbness and tingling in the median nerve distribution of the thumb, index finger, long finger, and radial half of the ring finger (palm not involved).
Numbness in the entire hand (autonomic disturbance associated with CTS)
Nocturnal aggravation of hand symptoms.
Pain in wrist at night that can be shaken out.
Pain in wrist after frequent use of hands and wrists.
Dropping or difficulty in holding items.
Pain referred more proximally in the upper limb.

2. Provocative clinical tests

Provocative clinical tests (also referred to as "clinical signs") commonly used to diagnose CTS during the physical examination involve specific maneuvers that elicit pain, numbness or tingling in the median-nerve portion of the wrist.

Two of the best known are the Phalen sign[25] and the Tinel sign.[26] For the Phalen sign, tingling in the median nerve distribution is induced by full flexion (or full extension for reverse Phalen) of the wrists for up to 60 seconds. The patient places both elbows on a horizontal surface with the forearms vertical, and allows the wrists to flex by gravity. If the patient feels numbness or tingling within one minute, the test is positive. For the Tinel sign, gentle tapping over the median nerve in the carpal tunnel region elicits tingling in the nerve's distribution. The examiner taps lightly on the palmar aspect of the wrist, over the carpal tunnel. If the patient feels tingling, the test is positive (Chapell 2003).

Possible: tingling, numbness, decreased sensation and/or pain in at least one of digits 1,2, or 3.
Unlikely: no symptoms in digits 1,2, or 3 (Katz 1990a).

[24] Table adapted from Hennessey 1997.

[25] This is not written as "Phalen's sign." The apostrophe followed by an "s" is inappropriate (Hennessy 1997).

[26] This is not written as "Tinel's sign." The apostrophe followed by an "s" is inappropriate. The first person to describe this sign was Hoffmann in March of 1915. Tinel did not describe it until October of the same year, hence technically it should be referred to as the Hoffmann-Tinel sign. (Hennessy 1997). " Tinel" is used throughout this document to refer to the Hoffmann-Tinel sign.

Table 2 summarizes a variety of provocative clinical tests currently in use to diagnose carpal tunnel syndrome. There is evidence of diagnostic accuracy for only a small subset of these.[27] With the exception of thenar atrophy, all clinical signs rely on subjective input (patient report or patient effort) and so cannot be considered objective.

TABLE 2. PROVOCATIVE CLINCAL TESTS USED TO DIAGNOSE CTS[28]

PROVOCATIVE CLINICAL TEST	DESCRIPTION
Closed fist test	If the patient feels tingling within one minute of making a fist, the test is positive.
Combined Phalen sign and Durkan compression test	With the patient's elbow extended, the forearm in supination, and the wrist flexed to 60 degrees, the examiner uses one thumb to apply pressure over the carpal tunnel. If the patient feels tingling or numbness within 30 seconds, the test is positive.
Decreased muscle strength	Maximum strength exerted by the patient on a measurement device.
Durkan compression test or carpal compression test (CCT)	The Durkan test is also called the carpal compression test. There are two variants of this test, a manual carpal compression test (mCCT) and an instrumented carpal compression test. In the manual carpal compression test, with the patient's wrist in a neutral position and the forearm supinated, the examiner uses his/her thumbs to compress the wrist at the median nerve. If the patient feels numbness or tingling within 30 seconds, the test is positive. In the instrumented carpal compression test, a device is used to provide direct measurement of the amount of pressure necessary to elicit symptoms of carpal tunnel syndrome (Durkan 1991, 1994).
Flick test	The patient is asked: "What do you do with your hands when your symptoms are worst?" If the patient shakes or flicks the hands, the test is positive.
Gilliat tourniquet test	The examiner inflates a blood pressure monitor on the patient's arm proximal to the elbow. If the patient feels numbness or tingling within one minute, the test is positive.
Grip strength	Forced measure when patient squeezes a measurement device using the whole hand.
Hypesthesia	Also called hypoesthesia, it refers to decreased sensitivity to touch.
Pain on VAS	Pain as measured by a visual analog scale (VAS) in which the patient rates the subjective degree of pain by placing a mark on a graphical bar.
Paresthesia in APB	Tingling in the abductor pollicus brevis (APB) muscle of the hand.

[27] See Table 8.
[28] This table is adapted from Table 7 in Chapell (2003) and from Table 1 in Massy-Westropp (2000). There is evidence of diagnostic accuracy for only a small subset of these provocative clinical tests.

TABLE 2. PROVOCATIVE CLINICAL TESTS USED TO DIAGNOSE CTS (continued)

PROVOCATIVE CLINICAL TEST	DESCRIPTION
Phalen sign	Also called the wrist flexion test. Patient places both elbows on a horizontal surface with the forearms vertical, and allows the wrists to flex by gravity. If the patient feels numbness or tingling within one minute, the test is positive.
Pinch strength	Forced measure when patient squeezes a measurement device using the thumb and a finger.
Symptoms measured systematically (includes hand symptom diagram)	Any symptom of carpal tunnel syndrome such as pain, tingling, or numbness, as measured by a questionnaire or a hand symptom diagram.
Symptoms during ultrasound	Whether the patient experiences carpal tunnel symptoms when the wrist is stimulated with an ultrasound transducer.
Reverse Phalen sign	This test is also called the wrist extension test. The patient extends both wrists and fingers. If the patient feels numbness or tingling within two minutes, the test is positive.
Thenar atrophy	The degree of wasting in the thenar muscle of the hand.
Thenar weakness	The degree of weakness in the thenar muscle of the hand.
Hoffman-Tinel sign	This test is also called the Tinel sign. The examiner taps lightly on the volar aspect of the wrist in the region of the carpal tunnel. If the patient feels tingling, the test is positive.

3. Sensory tests

Sensory tests for carpal tunnel syndrome typically involve measurement of a patient's threshold for detection of a sensory stimulus. For example, in the Semmes-Weinstein test, the examiner touches the patient with monofiliments, and the test is considered positive if the patient's sensitivity to the monofiliments falls outside normal limits. Another example is the two-point discrimination test in which the examiner touches two closely spaced prongs to the patient's fingers. The test is considered positive if the patient cannot discriminate the prongs when they are 5 millimeters apart (Chapell 2003).

Table 3 summarizes sensory tests currently in use to diagnose CTS. There is little evidence to support use of these tests for CTS diagnosis.[29]

[29] See Table 6.

TABLE 3. SENSORY TESTS USED TO DIAGNOSE CTS[30]

SENSORY TEST	DESCRIPTION
Current perception	Whether the patient's threshold for perception of electrical current is within normal limits.
Moving two-point discrimination	The examiner touches two closely-spaced prongs to the pulp of the patient's digits and moves them distally. The test is positive if the patient cannot discriminate the prongs when they are 4-6 millimeters apart.
Object identification	The patient blindly feels wooden shapes and is asked to identify them.
Pinprick sensation	Whether the patient has normal pinprick-induced sensation.
Pressure measurement	Whether the patient's threshold for perception of pressure is within normal limits.
Ridge threshold	The patient puts an index finger on a circular disc that has a small ridge. If the patient's threshold for detection of the ridge is abnormal, the test is positive.
Semmes-Weinstein monofiliment	This test is also called the von Frey hairs test. The examiner touches the patient with a series of standardized nylon monofilaments, and records the smallest monofilament the patient can detect.
Static two-point discrimination	The examiner touches two closely spaced prongs to the pulp of the patient's digits and holds them still. The test is positive if the patient cannot discriminate the prongs when they are 5 millimeters apart.
Temperature measurement	Whether the patient's threshold for perception of temperature, heat, pain or cold pain is within normal limits.
Vibrometer	An instrument vibrates at varying frequencies, and the patient's threshold for detection of vibration is determined. If the threshold falls outside normal limits, test is positive.

4. Electrodiagnostic Studies (EDS)

Electrodiagnostic studies (EDS) are also used in the diagnosis of carpal tunnel syndrome. Electrodiagnostic studies include electromyography (EMG) and the nerve conduction study (NCS). A neurologist or physiatrist performs these examinations. Abnormalities on EDS testing, in association with specific symptoms and the results of provocative clinical tests, can contribute to the diagnosis of carpal tunnel syndrome and can also provide an assessment of the severity of the nerve damage. Results are

[30] This table is adapted from Table 8 in Chapell (2003) and from Table 1 in Massy-Westropp (2000). There is little evidene to support the use of these tests for CTS diagnosis.

compared with tables of normative values: damaged nerves produce slower conduction velocities and smaller amplitudes (Jordan 2002). The normal values used for assessing the nerve in question should be derived using a comparable matched cohort.

NCS and EMG are distinctly different electrodiagnostic techniques, although they are often performed sequentially for the evaluation of clinical problems (Jablecki 1993). A summary of nerve conduction parameters appears in Table 4.

a. The nerve conduction study (NCS)

The purpose of the nerve conduction study is to determine if there is a time delay, a change in intensity, or a reduction in velocity of a nerve impulse between one section of a peripheral nerve and another. In the case of CTS, any delay of motor and sensory impulses traveling across the carpal tunnel is of interest.

In a nerve conduction study, electrodes are placed in two locations along a nerve; the nerve is stimulated from one electrode, and the impulse is recorded from the other electrode. Tests can be performed on either the median nerve, the ulnar nerve, or the radial nerve, and can assess either motor or sensory function. The placement of the electrodes in sensory nerve conduction tests can be either orthodromic (stimulating electrodes are placed distal to recording electrodes) or antidromic (stimulating electrodes are placed proximal to recording electrodes). Other aspects of the nerve impulse such as latency, amplitude and velocity can also be measured. Some investigators compare two or more nerve conduction tests when attempting to diagnose CTS (e.g., compute a difference between two latencies). These comparisons are referred to as composite nerve conduction tests (Chapell 2003).

b. The electromyogram (EMG)

In an electromyogram, a sterile needle electrode inserted through the skin into the belly of a muscle is used to evaluate the spontaneous electrical activity in that muscle as it undergoes voluntary contraction. Pathological changes in nerves and muscle, including underlying muscle denervation and metabolic abnormalities, may be detected.

5. Imaging tests

Imaging tests use a variety of methods to observe the internal anatomy of the body. Imaging tests for carpal tunnel syndrome include magnetic resonance imaging (MRI), computed tomography (CT) scan, x-ray film, and ultrasound. Using these methods, investigators attempt to measure the size of anatomical areas within the carpal tunnel or that may be affected by carpal tunnel syndrome. The potential utility of computed tomography, magnetic resonance imaging and ultrasonography for CTS diagnosis is still being determined and they remain primarily research tools (D'Arcy 2000). No imaging studies are presently considered routine in diagnosing CTS (Ashworth 2002).

TABLE 4. SUMMARY OF NERVE CONDUCTION PARAMETERS[31]

TEST	DEFINITION
Nerves tested	
Median nerve	The central nerve that is believed to be impaired in CTS. It innervates the thumb, index, middle and ring fingers.
Ulnar nerve	The nerve on the medial side of the forearm that innervates the ring and little fingers. Some researchers compare median and ulnar nerve conduction tests to diagnose CTS.
Radial nerve	The nerve on the lateral side of the forearm that innervates the thumb. Some researchers compare median and radial nerve conduction tests to diagnose CTS.
Motor or sensory	Whether the test assesses motor or sensory function.
Orthodromic or antidromic	The relative placement of the stimulating electrodes. If the stimulating electrode is distal to the recording electrode (i.e., the stimulator is further from the torso), the test is orthodromic. Conversely, if the stimulating electrode is proximal to the recording electrode (i.e., the stimulator is closer to the torso), the test is antidromic. These terms apply to sensory but not to motor tests.
Electrode Placement Sites	
Abductor pollicus brevis muscle (APB)	A muscle in the hand that is used to record median motor parameters.
Abductor digiti minimi (ADM)	A muscle in the hand that is used to record ulnar motor parameters.
Parameters Measured	
Latency	The time in milliseconds between stimulation and recording of an electrical impulse.
Onset latency	The time in milliseconds between stimulation and recording of an electrical impulse when measured to the beginning of action potential.
Peak latency	The time in milliseconds between stimulation and recording of an electrical impulse when measured to the largest amplitude of action potential.

[31] Adapted from Table 9 in Chapell (2003).

Parameters Measured (continued)	
Velocity	Speed of nerve conduction in meters per second (m/s).
Amplitude	Size of the action potential in microvolts (μV).
Presence/absence	Whether the nerve action potential was recordable. In severe cases, some action potentials may not be recordable.
Inching test	A series of nerve conduction tests designed to locate specific areas of nerve slowing. It can be performed orthodromically or antidromically. Electrodes are placed in 9-12 locations which are each a small distance (e.g., 1 cm) apart. By stimulating a fixed site (e.g., the middle finger) and recording at several locations (e.g., 9 evenly-spaced locations along the wrist), researchers can measure the nerve latencies and velocities for each segment along the nerve.

TABLE 5. IMAGING TESTS USED TO DIAGNOSE CTS[32]

IMAGING TEST	DESCRIPTION
Film	Plain film radiograph (x-ray)
CT	Computed tomography scan
MRI	Magnetic resonance imaging scan
Ultrasound	Ultrasonic imaging

B. Reporting the evidence: the primary evidence base

Table 6 presents summaries and critical appraisal of the 8 diagnostic studies that met the inclusion criteria.[33] We appraised the studies that met the inclusion criteria according to their validity, the importance of their results, and their applicability to the WCB-Alberta population.[34]

This set of original research studies forms the primary diagnostic evidence base. In our opinion, these studies represent the best scientific evidence currently available on the

[32] This table is adapted from Table 10 in Chapell (2003). The potential utility of imaging tests for CTS diagnosis is still being determined and they remain primarily research tools.
[33] Inclusion criteria are detailed in the Methodology section of this background paper.
[34] See Appendix G for the worksheets used to critically appraise the studies on diagnosis of CTS.

diagnosis of carpal tunnel syndrome. First author, title and date, study type, authors' conclusions, critical appraisal and level of evidence are included for each study. Table 7 presents the evidence on the accuracy of specific diagnostic techniques found in these 8 studies. The studies in the evidence base are organized by category (symptom report, provocative clinical testing, examination-based clinical diagnosis) and within those categories, by descending level of evidence.

Whenever possible, we calculated sensitivities, specificities and likelihood ratios for a diagnostic technique from the primary data included in the paper. Sensitivities and specificities were not calculated, and are not included, if the data were not statistically significant.

The evidence base on individual diagnostic tests for carpal tunnel syndrome is small, even though the total number of articles on diagnostic tests for CTS is large. This is both because so many different diagnostic tests have been described, and because the studies themselves are of widely varying methodological quality (Chapell 2003). Without scrutiny of the methodology of the research studies assessing diagnostic methods for CTS, one could be misled to act on the results of a test for which there is little supporting scientific evidence (Massy-Westropp 2000).

C. Findings: answers to the research questions on diagnosis of CTS

Question 1.

How is a clinical diagnosis of carpal tunnel syndrome established?

Clinical diagnosis of carpal tunnel syndrome is generally established based on the patient's history (symptoms) and findings during the physical examination (provocative clinical tests). Each item of history and each item on physical examination represents a diagnostic test, as post-test probabilities are generated that are modified with each new finding (Jaeschke 1994). Taking an additional history to exclude other diagnoses will increase confidence in the initial diagnosis (Stevens 1999).

There is no consensus on which items from the patient interview and physical examination most accurately predict the diagnosis of carpal tunnel syndrome (D'Arcy 2000), and there was insufficient evidence for us to identify a single "best" clinical diagnostic method. Reliability and accuracy of certain clinical diagnostic tools, however, appear to support their use as components of an examination-based clinical diagnosis of CTS.

In our systematic review, the Phalen test was most consistently identified as accurate in high quality studies (greatest "coherence" of evidence). The manual carpal compression test appears to be another of the more accurate provocative clinical tests. The evidence suggests that the hand symptom diagram (which is based on the premise that an accurate clinical history can be a valuable predictor of CTS) is also a useful diagnostic tool.

Although few studies address the issue, combinations of independent tests (models) likely perform better diagnostically than do single tests (Fertl 1998, Katz 1990a, Szabo 1999).

TABLE 6. STUDIES MEETING THE INCLUSION CRITERIA: DIAGNOSIS OF CTS

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Symptom Report				
Katz, J. A self-administered hand symptom diagram for the diagnosis and epidemiologic study of carpal tunnel syndrome. The Journal of Rheumatology 1990.	Consecutive blinded study of patients presenting to NCS laboratory for evaluation of upper extremity discomfort. Comparison of diagnostic utility of Hand Symptom Diagram to NCS.	The hand diagram is a useful diagnostic tool and may be valuable for occupational and population screening.	Inter observer reliability was high (Kappa 0.84-0.91) with low negative likelihood ratios (0.17) but unhelpful positive likelihood ratios.	1
Stevens, J. Symptoms of 100 patients with electromyographically verified carpal tunnel syndrome. Muscle and Nerve 1999.	Two part study. Second part is a blinded case control study comparing diagnostic utility of hand symptom diagrams and symptom questionnaires to combined clinical assessment and NCS.	A wide range of sensory symptoms can be seen in CTS. Symptoms are reported most commonly in the median and ulnar digits, followed by the median digits only and a glove distribution. Screening for CTS should include patients who experience paresthesias and pain in almost any distribution in the hand.	It is not clear what criteria were used to define and select the control populations. No control and experimental comparison table was provided. Methodology used for "rating" the hand symptom questionnaire and diagrams by "experts" was not adequately described.	1

TABLE 6. STUDIES MEETING THE INCLUSION CRITERIA: DIAGNOSIS OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Provocative clinical testing				
Fertl, E. The serial use of two provocative tests in the diagnosis of carpal tunnel syndrome. Acta Neurol Scand 1998.	Prospective, controlled study comparing the diagnostic utility of several clinical tests.	The serial application of the newly proposed manual carpal compression test (mCCT) and Phalen test (PT) is very useful in the clinical diagnosis of CTS. This finding facilitates the clinical diagnosis by the primary physician, it helps to improve referral decisions to electrophysiological departments and other ancillary examinations and may reduce costs.	It is not clear that the manual carpal compression test can be applied widely by a broad physician population.	1
MacDermid, J. Inter-rater agreement and accuracy of clinical tests used in the diagnosis of carpal tunnel syndrome. Work 1997.	Blinded study of symptomatic patients referred to a hand clinic, designed to examine the inter-rater agreement and accuracy of seven clinical tests.	The most accurate test was the Phalen wrist flexion test. Good accuracy was demonstrated by pinch and vibration tests. The Tinel sign was characterized by lower sensitivity, but false positives were rare. Wrist extension and tethered median nerve tests had poor sensitivity. Semmes-Weinsteim monofiliment testing was very sensitive, but a high number of false positives occurred when "normal" was classified at 2.83. Reliability and accuracy supports their use as components of a clinical diagnosis of CTS.	Inter observer reliability and accuracy were high for Phalen, pinch and wrist extension tests.	1

TABLE 6. STUDIES MEETING THE INCLUSION CRITERIA: DIAGNOSIS OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Provocative clinical testing (cont)				
DeSmet, L. Value of clinical provocative tests in carpal tunnel syndrome. Acta Orthopaedica Belgica 1995.	Non-blinded controlled study of hands in one surgeon's practice to assess the value of 5 provocative tests for CTS diagnosis. Normal controls.	Compared to normal controls the Tinel sign and the closed fist test are highly specific; compression test is not useful to discriminate between symptomatic patients with and without EMG disturbances. The closed fist test is specific in these situations.	Calculated sensitivities and specificities based on comparison to asymptomatic controls dropped considerably when a more appropriate comparison group was used (patients with paresthesias and negative EMG studies). In that instance only the closed fist test showed a useful degree of accuracy to rule in the presence of CTS.	2

TABLE 6. STUDIES MEETING THE INCLUSION CRITERIA: DIAGNOSIS OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Provocative clinical testing (cont)				
Gerr, F. The sensitivity and specificity of tests for carpal tunnel syndrome vary with the comparison subjects. Journal of Hand Surgery (British and European Volume) 1998.	Blinded cross-sectional study of symptomatic patients referred to an electromyography center. Designed to test the hypothesis that use of asymptomatic subjects free of electrophysiologic evidence of CTS results in improved test performance in comparison with symptomatic subjects free of electrophysiologic evidence of CTS.	For all the diagnostic tests studied (Phalen Test, Tinel Sign, thenar weakness, thenar atrophy, abnormal vibration perception, and two point discrimination), the proportion of subjects who had a false positive clinical test result was much higher in the electrophysiologically normal subjects who had CTS compatible hand symptoms than in the electrophysiologically normal subjects who were asymptomatic. These results suggest that many studies that have evaluated diagnostic tests for CTS have produced falsely optimistic estimates of the test's performance due to the use of asymptomatic comparison subjects. Our results demonstrate that the clinical tests discriminated between symptomatic and asymptomatic subjects, not between those with and without electrophysiological evidence of CTS. This indicates the clinical tests are therefore useless in distinguishing those symptomatic patients who actually have CTS from those who do not. Spectrum bias affects the observed performance of commonly used clinical tests for CTS and is likely to be responsible for the widely divergent estimates of sensitivity and specificity for the Phalen test and Tinel sign observed in the published literature.	This study, which illustrates the effect of spectrum bias on test performance, failed to demonstrate any useful degree of accuracy for any of the tests studied.	2

TABLE 6. STUDIES MEETING THE INCLUSION CRITERIA: DIAGNOSIS OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Examination-based clinical diagnosis				
Gunnarsson, L. The diagnosis of carpal tunnel syndrome. The Journal of Hand Surgery 1997.	Consecutive blinded study of patients referred to a CTS surgery clinic. Compared diagnostic utilities of clinical examination and nerve conduction studies to relief of CTS symptoms after carpal tunnel release surgery.	Clinical examination by an experienced doctor seems to be sufficient if there are typical symptoms of carpal tunnel syndrome, but if there is a history of pain, atypical symptoms or earlier fractures in the arm, wrist or hand, it is important to add a neurophysiological examination.	The reference standard (expert opinion) was not applied to all of the study subjects. This would decrease the false positive rate.	3
Szabo, R. The value of diagnostic testing in carpal tunnel syndrome. The Journal of Hand Surgery 1999.	Non-consecutive, non-blinded comparison of clinical examination tests to various reference standards.	Our findings support the use of clinical history and physical examination as the primary method of diagnosing carpal tunnel syndrome. The addition of nerve conduction studies is unnecessary in most cases.	The study was not blinded. The reference standards used to define "control" groups were not adequately defined, and were likely different from those of the CTS positive group.	3

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (BY STUDY)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	POSITIVE LIKELIHOOD RATIO[35]	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Symptom report					
Katz, J. A self-administered hand symptom diagram for the diagnosis and epidemiologic study of carpal tunnel syndrome. The Journal of Rheumatology 1990.	Hand Symptom Diagram rating *(a rating of classic, probable or possible CTS)*	1.25 (1.1, 1.4)	0.17 (0.04,0.7)	0.96	0.23
Stevens, J. Symptoms of 100 patients with electromyographically verified carpal tunnel syndrome. Muscle and Nerve 1999.	Hand Symptom Diagram (HSD) Hand Symptom Questionnaire (HSQ) Combined HSD and HSQ	2.07 1.91 1.77	0.44 0.42 0.24	0.71(0.66,0.77) 0.74(0.70,0.77) 0.88(0.85,0.92)	0.66(0.55,0.76) 0.61(0.53,0.70) 0.51(0.42,0.59)

[35] Positive and negative likelihood ratios were calculated for each diagnostic method using the primary data and EBM Calc (EBM Toolkit 2003).

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (continued)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Provocative clinical testing					
Fertl, E. The serial use of two provocative tests in the diagnosis of carpal tunnel syndrome. Acta Neurol Scand 1998.	Phalen test (PT)	9.9	0.23	0.79	0.92
	Manual carpal compression test (mCCT)	10.4	0.18	0.83	0.92
	Serial use mCCT and Phalen test	11.5	0.09	0.92	0.92
DeSmet, L. Value of clinical provocative tests in carpal tunnel syndrome. Acta Orthopaedica Belgica 1995 *The sensitivities, specificities and likelihood ratios that follow are from, or are calculated using data from, De Smet's Table III: Calculated values compared to patients with paresthesias and normal EMG studies.*	Phalen	1.36 (0.91, 2.1)	0.28(0.09,0.89)	0.91	0.33
	Durkan	0.94(0.60,1.48)	1.11 (0.46, 2.6)	0.63	0.33
	Closed fist	7.3 (1.1, 49)	0.43(0.25,0.73)	0.61	0.92

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (continued)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Provocative clinical testing (cont)					
Gerr, F. The sensitivity and specificity of tests for carpal tunnel syndrome vary with the comparison subjects. Journal of Hand Surgery (Br) 1998.	Phalen	2.39	0.36	0.75	0.68
	Tinel	0.37	2.30	0.25	0.32
	Thenar weakness	1.1(0.77,1.4)	0.97(0.6,1.56)	0.63	0.38
	Thenar atrophy	0.34(0.22,0.5)	4.17(2.3,7.5)	0.28	0.17
	Abnormal vibration perception (index finger)	0.87(0.67,1.1)	1.32(0.79,2.2)	0.61	0.29
	Two point discrimination >=5mm (index finger)	0.44(0.28,0.7)	1.99(1.37,2.9)	0.28	0.36

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (continued)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	Kappa	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Provocative clinical testing (cont)						
MacDermid, J. Inter-rater agreement and accuracy of clinical tests used in the diagnosis of carpal tunnel syndrome. Work 1997.	Phalen	0.88	8.70	0.14	0.87	0.90
	Vibration (tuning fork)	0.71	3.90	0.16	0.77	0.80
	Pinch	0.76	6.00	0.32	0.72	0.88
	Wrist extension	0.72	18.80	0.26	0.75	0.96
	Tinel	0.81	9.80	0.44	0.59	0.94
	Tethered median nerve	0.49	10.4	0.51	0.52	0.95
	Semmes-Weinstein monofiliment	0.22	2.20	0.23	0.86	0.60[36]

[36] Sensitivities and specificities in the table represent the best value assigned by either of two different testers (MacDermid 1997).

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (continued)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Examination-based clinical diagnosis					
Gunnarsson, L. The diagnosis of carpal tunnel syndrome. The Journal of Hand Surgery 1997.	*MEDICAL HISTORY*				
	Numbness in thumb, index and long finger	1.28	0.19	0.95	0.26
	Numbness disappears by shaking hands	1.50	0.33	0.90	0.30
	Reduced sense of touch in thumb, index and long finger	1.18	0.91	0.39	0.67
	White fingers	1.41	0.92	0.24	0.83
	CTS hand symptom diagram (definite compared to possible/improbable)	2.13	0.49	0.66	0.69
	RESULTS OF TESTS/EXAMINATIONS				
	Neurophysiology (nerve conduction velocities in the median and ulnar nerves)	6.54	0.17	0.85	0.87
	Palm-wrist/wrist-elbow NCV	6.20	0.23	0.80	0.87
	Clinical examination (Phalen, Tinel, asked about numbness, reduced sense of touch)	4.70	0.08	0.94	0.80
	Phalen	1.65	0.29	0.86	0.48
	Tinel	1.44	0.67	0.62	0.57

TABLE 7. THE EVIDENCE ON THE ACCURACY OF CTS DIAGNOSTIC TECHNIQUES (continued)

STUDY	DIAGNOSTIC TECHNIQUES EVALUATED	POSITIVE LIKELIHOOD RATIO	NEGATIVE LIKELIHOOD RATIO	SENSITIVITY	SPECIFICITY
Examination-based clinical diagnosis (cont)					
Szabo, R. The value of diagnostic testing in carpal tunnel syndrome. The Journal of Hand Surgery 1999.	Phalen	2.58	0.35	0.75	0.71
	Tinel	3.76	0.43	0.64	0.83
	Durkan	2.60	0.17	0.89	0.66
	Hand Diagram	4.75	0.28	0.76	0.84
	Night Pain	2.30	0.07	0.96	0.59
The sensitivities, specificities and likelihood ratios that follow are from, or are calculated using data from, Szabo's Table 3, "definite carpal tunnel syndrome" patients, normal volunteers and other patients with hand problems.	Semmes-Weinstein neutral	2.16	0.50	0.65	0.70
	Semmes-Weinstein Phalen	2.80	0.24	0.83	0.70
	Grip	0.80	1.36	0.48	0.38
	Key pinch	0.69	1.29	0.33	0.52
	3-Jaw pinch	0.84	1.16	0.43	0.49
	Tip pinch	1.01	0.92	0.65	0.38[37]

[37] Results from Szabo 1999 Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Values for Carpal Tunnel Syndrome Tests for Group 1 (Definite Carpal Tunnel Syndrome), Group 2 (Other Hand Problems), and Group 3 (Normal Volunteers).

These conclusions are based on evidence derived from populations of symptomatic patients referred to electrodiagnostic laboratories (Katz 1990a, Fertl 1998, Gerr 1998, Stevens 1999), surgery departments or surgeons' practices (DeSmet 1995, Gunnarsson 1997, Szabo 1999), or to a hand clinic (MacDermid 1997). They are therefore most applicable to claimants with severe enough symptoms to warrant such a referral. There are no data addressing the value of physical diagnosis in patients presenting to primary care physicians with symptoms suggestive of CTS (D'Arcy 2000). Test accuracy may change with different mixes of disease severity, different distributions of competing conditions (Jaeschke 1994), varying experience and skill of clinical examiners (MacDermid 1997), or different sets of personal incentives and constraints. If results are to be generalized to the primary care setting, it must be done cautiously (D'Arcy 2000).

It should be noted that both history and physical examination rely on subjective reporting of symptoms, sensation or pain: there are no objective examination-based clinical tests for median nerve impairment.

Question 2.

What are the respective roles of examination-based clinical diagnosis and of electrodiagnostic studies (EDS) in the diagnosis of carpal tunnel syndrome? Is either necessary? Is either sufficient? When, if ever, are both necessary?

Examination-based clinical diagnosis of carpal tunnel syndrome is necessary, but not always sufficient, while electrodiagnostic studies alone are never sufficient (Rempel 1998).

A small subset of patients may be managed without electrodiagnostic studies (Katz 1990b): in cases where clinical symptoms and signs are well defined, electrodiagnosis may not be necessary (Graham 2001). If surgery is being contemplated, [38] however, or if there is uncertainty about the clinical diagnosis, electrodiagnostic confirmation of the clinical diagnosis is desirable (Stevens 1999).

Use of only electrodiagnostic study findings is not recommended: a positive electrodiagnostic finding in the face of absent symptoms cannot lead to a diagnosis of carpal tunnel syndrome. Although the electrodiagnostic study alone has sometimes been used as a "gold standard" for CTS diagnosis because it is considered an objective test and because presumably it measures the underlying pathophysiologic process of CTS, there are problems with using electrodiagnostic findings as the sole diagnostic tool:

- Although electrodiagnostic study findings are considered the most accurate single CTS diagnostic test, false negatives and false positives are well documented (Rempel 1998).

- Carpal tunnel syndrome is, by definition, a clinical syndrome with a characteristic symptom complex and, in severe cases, clear physical examination findings.

[38] The workers' compensation jurisdictions of both Washington and Oregon, for example, specify that positive electrodiagnostic findings are a necessary pre-requisite for authorization of CTS surgery (WSDLI 2002, Ross 1997).

Diagnosis based only on electrodiagnostic study ignores these additional data that are likely to improve diagnostic accuracy (Rempel 1998).

- Studies of patients referred to electrodiagnostic centers estimate the specificity of electrodiagnostic study findings to be 90% or better. In a population with a high prevalence of carpal tunnel syndrome (those referred to an electrodiagnostic center) the positive predictive value associated with this specificity may be acceptable. Among other populations, however, for whom the prevalence of carpal tunnel syndrome is much lower, the false positive rate will be considerably greater, and the positive predictive value will be reduced (Rempel 1998).

- There is a significant subset of patients whose electrodiagnostic findings fall outside of the normal range but who do not have, and do not later develop, a clinical picture consistent with carpal tunnel syndrome (Rempel 1998).

EDS findings must be correlated with the history and physical examination. Electrodiagnostic studies increase or decrease the probability of carpal tunnel syndrome as the correct diagnosis, and their accuracy is good when properly performed. Used in combination with the clinical assessment, electrodiagnostic studies provide additional pieces of data to be interpreted in the context of the individual's symptoms and what physical findings may, or may not, be present (Graham 2001).

Electrodiagnostic studies are the most objective test available to demonstrate median nerve deficit. In contrast, with the exception of thenar wasting, all examination-based clinical diagnostic tools rely on subjective input.

Question 3.

Are there qualifications and technical limits on the interpretation of electrodiagnostic studies?

There are a number of qualifications and technical limits on the interpretation of electrodiagnostic studies. Electrodiagnostic methods are standardized neither in protocol nor in interpretation, and so like symptoms and provocative clinical tests they require a stringent review (Massy-Westropp 2000). Electrodiagnosis is by no means a perfect reference standard.

Technical factors that influence the results of NCS include amplifier gain and filter settings; electrode size, shape and material; distance between stimulating and recording electrodes; distance between recording electrodes; and limb temperature. Pathologic conditions which cause nerve damage also alter the results of NCS by slowing or blocking nerve conduction. The technical factors that influence the results of EMG include amplifier gain, filter settings and electrode size, shape and material. In addition, test conditions - for example, temperature, electrode size, distance between electrodes, and amplifier gain - must be controlled (Jablecki 1993).

EDS is neither a completely standardized nor a completely objective technique. There are gradations of normal nerve function in the general population, for example, and as different clinicians use different normal values, the criteria by which a diagnosis of carpal tunnel syndrome is made may vary from laboratory to laboratory.

The results of electrodiagnostic studies are operator dependent. Quality and accuracy varies between laboratories and neurophysiologists (Katz 1990b). The clinical problem dictates the study strategy (the choice and number of nerves and muscles tested). The EDS is an extension of the neurological examination and its value derives entirely from the thoroughness, competence and clinical acumen of the eletromyographer. Moreover, it is difficult for someone who is not familiar with electrodiagnostic techniques to assess the strategy employed or to assess the quality of the evaluation simply by reading the written report (EMG-Online 2000).

Nevertheless, due to the combination of its relative objectivity and its accuracy when properly performed, many physicians rely on electrodiagnosis as the best available diagnostic standard for carpal tunnel syndrome (D'Arcy 2000), and agree that certain electrophysiological abnormalities support a diagnosis of carpal tunnel syndrome (Verdugo 2003).

Question 4.

How accurate is examination-based clinical diagnosis? How accurate are electrodiagnostic studies in symptomatic individuals?

The clinical usefulness of a diagnostic test is largely determined by the accuracy with which it identifies the target disorder. The predictive value of the diagnostic tests for carpal tunnel syndrome is disputed (Szabo 1999). Our findings, which are based on the evidence provided in the studies that met our inclusion criteria, appear below.

We include two different types of accuracy measures in our analysis of diagnostic tests for carpal tunnel syndrome: sensitivities and specificities, and likelihood ratios (LRs).[39]

The sensitivity of a diagnostic test is the proportion of truly diseased persons, as identified by the diagnostic "gold standard" who are identified as diseased by the test under study. The specificity of a diagnostic test is the proportion of truly nondiseased persons, as identified by the diagnostic "gold standard," who are identified as nondiseased by the test under study.

Likelihood ratios indicate by how much a given diagnostic test will raise or lower the probability of the target disorder. The likelihood ratio for a test compares the likelihood of that result in patients with disease to the likelihood of that result in patients without the disease.

The Positive Likelihood Ratio (LR+) tells us how much to increase the probability of disease if the test is positive (and corresponds to the clinical concept of "ruling in" disease), while the Negative Likelihood Ratio (LR-) tells us how much to decrease it if the test is negative (and corresponds to the clinical concept of "ruling out" disease).[40]

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[39] Use of the likelihood ratio (LR) is recommended by the Evidence Based Medicine Working Group (Jaeschke 1994) because it is simpler and more efficient than the older (and in their estimation less useful) concepts of sensitivity and specificity.

[40] The LR for a negative result (negative likelihood ratio or LR-) = (1-sensitivity)/specificity. The LR for a positive result (positive likelihood ratio or LR+) = sensitivity/(1-specificity). The likelihood ratios in this

Test information is only valuable if it changes the probability of disease enough to alter diagnosis or treatment. As a general rule:

- LRs >10 or <0.1 cause large changes in likelihood;
- LRs 5-10 or 0.1-0.2 cause moderate changes in likelihood;
- LRs 2-5 or 0.2-0.5 cause small changes in likelihood; and
- LRs between <2 and 0.5 cause little or no change in likelihood (Jaeschke 1994).

Likelihood ratios, sensitivities and specificities of the diagnostic methods assessed by studies in the primary evidence base are found in Table 7.

The diagnostic methods in Table 8 were selected and ordered based on the of level of evidence of the study in which the test appeared, the number of independent studies in the evidence base that cited the test as useful (coherence of evidence), and the size of the likelihood ratios (clinical importance). In our opinion, Table 8 includes the more robust clinical diagnostic methods for carpal tunnel syndrome.

The evidence on clinical diagnosis of CTS indicates that the preponderance of clinical diagnostic techniques are more useful for suggesting the presence of (rather than the absence of) CTS: more high quality studies show better specificities and positive likelihood ratios. Clinical diagnostic methods most useful for suggesting the presence of CTS included the Phalen sign, the Durkan carpal compression test, the Hand Symptom Diagram and the Tinel sign.

Only one study that met the inclusion criteria evaluated electrodiagnostic testing (Gunnarsson 1997). The results of that study indicate that both nerve conduction velocities in the median and ulnar nerves, and palm-wrist/wrist-elbow nerve conduction velocity generate only moderate shifts in pre-post test probability.

Question 5.

How can a physician distinguish between CTS and other conditions with similar symptoms (e.g. tendonitis)?

As indicated by the data in Tables 8 and 9, it is difficult to "rule out" carpal tunnel syndrome. The sensitivities and specificities of the available diagnostic tools are not very good.

In a case of carpal tunnel syndrome, complaints should be localized to the palmar aspect of the first to the fourth fingers and the distal palm (the sensory distribution of the median nerve at the wrist). Numbness predominantly in the fifth finger or extending to the hypothenar eminence or dorsum of the hand should suggest other diagnoses.

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background paper were calculated from the primary data using the EBM statistical calculator (EBM Toolkit 2003). More information on likelihood ratios is found in Appendix J.

TABLE 8. THE MORE ACCURATE CLINICAL DIAGNOSTIC METHODS (BY METHOD)

Clinical diagnostic technique, author and level of evidence	Positive Likelihood Ratio	Negative Likelihood Ratio	Sensitivity	Specificity
Phalen				
Fertl (1)	9.90	0.23	0.79	0.92
MacDermid (1)	8.70	0.14	0.87	0.90
DeSmet (2)	1.36	0.28	0.91	0.33
Gerr (2)	2.39	0.36	0.75	0.68
Gunnarsson (3)	1.65	0.29	0.86	0.48
Szabo (3)	2.58	0.35	0.75	0.71
Durkan Carpal Compression Test[41]	10.4	0.18	0.83	0.92
Fertl (1)	0.94	1.11	0.63	0.33
DeSmet (2)	2.60	0.17	0.89	0.66
Szabo (3)				
Hand Symptom Diagram				
Katz (1)	1.25	0.17	0.96	0.23
Stevens (1)	2.07	0.44	0.71	0.66
Gunnarsson (3)	2.13	0.49	0.66	0.69
Szabo (3)	4.75	0.28	0.76	0.84
Tinel				
MacDermid (1)	9.80	0.44	0.59	0.94
Gerr (2)	0.37	2.30	0.25	0.32
Gunnarsson (3)	1.44	0.67	0.62	0.57
Szabo (3)	3.76	0.43	0.64	0.83
Serial mCCT and Phalen				
Fertl (1)	11.5	0.09	0.92	0.92
Wrist Extension				
MacDermid (1)	18.80	0.26	0.75	0.96
Closed Fist				
DeSmet (2)	7.30	0.43	0.61	0.92
2 Point Discrimination				
Gerr (2)	0.44	1.99	0.28	0.36

[41] Fertl and DeSmet performed manual carpal compression tests (mCCT); Szabo's was piston calibrated.

TABLE 9. ACCURACY OF ELECTRODIAGNOSTIC TECHNIQUES FOR CTS

Electrodiagnostic technique, author and level of evidence	Positive Likelihood Ratio	Negative Likelihood Ratio	Sensitivity	Specificity
Neurophysiology (nerve conduction velocities in median and ulnar nerves)				
Gunnarsson (3)	6.54	0.17	0.85	0.87
Palm-wrist/wrist-elbow NCV				
Gunnarsson (3)	6.20	0.23	0.80	0.87

Pain in the epicondylar region of the elbow, upper arm, shoulder or neck is more likely to be due to other musculoskeletal diagnoses (eg, epicondylitis) with which CTS is commonly associated. This more proximal pain should also prompt a careful search for other neurologic diagnoses (eg cervical radiculopathy).

The characteristics of the main symptom (paresthesias) of carpal tunnel syndrome require differential diagnosis from ulnar nerve compression syndromes, thoracic outlet syndrome, hand-arm vibration syndrome, and cervical nerve root compression (Sluiter 2001).

Question 6.

Which forearm conditions co-exist with CTS? With what frequency?

Carpal tunnel syndrome often co-exists with other common forearm conditions that may be associated with or mimic CTS and must be distinguished and treated. They include cervical radiculopathy, tendonopathy (Jablecki 1993), arthritis at the base of the thumb, "trigger fingers," De Quervain's tendonopathy, C6 radiculopathy, hand-arm vibration syndrome, cervical spine manipulation, and compression at the thoracic outlet, the forearm or the elbow.

No studies meeting the inclusion criteria addressed the frequency with which forearm conditions co-exist with CTS, and data on prevalence of those conditions would likely suffer from the same comparative problems for diagnosis as does prevalence data on carpal tunnel syndrome.

V. CAUSATION OF CARPAL TUNNEL SYNDROME

A. Relevant background information

1. What is a cause?

Rothman (1986) defined a cause as "an event, condition or characteristic that plays an essential role in producing an occurrence of the disease." There is causation, in other words, only when one factor necessarily alters the probability of a second.

Causality is the relating of causes to the effects they produce. Most of epidemiology concerns causality and several types of causes can be distinguished. It must be emphasized that epidemiological evidence by itself is insufficient to establish causality, although it can provide powerful circumstantial evidence (EMB-Toolkit 2003).

2. What is risk?

Risk is the probability that an event will occur. In epidemiology, it is most often used to express the probability that a particular outcome will follow a particular exposure.

A risk factor is an environmental, behavioral or biologic factor, confirmed by temporal sequence, ideally in longitudinal studies, which, if present, directly increases the probability that a disease will occur, and if absent or removed reduces that probability. Risk factors are part of the causal pathway, or expose the host to the causal pathway (Burt 2001).

3. Carpal tunnel syndrome: an indistinct etiology

Precisely what factors predominate in the etiology of CTS is the subject of ongoing debate. Carpal tunnel syndrome has an indistinct, multifactorial etiology: often a single cause cannot be identified. A variety of contributing etiological factors and conditions can affect the median nerve in the carpal tunnel. These include:

- pathologies that modify the shape of the carpal tunnel (space occupying lesions such as the residual of a wrist fracture, tumors, flexor tenosynovitis, foreign bodies); and

- systemic pathologies or conditions that increase intra-tunnel pressure (local edema, pregnancy, obesity, diabetes mellitus, thyroid dysfunction, arthritis) (Patry 1998).

Carpal tunnel syndrome may have a spontaneous or idiopathic onset.

Carpal tunnel syndrome's multifactorial etiology makes it a complex and challenging subject for epidemiological study, potentially stemming from multiple risk factors (and potentially many causes). The presence of one risk factor does not negate other pathways with other causal roles.

Causal models for CTS are complicated by differences in personal susceptibility (it is unlikely that all individuals have equal susceptibility to any disorder) and genetic disposition, repeated exposures to low levels of the suspected causal agent(s), and a latency period that varies with individual susceptibility and severity of exposure.

Multifactorial causation is one reason the causation of CTS is controversial in the medical community. The disagreement centers on the relative importance of multiple causal factors of the disease, whether these factors are occupational or non-occupational, and to what degree. Several different risk factors may be in play in any given case of CTS, combining and interacting in ways that are difficult both to study and to understand. At the same time, it is necessary to distinguish between factors that aggravate the symptoms of carpal tunnel syndrome and factors actually responsible for the development of the condition (Gorsche 2001).

4. Inferring a causal relationship

Evaluating epidemiological literature for evidence of a possible causal relationship requires an understanding of the sequence of steps with which causality is generally inferred. The basis for this understanding rests on several key concepts. The first is that there is an exposure and the second is that there is an outcome of interest. The exposure can be one of any number of biological, physical, chemical or psychological events. The outcome is a disease condition. The third concept is that there is a statistically significant association between exposure and outcome (NRC&IOM 2001).

While a statistically significant association is a necessary condition for asserting a causal relationship, it is not a sufficient condition. Qualitative considerations about the plausibility of the purported causal relationship are just as important. Before an epidemiological association may be regarded as causal, other possible explanations like chance, bias and confounding must be excluded.

To this end, the association may be tested against a set of "characteristics," "conditions," "conventions," or criteria" commonly used to review individual research studies for their likelihood of generating causal inferences (Hill (1966);(1971), modified by Rothman (1986) and Susser (1991)). These "conditions" are designed to elicit specific pieces of empirical evidence that increase the confidence with which one can infer a cause-effect connection.

No single epidemiologic study will fulfill all criteria for inferring causality. When critically reviewing the epidemiological literature on carpal tunnel syndrome for possible cause-effect connections, we focused on three key criteria: temporality, strength of association, and coherence of evidence.

a. Temporality

Temporality, an absolute prerequisite for causality, requires that the cause be present before the effect is observed. If the "cause" did not precede the effect, then it cannot possibly have been a cause. If it cannot be established that the exposure preceded the outcome in time, then it cannot be established that the exposure caused the disease.

While prospectively designed studies ensure that the criterion of temporality is strictly adhered to (that is, that exposure preceded adverse health effect), the design of cross-sectional studies does not allow strict adherence to this criterion because both exposure information and adverse health outcome are obtained at the same point in time.

b. Strength of association

Strength of association refers to the magnitude of the measure of the association; the larger the summary measure, the more confident one can be that the putative association may be causal

(and the less likely the association is spurious). Weaker associations are more likely to be explained by undetected biases. The measures used include the relative risk (RR) and odds ratio (OR).

We used the ORs and RRs from the reviewed studies to examine the strength of the association between exposure to various risk factors and carpal tunnel syndrome, with the higher values indicating stronger association. We agreed that odds ratios greater than 2 suggest a clinically relevant strength of association between a factor and the presence of CTS.

c. Coherence of evidence

The evidence is coherent if a hypothesized causal association is compatible with pre-existing theory and knowledge (Susser 1991). Is the association biologically plausible? To what extent is the hypothesized causal association compatible with the natural history and biology of disease, with current knowledge of medicine, of statistics, and of biological mechanisms? How many independent original research studies meeting the inclusion criteria reached a similar conclusion?

B. Reporting the evidence: the primary evidence base

Table 10 presents summaries and critical appraisal of the 14 causation studies that met our inclusion criteria.[42] This set of original research studies forms the primary evidence base on causation of carpal tunnel syndrome. In our opinion, these studies present the best scientific evidence currently available on the causation of CTS. First author, title, date, study type, authors' conclusions and critical appraisal by members of the research team are included for each study. The studies are organized by category (risk factors, task and occupation) and, within those categories, they appear in descending chronological order.

The evidence on the causation of carpal tunnel syndrome is of relatively poor quality. This is because of the heterogeneity of the subject matter of the causation studies, the ethical constraints on experimental research in humans,[43] and the lack of longitudinal studies. Studies of disease causation must be observational and are more susceptible to bias and confounding than are experimental studies. Longitudinal studies of causation have the potential to provide the strongest evidence of a temporal, cause-effect relationship, but longitudinal studies of CTS causation are sparse.

Given relatively poor quality of the available evidence on causation of carpal tunnel syndrome, we do not assign numeric levels of evidence to the studies that met the inclusion criteria. We focus instead on their relative strengths and weaknesses, and evaluate the evidence they present based on criteria described in the Causation Evidence Assessment Guide developed specifically for use in this background paper.[44] We appraise the studies according to their validity, the importance of their results, and their applicability to the WCB-Alberta population.

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[42] Inclusion criteria are found in the Methodology section of the background paper.

[43] Well designed Randomized Controlled Trials (experimental studies) provide the highest level of evidence (Level 1), but there are ethical constraints on experimental research on humans, and it is not acceptable to expose subjects deliberately to potentially serious hazards, which limits the application of experimental methods in the investigation of disease etiology. Studies of disease causation must be observational and are more susceptible to bias and confounding than are experimental studies. Because studies of disease causation cannot be experimental, Level 2 is the highest level of evidence these studies can provide, although it may be possible to evaluate preventive strategies experimentally.

[44] A copy of our Causation Evidence Assessment Guide is found in Appendix H.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Risk Factors			
Hakim, A. The genetic contribution of carpal tunnel syndrome in women: a twin study. Arthritis and Rheumatism 2002.	Observational: blinded case-control classic twin study	Previous studies have ignored an underlying genetic susceptibility that could explain much of the variation or liability to CTS. This is the first study to explore the genetic component of CTS. Our data (the study group comprised unselected female twin pairs, between 20 and 80 years of age) show that up to half the liability to CTS in women is genetically determined, and this appears to be the single strongest risk factor. None of the individual environmental factors we measured were strongly related to CTS. The strongest risk factors for CTS appear to be genetic.	In this case control study which attended to selection bias, no significant association was demonstrated between studied environmental risk factors and the presence of CTS. Genetic predisposition appeared to be important.
Nathan, P. Predictors of carpal tunnel syndrome: An 11-year study of industrial workers. Journal of Hand Surgery 2002.	Longitudinal study. Prospective investigation of industrial workers (steel mill, meat/food packaging, electronics, plastics) over an 11 year period.	In 1984 we initiated a study of factors associated with carpal tunnel syndrome in industrial workers. Follow-up investigations were conducted in 1989 and in 1994-95. In the analytic sample, greater age, female gender, relative overweight, cigarette smoking, and vibrations associated with job tasks were found to significantly increase risk for dominant hand CTS. Other workplace factors (repetition, heavy lifting, keyboard use, force) did not approach conventional levels of statistical significance. Similar to other chronic non-infectious diseases, personal factors may play an important role in determining risk for CTS.	Cohort study over 11 years. Clinically significant multivariate ORs>2 were associated with age>50 (15.9[3.1-83.4]) and BMI quintiles>2; especially >28 (6.4[1.4,29.4]), gender (5.1[1.7, 15.5]), and exposure to vibrations (3.7[1.0,13.3]). However, like all surveys dependent on volunteers instead of patients presenting with symptoms, the import and extent of self-selection bias is not clear. The significant drop-out rate of 42% was a major threat to validity of the study.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Risk factors (continued)			
Ferrero, M. The carpal tunnel syndrome. Etiologic and prognostic role of biological and professional risk factors. Minerva Ortopedica E Traumatologica 2001.	Observational: cohort study	Our study of subjects with a diagnosis of CTS for which surgery was chosen shows that there are some individual factors that not only predispose subjects toward the development of CTS, but also influence the outcome of surgical treatment. These include menopause, BMI > 30, oral assumption of estroprogestinics, hypothyroidism and viral hepatitis, all of which seem not only to play an aetiological role but also to have a negative prognostic value. There was no evident statistically significant difference in the parameters for repetitiveness, force, synthetic index or weighted synthetic index in time for professional risk factors. No statistically significant difference was found in the blood tests.	This weak study, which reviewed co-morbidities in a surgically selected population, had no matched controlled cohort and no control for surgeons or for post operative activity. Biases may exist as not consecutive. Only 40% of those exposed to repetition and force were captured. This study suffered from a very weak statistical technique.
Roquelaure, Y. Prevalence, incidence and risk factors of carpal tunnel syndrome in a large footwear factory. International Journal of Occupational Medicine and Environmental Health 2001.	Observational: prospective cohort study	The prevalence and incidence of CTS in this blue collar workforce (six production units of a large, modern, mechanized footwear factory) were substantially higher than in the general population and in other industries. This study emphasizes the multifactorial nature of CTS, since personal factors and exposure to physical and psychosocial stressors at work independently affect the incidence of CTS. Psychosocial factors play a major role in the factory studied, which exposes its workers to a high level of physical load. In particular, high psychosocial distress seems to be a cause rather than a consequence of CTS.	This prospective cohort study apparently did not assess certain co-morbidities such as diabetes. It included self-reported and directly observed workstation exposure, but it is not clear that observers were blinded to the status of the workers. The prevalence of CTS (clinical diagnosis) was apparently higher than that generally reported. The dropout rate of 19% and the large number of variables studied for relatively few outcomes in the multivariate analysis may have reduced the study's statistical validity. The only statistically significant risk factors were obesity (BMI > 30kg/m^2) with an OR of 4.4 (1.1-17.1), and psychological distress at baseline with an OR of 4.3 (1.0, 18.6).

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Risk factors (continued)			
Solomon, D. Nonoccupational risk factors for carpal tunnel syndrome. J Gen Intern Med 1999.	Observational: case control study using an administrative database	We examined the relation between non-occupational risk factors and surgery for carpal tunnel syndrome in a population of subjects who had undergone an open or endoscopic carpal tunnel release procedure. Controls were frequency matched by age and gender with case subjects. Inflammatory arthritis conferred a nearly threefold increase in the risk of carpal tunnel surgery. Other significant risk factors were diabetes (40% increase in risk), hypothroidism (70% increase in risk), and hemodialysis, which was associated with a nine fold increase in risk of carpal tunnel surgery. Use of hormone replacement therapy appeared to be associated with a higher rate of requiring carpal tunnel release (80% increase). In addition, we found an unexpected 60% increase in risk of carpal tunnel release in patients taking corticosteroids, even in the absence of evidence for concomitant inflammatory arthritis.	This case control study using an administrative database of CTS surgery patients has selection bias (only CTS sufferers presenting for therapy were included), which threatens the validity of the study, and the author's conclusions may not apply to general CTS population. The only clinically significant relationship found was between CTS and inflammatory arthritis [OR=2.9 (2.2,3.8)].

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Task			
Babski-Reeves, K. Comparisons of measures for quantifying repetition in predicting carpal tunnel syndrome. International Journal of Industrial Ergonomics 2002.	Observational: case-control study with multiple cohorts of small size	The objective of this study of operators in a fish processing facility was to compare the accuracy of measures commonly used to quantify repetition (cycle time or CT), number of hand movements (HM) and exposure classification (EC) in predicting CTS and positive findings for CTS. Participant exposure to repetition was quantified through direct and video observation. For diagnosed CTS, HM were the only repetition measure found to have a significant relationship, and was tentatively concluded to be the best predictor. No statistically significant results were found for positive findings for CTS.	Clearly defined case-control study with multiple cohorts of small size designed to study different exposure classifications. Exposure assessors were blinded to the diagnosis. Operators were mostly female (94%) and no information was provided on co-morbidities such as diabetes and renal disease. Although no significant relationship between various repetitive measures and CTS was observed, a Type II error is possible. Point prevalence after 6 months exposure would omit all acute cases which are those more likely to be occupational.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Task (continued)			
Rucker, N. Predictive validity of the Strain Index in manufacturing facilities. Applied Occupational and Environmental Hygiene 2002.	Observational: variant of a retrospective longitudinal study. Investigators were blinded to health outcomes.	The Strain Index is a job analysis method for determining if workers are exposed to increased risk of developing distal upper extremity disorders. It relies on the measurement or estimation of six task variables that describe the exertional demands of the job (physical stress). The purpose of this study was to evaluate its predictive value. The results of this study demonstrate that the Strain Index is able to effectively identify hand activities that do and do not place workers at increased risk of distal upper extremity disorders at two manufacturing plants. They also demonstrate that the Strain Index has external validity as a method for distal upper extremity musculoskeletal risk assessment.	This study attempted to identify activity or task versus job specific risks. The retrospective assessment of disorders was done by researchers blinded to the results of the subjects' strain hazard classification. The study's sample size was small, however, and included only 3 cases of CTS, making it unclear if the observed strain index accuracy pertains to predicting risk for CTS.
Stevens, J. The frequency of carpal tunnel syndrome in computer users at a medical facility. Neurology 2001.	Observational: case control study	Comparison of the characteristics of the employees at a medical facility (all frequent computer users) with and without CTS revealed no differences that might implicate computer keyboard use as the causative factor in the CTS cases. The affected and unaffected had similar occupations, years using a computer, and time using the computer during the day. With clinically defined criteria, CTS was found in 10.5% and electrodiagnostically confirmed in 3.5% of computer users at our facility. This is comparable to estimates of frequency of CTS in the general population and suggests that using a computer in the setting studied does not enhance risk of CTS.	Case control study of a group of computer users with and without CTS. Self-reporting of hand paresthesias was used to screen for further assessment of CTS, introducing selection bias. Use of NCS in approximately 10% introduced verification bias. The sample size of workers with symptoms, CTS clinical testing and NCS was consequently small (n=37). Therefore, although the authors were unable to detect any significant relationship between CTS and computer use, a Type II error is possible.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Task (continued)			
Tang, X. Carpal tunnel syndrome: a retrospective analysis of 262 cases and a one to one matched case-control study of 61 woman pairs in relationship between manual housework and carpal tunnel syndrome. Chinese Medical Journal 1999.	Observational: retrospective 1:1 matched case control study	The results of our matched case control series of woman pairs showed that washing clothes and rolling and/or kneading dough manually seem to contribute to the onset of CTS, whereas knitting woolen sweaters does not.	Case control study where groups appear matched for gender, age, and co-morbidities. Not clear whether risk exposure assessment was blinded to the presence or absence of CTS diagnosis. The ORs for washing clothes (3.9) and kneading/rolling dough (6.3) are associated with CIs that do not cross 1.
Chiang, H. Prevalence of shoulder and upper-limb disorders among workers in the fish processing industry. Scand J Work Environ Health 1993.	Observational: cross-sectional study	Shoulder girdle pain (30.9%), epicondylitis (14.5%) and carpal tunnel syndrome (15.0%) were the three most common disorders in this study of fish processing workers in eight factories. In this study, 4.5% of the male workers and 20.0% of the female workers were diagnosed as having clinical carpal tunnel syndrome. After adjustment for age, the odds ratio of the female workers was 2.6 times higher than that of the male workers. Workers were divided into three groups: (1) low force, low repetition, (2) high force or high repetition, and (3) high force and high repetition. Repetitiveness was not shown to be a statistically significant predictor of carpal tunnel syndrome in our study, but there was still a significant increasing trend for the prevalence of carpal tunnel syndrome as the degree of ergonomic factors increased from group I to group III.	The OR in this study was borderline, although there was a statistical "trend" for a dose-response relationship. The statistics in this study are weak, and the proportion of participants and non-participants is not stated. No demographic comparisons are made and the number of subjects in each category is not stated. Prevalence x-section only. "High repetition" is defined as one movemement/30 seconds which is unrealistically slow and would not apply to most assembly line conditions in Alberta.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Occupation			
Gorsche, R. Comparison of outcomes of untreated carpal tunnel syndrome and asymptomatic controls in meat packers. Occupational Medicine 2002.	Observational: case control study	The role of ethnicity, gender, age, body mass index, and use of tools in the causation of CTS was examined in workers at a meatpacking plant. Work-related CTS, as defined by symptoms and physical signs, was found in 21% of the population; higher than in the general population, but not significantly different from reported prevalence data from older plants. No relation was found between ethnicity, age, body mass index, and the presence of CTS symptoms or signs.	This case-control study compared symptomatic individuals with positive clinical findings for CTS to comparable symptom-free co-workers. Similar "exposure" opportunities appeared to be present in both groups, and co-morbidities were analyzed. No significant causal relationship was demonstrated. It is not clear whether the lack of NCS testing could have changed prevalence data or conclusions.
Dryson, E. The distribution of occupations in two populations with upper limb pain. Int J Occup Environ Health 2001.	Observational: case series	This study of two geographically distinct populations with upper limb pain showed increased rates of manual occupations for epicondylitis and carpal tunnel syndrome subjects in the one population studied for this, which suggests cause and effect. It showed overrepresentation of some clerical occupations in subjects with pain syndromes or non-specific occupational overuse syndrome in both populations, for which, within the limitations of this study, there is no explanation. This study is presented as a descriptive one with some interesting associations that clearly need confirmation in other populations.	This case series study with a small predominantly female (80%) CTS group (n=53), but a large and appropriate comparison group, analyzed causal relationships to occupation at the time of onset of symptoms rather than task-specific factors. Analysis is hampered by the nonspecific data in the comparison group, and co-morbidities were not addressed. Selection bias from single practice referral and systematic bias from variable likelihood of reporting symptoms (e.g. clerical workers) is a possibility.

TABLE 10. STUDIES MEETING THE INCLUSION CRITERIA: CAUSATION OF CTS (continued)

STUDY	STUDY DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL AND ASSESSMENT OF THE EVIDENCE
Occupation (continued)			
Frost, P. Occurrence of carpal tunnel syndrome among slaughterhouse workers. Scand J Work Environ Health 1998.	Observational: retrospective, un-blinded cohort study	All together 40 (4.6%) persons with CTS were identified among the study population of workers employed at a slaughterhouse or chemical factory. The prevalence of CTS was increased in the age group 35-49 years and among persons who had experienced earlier wrist trauma. There was an increasing risk according to cumulative exposure up to 6 to 10 years, after which the risk stayed almost constant, at a slightly lower level. This study supports the hypothesis that daily exposure to combined forceful and repetitive manual movements is a risk factor for CTS, and suggests that both level and duration of exposure is important in the provocation of CTS.	The retrospective work history introduces bias into this study. The odds ratio is >2.0, but there is not a clear dose response. Validity: cohort or similar exposure. Co-morbidities are controlled for and the follow-up period was sufficient but the study is unblended. Risk increases but only up to 6 years, possibly due to the Healthy Worker Effect.
Silverstein, B. Upper extremity musculoskeletal disorders at a pulp and paper mill. Applied Ergonomics 1996.	Observational: small cross-sectional study	On interview hand and wrist disorders were positively identified with number of years on the job in a pulp and paper mill, and working in the power and recovery area. Only years on the job was associated with CTS at the $p< 0.05$ level of significance, according to the case definition used in this study. However, abnormal median nerve findings on electrodiagnostic tests were negatively associated with high decision latitude ($p< 0.04$) (assessed by questionnaire). There was evidence that the job analysis was not able to fully describe the risk factors present in the paper machine department.	This small, complicated study (n=40) assessed for multiple upper extremity disorders, rather than CTS alone. CTS was diagnosed by history and clinical examination. Co-morbidities were studied, but not reported in context. The use of multivariate analysis, when the number of variables studied exceeded the number of outcomes in one group, and the exclusion of workers with wide ranges of exposure to the different work environments, seriously limit the study's validity and applicability.

C. Findings: answers to research questions on causation of carpal tunnel syndrome

Question 7.

Which (if any) of the following work-related activities are risk factors for CTS? Palmar impacting activities? Repetitive activities? Gripping activities? Grasping activities? Wrist posture? Are there others?

Five studies in the primary evidence base addressed the role of force, repetition, and/or force combined with repetition as risk factors for carpal tunnel syndrome. The evidence they present is mixed and conflicting.

While several studies (Chiang 1993, Frost 1998) report CTS risk associated with job tasks that require exposure to forceful and repetitive wrist motion, others (Ferrero 2001, Nathan 2002, Babski-Reeves 2002) did not demonstrate that association.

No research studies of palmar impacting activities, gripping activities, grasping activities, wrist posture, static load, local mechanical stresses, manual materials handling, pushing, pulling and carrying, grip type, impact loading, and unaccustomed activity, met the inclusion criteria.

Question 8.

Which (if any) of the following tasks increase the risk of CTS and to what degree? Driving? Sheet metal work? Use of tin snips/pliers? Keyboarding?

Tasks characterized by a high frequency but low force, i.e. computer key pad use, do not appear to be important precipitating factors for carpal tunnel syndrome. Stevens (2001) found no significant differences that might implicate computer keyboard use as a causative factor in CTS, although there may have been some methodological problems with this study.

No research studies that addressed driving, sheet metal work, and the use of tin snips or pliers met our inclusion criteria.

Question 9.

Does a static body posture increase the risk of CTS?

No research studies that addressed static body posture as a risk factor for CTS met our inclusion criteria.

Question 10.

Do the following work environmental factors increase the risk of CTS: Vibration (frequency, duration)? Temperature (what temperature)? Use of gloves? Others?

In a longitudinal study, Nathan (2002) found that vibrations associated with job tasks significantly increased the risk for dominant hand CTS. The study did not characterize or quantify the frequency or duration of the vibrations.

The relationship between temperature or wearing gloves and CTS is uncertain, as evidence in well-designed original research studies is lacking.

Question 11.

What are the systemic conditions that may cause or contribute to CTS? What is the magnitude of the effect?

A variety of systemic conditions or pathologies may cause or contribute to CTS.

It is thought that specific systemic pathologies (e.g. hypothyroidism) and conditions (e.g. pregnancy) may increase the pressure of extravascular fluid within the carpal tunnel and cause compression of the median nerve (Patry 1998).

In 56.8% of CTS cases, concomitant diseases or conditions are present; the most common are hormonal disorders (6.1%), diabetes (6.1%), pregnancy (4.6%) and thyroid disorders (1.4%) (Stevens 1992). Inflammatory arthritis has also been shown to be associated with CTS (Solomon 1999).

Question 12.

What is the relationship of anatomic structure (congenital or acquired, eg., degenerative changes to the wrist) to CTS?

The volume of the carpal tunnel may be reduced by abnormalities or fractures of the wrist bones, thickening of the anterior ligament, necrosis of the semilunar bone, and hand traumas or contusions. Tumors (lipomas, hemangiomas, lipofibromas, liposarcomas), synovial cysts, and tenosynovitis (rheumatoid, infectious or tubercular, or secondary to amyloidosis or gout) may increase the volume of structures within the tunnel (Patry 1998). Carpal tunnel size and wrist size have also been suggested as risk factors for CTS (Fed.Reg. 2000).

Question 13.

What individual characteristics (age, gender, body mass, personal habits, psychosocial variables, and genetic predispositions) are risk factors for CTS?

Individuals differ in their susceptibility to developing CTS based on individual characteristics including age (Nathan 2002), Body Mass Index (BMI) (Nathan 2002, Ferrero 2001), and gender (Nathan 2002). The relationship of CTS and BMI may involve increased fatty tissue within the carpal canal or increased hydrostatic pressure throughout the carpal canal in obese persons compared with slender persons (Fed.Reg. 2000). In a well-designed case-control twin study, Hakim (2002) demonstrated that genetic predisposition may also play a major role in the causation of CTS, and Roquelaure (2001) concluded that high psychosocial distress may be a cause rather than a consequence of CTS.

Although age may be a prognostic factor, we found no evidence that supports age as a specific independent risk factor for carpal tunnel syndrome. It is not age per se, but certain co-morbidities that go with age that are risk factors for carpal tunnel syndrome. Correction for age-related neurological factors in electrodiagnostic studies may be necessary in order not to over-diagnose CTS in an older population.

Question 14.

Which co-existing forearm conditions may cause or contribute to CTS?

Forearm conditions that may co-exist with carpal tunnel syndrome include cervical radiculopathy, tendonitis (Jablecki 1993), arthritis at the base of the thumb, "trigger fingers,"

De Quervain's tendonitis, C6 radiculopathy, hand-arm vibration syndrome, cervical decompression, and compression at the thoracic outlet, the forearm or the elbow.

No studies meeting the inclusion criteria addressed a potential causal relationship between any of these co-existing forearm conditions and CTS.

Question 15.

Do prior episodes of cervical nerve root irritation pre-dispose to CTS (is there a scientific basis for the "double crush" theory)?

The "double crush" theory proposes that if a nerve is compressed at two separate places (often at a considerable distance from each other) even though the degree of compression at one or both sites is insufficient to cause symptoms (i.e. sub-clinical), the cumulative impairment of conduction caused by the double compression could be sufficient to cause symptoms of motor or sensory impairment (for example, in a case of cervical root compression plus CTS) (Fleming 2000). The theory is a controversial one within the medical community.

According to the double crush hypothesis, very strict neuro-anatomical accuracy must be applied. A diagnosis of double crush syndrome could only be made if the identical nerve fibers were compressed at the two sites (for example, median nerve fibers in the carpal tunnel and exactly the same median nerve fibers in the portion of the cervical nerve root through which they travel). Also, the clinical manifestation of double crush syndrome would arise from impaired nerve conduction, and would likely consist of neurological deficit such as muscle weakness or wasting or sensory deficit, rather than vague pain (Fleming 2000).

To determine whether scientific proof exists for the "double crush" theory, we conducted a separate review of the literature published on the theory for the past five years.

We found that while the double crush theory is actively under investigation, the research, (which is mostly basic/animal research), is in its infancy. This theory is being tested, but it is experimental and unproven and has by no means entered the mainstream of medical thought. Its applicability to clinical medicine is not clear at this point.

Question 16.

What constitutes recurrence of CTS and what constitutes continuation of CTS?

Recurrence of CTS is the return of the disease and its symptoms after apparent recovery. Ongoing disease and symptoms constitute continuation.

The concepts of recurrence and continuation rest on the assumption that non-resolution or return of symptoms is not a result of misdiagnosis of another syndrome or condition as CTS.

Question 17.

Which work related activities or conditions may predispose to CTS in both wrists?

It is a common experience in clinical practice that many patients affected with carpal tunnel syndrome complain of symptoms in both hands, and it has recently been postulated that CTS is bilateral in almost all cases (with similar nerve impairment), and that most cases of unilateral CTS will probably become bilateral (Padua 1998). Carpal tunnel syndrome in both

wrists may indicate the presence of genetic, systemic or anatomic risk factors for the condition. Bilateral carpal tunnel syndrome should prompt a review for systemic medical conditions that may cause peripheral neuropathy.

We were unable to identify any specific work related activity that may predispose to bilateral carpal tunnel syndrome. In relation to work-related risk factors, each hand appears to be at independent risk depending on that hand's activity (Falck 1983), and it is reasonable to assess each hand individually.

IV. TREATMENT OF CARPAL TUNNEL SYNDROME

A. Relevant background information

The resolution of symptoms and the preservation of hand function are goals of treatment for carpal tunnel syndrome (Gorsche 2001). Treatment includes non-surgical (or "conservative") treatment and surgical treatment. A significant number of CTS patients will improve with no treatment (Padua 2001) which may help explain why many unproven alternative therapies claim success (Gorsche 2001).

The basis of appropriate treatment for CTS is a rigorous diagnosis, unfortunately complicated by the absence of an agreed upon diagnostic "gold standard" for verifying the presence or absence of the syndrome (Rempel 1998). Inaccurate diagnosis is a common cause of failed treatment.

1. Non-surgical ("conservative") treatment

Non surgical therapies currently in use include exercises, wrist splints, injection of anti-inflammatory steroids, therapeutic ultrasound, activity or ergonomic modification, anti-inflammatory drugs, vitamins, laser therapy, chiropractic treatment and neuromagnetic therapy. There is little or no evidence for the effectiveness of some of these therapies.[45]

Non-surgical treatment of carpal tunnel syndrome is based on what is known about the pathogenesis and pathophysiology of CTS. Splinting is recommended to keep the wrist in a neutral position that results in the lowest intra-canal pressure and therefore the least pressure on the median nerve. Night splints prevent the incursion of the lumbrical muscles into the distal carpal tunnel (which occurs during wrist flexion during sleep) and reduce intra-canal pressure (Gorsche 2001). Stretching exercises for CTS are prescribed because it is hypothesized that stretching may relieve compression in the carpal tunnel, better joint posture may decrease nerve compression, and blood flow may be improved to the median nerve (O'Connor 2003a).

2. Surgical treatment

Except in rare emergencies, surgery is performed electively in an effort to improve symptoms, function and quality of life (Katz 1995). Surgery is intended to relieve symptoms by creating greater space in the carpal canal (O'Connor 2003a). It is usually an outpatient procedure performed in an ambulatory surgical center under regional anesthesia.

The standard surgery for CTS is the transection of the transverse carpal ligament, either by open incision or endoscopic surgery. Whether open incision or endoscopic surgery is performed depends on surgeon preference, surgeon experience, clinical circumstances and available facilities.

Associated procedures sometimes include ligament repair or neural surgery. Ligament reconstruction involves the reattachment of the transected ends of the transverse carpal ligament in such a way that the overall ligament is lengthened, resulting in an enlargement of the carpal tunnel and relief of the pressure on the median nerve. Neural surgery (external or internal neurolysis or epineurotomy of the median nerve) is sometimes performed immediately

[45] See Table 11, Studies Meeting the Inclusion Criteria: Treatment of Carpal Tunnel Syndrome, and the answer to Question 18.

following the division of the transverse carpal ligament, although it is not clear that this technique improves outcomes (Cobb 1996).

Various subspecialties of surgeons (general surgeons, hand surgeons, plastic surgeons, neurosurgeons and orthopedic surgeons) perform carpal tunnel surgery. This contributes to a nonstandardized and sometimes ambiguous use of terms. The term "neurolysis", for example, is used to encompass several different procedures including removal of adhesions and scar tissue from the connective tissue surrounding the nerve (the epineurium), relieving pressure within the epineurium by means of a longitudinal incision, or removal of a segment of epineurium, in an effort to decompress the nerve and allow it to glide freely (Chapell 2003).

Most surgical complications associated with open carpal tunnel release result from inappropriately placed incisions (Hunt 1994). Complications following carpal tunnel release have been reported in 1% to 25% of patients, and include infection (Cobb 1996), injury to the thenar motor branch, injury to the median nerve itself, bleeding and failure to resolve symptoms. A tender scar is the post-operative complication that most often hampers return to work (Gorsche 2001). Persistent and/or recurrent symptoms may also bother patients following surgery. Reasons for persistence of symptoms following surgical release include incorrect diagnosis, inadequate decompression, and iatrogenic nerve injury (O'Connor 2003b).

3. No treatment

Patients who have mild, occasional symptoms are not necessarily treated (Verdugo 2003); their symptoms are sometimes managed with observation alone (Hunt 1994, Padua 2001). If the patient is involved in activities where full wrist function is required, conservative treatment remains an option.

B. Reporting the evidence: the primary evidence base

Table 11 presents summaries and critical appraisal of the 17 treatment studies that met the inclusion criteria. We appraised the studies that met the inclusion criteria according to their validity,[46] the importance of their results, and their applicability to the WCB-Alberta population.

This set of clinical research studies forms the primary evidence base on treatment of carpal tunnel syndrome. In our opinion, these studies represent the best scientific evidence currently available. First author, title and date, study type, authors' conclusions, critical appraisal and level of evidence are included for each study. The studies are organized by category (surgical treatment, surgical and non-surgical treatment compared, non-surgical treatment, no treatment) and within those categories, by descending level of evidence.

When addressing the research questions on treatment of carpal tunnel syndrome, we emphasize data from controlled trials. Controls are necessary to account for changes that occur over time that are due not to treatment but instead to rest, modifications in activity, and so on. Carpal tunnel syndrome is often a progressive disease, but as remissions can occur, even in untreated persons (Padua 2001), and a significant proportion of CTS cases resolve

[46] The validity of a treatment study has to do with the accuracy of the results and considers whether the treatment effect reported in the article represents the true direction and magnitude of the treatment effect. Do the results of the study represent an unbiased estimate of the treatment effect, or have they been influenced in some systematic fashion to lead to a false conclusion? (Guyatt 1993&1994). See Appendix I for the worksheets used to critically appraise the treatment studies.

spontaneously (Marshall 2002), only controlled trials can provide evidence for the true effectiveness of various treatment options.

Several caveats with respect to interpretation of the treatment studies in the evidence base must be noted. It has been reported that factors that predict good or poor CTS treatment outcomes may not be the same in a workers' compensation population as in a general population. Comparable therapeutic modalities have worse outcomes among workers' compensation patients, biologic severity of CTS does not appear to be a significant predictor of outcome, outcomes after CTS surgery are strongly correlated with the duration of post-operative disability, and CTS patients receiving workers' compensation have more difficulty with post treatment functional activities (Katz 1997, Franklin 1996, Chapell 2003). If results of CTS treatment studies are extrapolated from a general population to a workers' compensation population, it should be with caution.

C. Findings: answers to research questions on treatment of carpal tunnel syndrome

Question 18.

Which surgical and non-surgical treatments have been shown to be effective in the therapy of CTS?

Surgical treatment

None of the experimental studies in our evidence base compared surgical treatment to no treatment or placebo. This makes it difficult to determine, in strict scientific terms, whether surgery benefits patients. Although absence of evidence is not evidence of absence of efficacy, the lack of trials that incorporate these controls complicates evaluation of the effectiveness of surgery (Chapell 2003).

Two studies meeting our inclusion criteria (Ferdinand 2002, MacDermid 2003) looked at whether endoscopic or open carpal tunnel release surgery results in better outcomes. Neither study showed a statistical difference in benefit between the two procedures.

Surgical and non-surgical treatment compared

Three studies meeting our inclusion criteria compared the effectiveness of surgical and non-surgical treatment for carpal tunnel syndrome.

In a well-designed randomized trial, Gerritsen (2002a) concluded that treatment with open carpal tunnel release surgery resulted in better outcomes than treatment with wrist splinting. Patient selection in this trial, however, was restricted by exclusion of underlying causes of CTS, history of wrist trauma or concomitant severe thenar atrophy, which reduced the trial's applicability to typical clinical practice.

Katz (1998) and DeStefano (1997) concluded that CTS surgery is more effective than non-surgical treatment, although both these studies suffered from design flaws that make strong inference difficult.

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Surgical treatment				
Ferdinand, R. Endoscopic *versus* open carpal tunnel release in bilateral carpal tunnel syndrome: A prospective, randomised, blinded assessment. The Journal of Bone and Joint Surgery (Br) 2002.	Experimental: prospective, randomized, blinded pre- and post- operative assessment	Patients with confirmed bilateral idiopathic carpal tunnel syndrome were randomized to undergo endoscopic release by the single portal Agee technique to one hand and open release to the other. At all stages of postoperative assessment, the endoscopic technique had no significant advantages in terms of return of muscle strength and assessment of hand function, grip strength, manual dexterity or sensation. In comparison with open release, single-portal endoscopic carpal tunnel release has a similar incidence of complications and a similar return of hand function, but is a slightly slower technique to undertake.	This small prospective study (where the assessor of post-operative hand function was NOT blinded to the pre-operative hand function status) showed no statistical difference in return of hand function, patient reported resolution of symptoms, or patient satisfaction. Small sample size means that lack of difference in outcomes between two techniques does not necessarily infer equivalence. It is unlikely that the reported (mean) difference of 2 minutes in operating time is clinically significant.	1b
MacDermid, J. Endoscopic versus open carpal tunnel release: A randomized trial. The Journal of Hand Surgery 2003.	Experimental: unbalanced randomized, blinded clinical trail	This study compared the outcomes in patients assigned to either endoscopic carpal tunnel release or traditional open carpal tunnel release. Both groups improved on all outcomes. No differences were observed in primary outcomes between the groups at either baseline or follow-up at 1, 6, or 12 weeks after surgery. No significant complications occurred in either group. Grip strength and pain were significantly better at 1 and 6 weeks in the endoscopic group although the differences dissipated by 12 weeks. No significant differences occurred in other secondary outcomes. Long-term satisfaction was lower in the endoscopic group, attributable to a 5% rate of re-operation. No substantive difference in benefit was shown for these two methods of carpal tunnel release.	Although there were no obvious demographic or baseline data to suggest this, the study design of unbalanced randomization runs the risk of failed randomization when small sample sizes are used. The assessment of statistical significance in this study was thwarted by the lack of reporting primary data. Small sample size means that lack of difference in outcomes between two techniques does not necessarily infer equivalence.	2b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Surgical and non-surgical treatment compared				
Gerritsen, A. Splinting vs surgery in the treatment of carpal tunnel syndrome. JAMA 2002.	Experimental: randomized controlled clinical trial	In the intention-to-treat analysis, surgery was more effective than splinting on all outcome measures. The success rates (based on general improvement) after 3 months were 80% for the surgery group vs 54% for the splinting group, which is a difference of 26%. After 18 months, the success rates increased to 90% for the surgery group vs 75% for the splinting group, which is a difference of 15%. However, by that time 41% of patients in the splint group had also received surgery treatment. In conclusion, treatment with open carpal tunnel release surgery resulted in better outcomes than treatment with wrist splinting for patients with CTS.	A well-designed randomized trial. Patient selection in this trial, however, was restricted by exclusion of underlying causes of CTS, history of wrist trauma or previous treatment, or concomitant severe thenar atrophy, reducing its applicability to typical clinical practice. It is not clear if the "reduced" efficacy of surgery over time is merely secondary to splint-group patients receiving surgery with accrual of benefit to the splint-group under the intention-to-treat protocol.	1b
Katz, J. Maine carpal tunnel study: outcomes of operative and non-operative therapy for carpal tunnel syndrome in a community-based cohort study. The Journal of Hand Surgery 1998.	Observational: prospective, community based study	Surgically treated patients demonstrated improvements of 1.2 to 1.6 points on the 5-point Symptom Severity and Functional Status scales, which persisted over 30 months of follow-up. The non-operatively managed patients showed little change in clinical status at 6, 18, and 30 months. While workers' compensation (WC) patients had worse outcomes than non-recipients, 53% were completely or very satisfied with the results of the procedure 30 months after surgery. Carpal tunnel surgery offered excellent symptom relief and functional improvement, irrespective of the surgical approach, even in WC recipients. Work absence remained high in both surgically and non-operatively managed WC recipients.	The validity of results from this observational study is challenged by the lack of standardization for CTS diagnostic inclusion criteria, the failure to analyze a factor which may have been important in decisions about therapy (nerve conduction studies were done on 93% of the surgical treatment group, but only 53% of the conservative treatment group) and the cross-over versus intention-to-treat analysis.	2b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Surgical and non-surgical treatment compared (continued)				
DeStefano, M. Long-term symptom outcomes of carpal tunnel syndrome and its treatment. The Journal of Hand Surgery 1997.	Observational: retrospective follow-up study of a population-based case series	Among patients who received only non-surgical treatment, median duration of symptoms was between 6 and 9 months, but 22% had symptoms for 8 years or longer. Patients who had surgery were 6 times more likely to have resolution of their symptoms than were patients who did not have surgery. Patients who had surgery 3 or more years after their initial diagnosis of CTS were less than half as likely to have symptom resolution than were patients who had surgery within 3 years of diagnosis. The results indicate surgery is a highly effective treatment, but duration of CTS prior to surgery is a key determinant of surgical outcome.	The retrospective, uncontrolled nature of the study makes strong inference difficult. The population may not be representative of the WCB population: the majority of patients were female, and usually had bilateral CTS involvement. An interpretation of the results could be that CTS surgery benefits women with severe bilateral disease, but this does not provide guidance for management of others.	3b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment				
Chang, M. A randomized clinical trial of oral steroids in the treatment of carpal tunnel syndrome: a long term follow up. J Neurosurg Psychiatry 2002.	Experimental: randomized, blinded, placebo controlled prospective clinical trial	The purpose of this study was to determine the efficacy of a two week and a four week course of oral steroids in the conservative treatment of CTS. Our results show that a short low dose course of oral steroids is useful and effective in providing long term symptom relief in carpal tunnel syndrome. We therefore conclude that before advising surgery, conservative treatment – including splinting and systemic or local steroid use – should be given to all patients with carpal tunnel syndrome who do not have obvious motor and sensory impairment.	This randomized prospective trial measured the effects of different regimens of prednisolone on patients' self-reported global symptom assessment scores (GSS) for up to one year after therapy was given. The study's validity is threatened by greater than 20% drop-out rates in both groups. When intention-to-treat analysis was used, no statistically significant differences in outcomes were seen between the 2 treatment regimens.	1b
Wong, S. Local vs systemic corticosteroids in the treatment of carpal tunnel syndrome. Neurology 2001.	Experimental: prospective, randomized, double-blinded, parallel treatment study	The authors compared the effectiveness of low-dose, short-term oral prednisone vs local methylprednisololone injection. A single injection of 15mg methylprednisolone resulted in significant improvement in global symptom scores over a 12-week period. Local steroid injection is superior to oral steroid in the treatment of CTS.	A well-designed, randomized, double-blinded prospective trial, which controlled for co-morbidities and co-interventions. Although the sample size was small, randomization appears to have worked, complete follow-up attained, and treatment differences in global symptom scores presumed in sample size calculations were actually attained. The follow-up period was only 3 months, and the clinical significance of partial (and possibly temporary) reduction in (rather than abolishment of) symptoms is uncertain. Also, this treatment is often recommended to be used only once, owing to the risk of tendon rupture.	1b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Dammers, J. Injection with methylprednisolone proximal to the carpal tunnel: randomised double blind trial. BMJ 1999.	Experimental: randomized blinded placebo controlled clinical trial	The authors assessed the effect of a 40mg methylprednisolone injection proximal to the carpal tunnel in patients with CTS and concluded that such an injection may result in long term improvement and should be considered before surgical decompression.	This small (n=60) randomized, triple blinded, placebo-controlled trial (comprised mostly of middle-aged women) had complete follow-up, and assessed outcomes for up to a year after treatment. The trial suggests that one injection of methylprednisolone might prevent the need for surgery for up to one year.	1b
Walker, W. Neutral wrist splinting in carpal tunnel syndrome: a comparison of night-only versus full-time wear instructions. Arch Phys Med Rehabil 2000.	Experimental: randomized clinical trail	The objective of this study was to compare the effects of night-only to full-time splint wear instructions on symptoms, function and impairment in carpal tunnel syndrome. The results of this study provide added scientific evidence to support efficacy of neutral wrist splints in CTS and suggest that physiologic improvement is best with full-time splint wear instructions.	This short (6-week) small (n = 17) unblended study of a NCS laboratory referent, mostly male population failed to demonstrate any statistically significant difference in symptom or functional improvement between the two therapeutic modalities. Marginally significant differences in NCS motor distal latency were reported but are of uncertain clinical significance.	1b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Oztas, O. Ultrasound therapy effect in carpal tunnel syndrome. Arch Phys Med Rehabil 1998.	Experimental: patient-blinded, placebo-controlled, before and after treatment trial	Ultrasound therapy in carpal tunnel syndrome was comparable to placebo ultrasound in providing symptomatic relief, and the probability of a negative effect on motor nerve conduction needs to be considered.	This negative study included only females, was not consecutive (a source of referral bias), and investigators were not blinded, all of which threaten its validity. 12 of 18 cases of CTS were bilateral yet all hands were randomized. The average age was 51.5 with history of complaints greater than 6 months. There were no differences in NCS at the end of treatment. All groups including the placebo group benefited clinically.	1b
Ebenbichler, G. Ultrasound treatment for treating carpal tunnel syndrome: randomised "sham" controlled trial. BMJ 1998.	Experimental: randomized, double blind, "sham" controlled clinical trial	There are satisfying short to medium effects due to ultrasound treatment in patients with mild to moderate idiopathic carpal tunnel syndrome. Findings need to be confirmed, and ultrasound treatment will have to be compared with standard conservative and invasive treatment options.	This study was not consecutive, satisfactory improvement was not defined, and the 24% drop out rate (in a study of only 45 wrists) compromises its validity. At 6 months all patients showed an unsatisfactory outcome. Ultrasound treatments are time intensive (twice daily for 2 weeks then twice weekly for 5 weeks).	1b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Akalin, E. Treatment of carpal tunnel syndrome with nerve and tendon gliding exercises. Am J Phys Med Rehabil 2002.	Experimental: prospective, randomized, before-and-after treatment trial	A custom made neutral volar wrist splint was given to groups 1 and 2. The patients were instructed to wear the splints all night and during the day as much as possible for 4 weeks. The patients in group 2 were instructed to perform a series of nerve and tendon gliding exercises in addition to the splint treatment. Patients were evaluated with clinical parameters, a functional status scale, and a symptom severity scale. Although the results in group 2 were better than group 1, the difference was not statistically significant. Further investigations are required to establish the role of nerve and tendon gliding exercises in the treatment of carpal tunnel syndrome.	This study of 26 women and 2 men (homemakers and clerical workers, average age 52 years) found no difference between the two groups. There were no nerve conduction studies of outcomes.	1b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Rozmaryn, L. Nerve and tendon gliding exercises and the conservative management of carpal tunnel syndrome. Journal of Hand Therapy 1998.	Experimental: controlled retrospective study	In this study, patients presenting for treatment of carpal tunnel syndrome were divided into two groups. Patients in both groups were treated by standard conservative methods, and those in one group were also treated with a program of nerve and tendon gliding exercises. Of those who did not perform the exercises, 71.2% underwent surgery compared with only 43% of patients who did perform them. Thus a significant number of patients who would otherwise have undergone surgery for failure of traditional conservative treatment were spared surgical morbidity of a carpal tunnel release.	Retrospective study with diagnostic inclusion criteria by history; follow-up by telephone interview. Control and experimental group divergent by occupation. Control group made up of significantly more manual workers than clerical and significantly less nerve conduction study access. No observational control over compliance with exercise program. Exercise program 4 times daily and contrast baths 3-5 times daily would significantly reduce the work performed and may account for the differences since hand use was not a controlled confounder. Surgeon not blinded and persistence of symptoms was only criterion for surgery. Removal of manual workers or at least controlling for difference between the two cohorts might have eliminated any differences in outcomes.	2b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Davis, P. Comparative efficacy of conservative medical and chiropractic treatments for carpal tunnel syndrome: a randomized clinical trial. Journal of Manipulative and Physiological Therapeutics 1998.	Experimental: two-group, randomized, single blind clinical trial	There was significant improvement in perceived comfort and function, nerve conduction and finger sensation overall, but no significant differences between groups in the efficacy of either conservative medical care or chiropractic care. Carpal tunnel syndrome associated with median nerve demyelination but not axonal degeneration may be treated with commonly used components of conservative medical or chiropractic care.	Comorbidities were controlled and statistical power calculations included in this study. Function was assessed as an outcome. No differences were found between conservative medical and chiropractic groups.	1b
Naeser, M. Carpal tunnel syndrome pain treated with low-level laser and microamperes transcutaneous electric nerve stimulation: a controlled study. Arch Phys Med Rehabil 2002.	Experimental: randomized, double-blind placebo-control cross-over trial	This trial of mild to moderate CTS cases who failed standard medical or surgical treatment for 3 to 30 months investigated whether real or sham low-level laser therapy plus microamperes transcutaneous electric nerve stimulation applied to acupuncture points significantly reduces pain in carpal tunnel syndrome. Our results show significant decreases in McGill Pain Questionnaire score, median nerve sensory latency, and Phalen and Tinel signs after the real treatment series but not after the sham series. Patients could perform their previous work (computer typist, handyman, house painter, plumber) and all but one were stable for 1 to 3 years. A placebo effect was observed in 3 of the 11 cases: two placebo responders reported a greater than 90% reduction in pain after the first series of treatments that were sham.	This study was not consecutive, common comorbidities were not controlled, and the number of cases was small (11), all of which compromised its validity. Acupuncture points were used on hand, limb and paraspinal regions. Only 4 cases performed job tasks associated with CTS. The average age of study participants was 53.5 years. Conservative as well as surgical treatment failures were included. The failure to respond to standard medical or surgical therapy may be due to an incorrect initial diagnosis of CTS.	1b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
Non-surgical treatment (continued)				
Weintraub, M. Neuromagnetic treatment of pain in refractory carpal tunnel syndrome: an electrophysiological and placebo analysis. Journal of Back and Musculoskeletal Rehabilitation 2000.	Experimental: single blind, placebo controlled clinical trial	Percutaneous magnetic stimulation induced palliative pain relief, presumably via modulation of the unmyelinated C-fibers. Prior studies have suggested an influence on K+ inward rectification excitability. These observations suggest that wearing magnetized wrist wraps appears to be a novel therapeutic agent. However, the underlying neuropathology tends to be progressive.	This negative study had a small number of subjects (6) and was not blinded. The average age was >65 years. Pain relief rarely lasted more than 24 hours.	2b

TABLE 11. STUDIES MEETING THE INCLUSION CRITERIA: TREATMENT OF CTS (continued)

STUDY	DESIGN	AUTHORS' CONCLUSIONS	CRITICAL APPRAISAL	LEVEL OF EVIDENCE
No treatment				
Padua, L. Multiperspective follow-up of untreated CTS. A multi-center study. Neurology 2001.	Observational: cohort before – after outcome study	The objective of this study was to assess the course of untreated carpal tunnel syndrome. Included industrial and general population in 10-15 month follow-up. 20% lost to follow-up. 77% did not go to surgery. Predictive of a negative (surgical) outcome were milder symptoms initially; longer duration of symptoms initially; increasing age; bilateral symptoms; positive Phalen test at initial assessment. Predictive of positive outcome (no surgery) were: short duration of symptoms; severe initial symptoms; young age; hand stress at initial exam. We conclude that some patients with CTS improve spontaneously without surgical treatment.	Although the groups were clearly defined, and the study was blinded and consecutive, follow-up duration was barely sufficient and only referent patients were included so spectrum bias is possible. Statistical assessment was appropriate. OR included and significant associations were >2.0. One major fault is that hand stress is considered a positive prognostic sign yet 68% of cases altered their hand activity at work or play after initial assessment: a major outcome bias.	2b

Non-surgical treatment

Several studies meeting our inclusion criteria addressed the effectiveness of various non-surgical treatments for carpal tunnel syndrome.

- Oral and injected steroids

Chang (2002) found that a short low dose course of oral steroids is useful and effective in providing long term symptom relief in carpal tunnel syndrome, but the validity of this study was threatened by the greater than 20% dropout rate in both patient groups.

In a well-designed trial, Wong (2001) found that local steroid injection is superior to oral steroid in the treatment of CTS. Dammers (1999) found that one injection of methylprednisolone might delay the need for carpal tunnel surgery for up to one year. Since repeated injections carry the risk of tendon rupture and nerve damage (Weinreb 2000), the clinical application of the procedure is unclear.

- Splinting

One trial meeting our inclusion criteria (Walker 2000) compared the effectiveness of night-only versus full time splint wear instructions, but failed to demonstrate any statistically significant difference in symptom reduction or functional improvement between the two therapeutic modalities.

- Ultrasound

The evidence in the two studies that met the inclusion criteria is inconclusive. Oztas (1998) and Ebenbichler (1998) both explored the effectiveness of ultrasound therapy for carpal tunnel syndrome. Oztas found that ultrasound therapy was comparable to placebo, while Ebenbichler reported that improvement was significantly more pronounced in actively treated rather than in sham treated wrists. The validity of both studies was threatened by flaws in study design.

- Nerve and tendon gliding exercises

The evidence on the effectiveness of nerve and tendon gliding exercise for treatment of carpal tunnel syndrome is mixed and conflicting. Akalin (2002) found no statistically significant difference in outcome between patients instructed to perform nerve and tendon gliding exercises and those who were not, while Rozmaryn (1998) concluded that the exercises were effective.

- Chiropractic treatment

Only one study meeting our inclusion criteria addressed the use of chiropractic treatment for carpal tunnel syndrome. Davis (1998) found no significant differences in efficacy between conservative medical and chiropractic care.

- Treatment with low-level laser

Naeser (2002) investigated whether real or sham low-level laser therapy plus microamperes transcutaneous electric nerve stimulation applied to acupuncture points significantly reduces

pain in carpal tunnel syndrome and concluded that there were significant decreases in McGill pain questionnaire score, median nerve sensory latency, and Phalen and Tinel signs after real treatment but not after the sham series. A placebo effect was observed in 3 of the 11 cases, and the study's validity was threatened by problems with study design.

- Neuromagnetic treatment

One study meeting the inclusion criteria (Weintraub 2000) addressed the efficacy of neuromagnetic treatment for carpal tunnel syndrome. No statistically significant beneficial effect was demonstrated, and pain relief rarely lasted more than 24 hours.

Question 19.

Is it possible to identify those cases in which CTS would be best treated with surgery? Non-surgical therapy? Both?

The patients making up the study populations in our treatment evidence base were predominately middle aged and female. A few of the studies also listed their neuroelectrical characteristics, symptom characteristics, and other variables. The extent to which the patients in these studies represent appropriate candidates for surgical and non-surgical treatment, however, is unclear: patients included in published studies of a procedure are frequently subsets of patients who are the best candidates for that procedure (Chapelle 2003).

As none of the studies meeting the inclusion criteria directly address the specific indications for surgical or non-surgical treatment of carpal tunnel syndrome, we cannot outline a definitive model for an evidence-based therapeutic approach.

The consensus of medical opinion is that, in the majority of cases, a course of appropriate conservative management of carpal tunnel syndrome should be attempted before advising surgery. Based on review of the literature and expert consensus, for example, in 1993 the Quality Standards Subcommittee of the American Academy of Neurology issued a practice parameter for carpal tunnel syndrome that recommends treatment of CTS with noninvasive options first, and open carpal tunnel release only if noninvasive treatment proves to be ineffective (AAN 1993b). Selection of conservative therapies should be grounded in the best available evidence.

Subsequently, the Washington State Department of Labor and Industries and Oregon's Workers' Compensation Division both developed medical treatment guidelines for carpal tunnel syndrome, based on a synthesis of the evidence in the medical literature, community input, expert opinion, outcomes research and national standards. The Washington and Oregon guidelines concur that in general, surgical intervention for carpal tunnel syndrome should be considered only if the worker has a positive clinical history and physical examination, abnormal nerve conduction studies, and conservative treatment has failed (WSDLI 2002, Ross 1997).

Exceptions may be made if there is obvious thenar wasting. In such cases, expedited medical and surgical assessment is required due to the risk of progressive and permanent neurological damage. Surgical consultation should also be made in the initial treatment phase if there is severe sensory disturbance, or a history of acute or traumatic onset.

Carpal tunnel syndrome that has been appropriately diagnosed and that does not resolve with conservative measures, or carpal tunnel syndrome that is rapidly progressing, may require surgical intervention. In the vast majority of cases, electrophysiological testing should be performed prior to surgery to confirm the diagnosis.

Cases of CTS that fail to improve with appropriate conservative treatment should undergo a baseline investigation to rule out other associated diseases. If there is a history of previous trauma to the wrist or hand an x-ray should be ordered (Gorsche 2001). Treatment of comorbidities that contribute to carpal tunnel syndrome should be attempted and may be effective (Chapell 2003). CTS in the presence of systemic disease, large mass lesions at the wrist, major bony deformity, or infection requires treatment of primary disease first (AAN 1993b). Surgical treatment is usually offered to electrodiagnostically confirmed cases (Gorsche 2001) with no underlying reversible disorder.

The evidence suggests that patients with severe symptoms on initial assessment may respond best to conservative treatment. For patients who fail to resolve promptly, early intervention leads to successful outcomes (Gorsche 2001).

Question 20.

What indicators suggest that a patient can reasonably be expected to return to work following a course of conservative therapy or surgery? When should this return be expected?

A range of biomedical and non-biomedical variables influence return to work, both directly and indirectly, by influencing symptom relief (Katz 1997). Following surgery, most patients can return to light hand use following the removal of sutures, but may not tolerate the use of tools that require a power grip for an average of six to eight weeks (Gorsche 2001).

Only one of the studies meeting the inclusion criteria addressed return to work. Katz (1998) reported that among workers' compensation recipients, about one third remained out of work because of CTS 6 months following surgery, and 18% of surgical patients and 13% of non-operatively treated patients remained out of work because of carpal tunnel syndrome at 30 months.

Question 21.

Is there a role for pre- and post-operative electrodiagnostic testing in assessing work return, recurrence or prognosis?

None of the studies meeting the inclusion criteria addressed the role of pre- and post-electrodiagnostic testing in assessing return to work, recurrence or prognosis, hence we are unable to reach an evidence-based conclusion on these issues.

Question 22.

Which environmental adaptations have been shown to prevent or help manage CTS? Which ergonomic adaptations? Are safety programs effective?

No studies in the evidence base address environmental and ergonomic adaptations to prevent or manage CTS, or the question of the effectiveness of safety programs.

Based on the pathogenesis and pathophysiology of carpal tunnel syndrome, however, as well as the studies in the evidence base on the causation of CTS, it seems plausible that

modifications in certain types of hand use (avoidance of certain types of vibration and force, for example) could help prevent and manage carpal tunnel syndrome.

Question 23.

What is the appropriate treatment for a "failed" carpal tunnel release?

In cases of surgical failure, a complete reassessment by the surgeon and clinician is indicated. The patient should undergo a thorough re-examination and repeat electrodiagnostic assessment to rule out other, less common causes of peripheral neuropathy (Gorsche 2001). A second opinion by a surgeon competent in the treatment of hand and wrist disorders may help determine the need for repeat surgery.

Question 24.

Is there a relationship between the patient's age and specific treatment outcomes?

There is nothing in the evidence base that suggests that age is a specific demographic variable that predicts a positive or negative outcome after treatment for carpal tunnel syndrome.

VII. CONCLUSIONS

The Canadian workforce is aging and is characterized by the increasing participation of women. Canadians - both men and women - are living longer. These demographic trends have potentially profound implications for Canadian workers' compensation systems, as conditions like carpal tunnel syndrome - more common among women and older people - become increasingly prominent.

Despite the large number of research studies on carpal tunnel syndrome, controversy persists among physicians about its extent and etiology, the contribution of occupational and non-occupational risk factors to its development, the criteria used to diagnose it, the outcomes of various treatment methods, and the appropriate strategies for intervention and prevention. Confusion in the general public is compounded by the poor quality of the information on carpal tunnel syndrome found in the popular media: many patients are misinformed about carpal tunnel syndrome.

The purpose of this research is to identify a current, valid, clinically important and applicable foundation of peer-reviewed scientific evidence that can be used to make evidence-based decisions about the diagnosis, causation and treatment of carpal tunnel syndrome. A thorough and systematic review of the medical literature was followed by critical appraisal of the studies that met our inclusion criteria according to the studies' validity, the importance of their results, and their applicability to the WCB-Alberta population.

In general, studies on diagnosis and treatment of carpal tunnel syndrome provide stronger evidence than do studies on CTS causation. This is because of the heterogeneity of the subject matter of the causation studies, the ethical constraints on experimental research in humans (studies of disease causation must be observational and are more susceptible to bias and confounding than are experimental studies), and the lack of longitudinal studies on causation of carpal tunnel syndrome. Longitudinal studies of causation have the potential to provide the strongest evidence of a temporal, cause-effect relationship.

While gaps in the evidence prevent us from drawing firm conclusions in some areas, we are able to reach consensus on a number of essential points.

Rigorous diagnosis of carpal tunnel syndrome is the basis of appropriate treatment: the importance of an accurate medical diagnosis cannot be overstated. CTS diagnosis is vastly complicated by the lack of agreement on a "gold standard" diagnostic method for definitively verifying the presence or absence of CTS. Despite their limitations, electrodiagnostic studies are the most objective tests available to demonstrate median nerve deficit, and their accuracy is good when properly performed. If surgery is being contemplated, electrodiagnostic confirmation of the clinical diagnosis is desirable. Use of electrodiagnostic study findings as the sole diagnostic tool is not recommended: EDS findings must be correlated with the history and physical examination, and the evidence shows that certain clinical diagnostic tools are significantly more accurate than others in suggesting the presence of carpal tunnel syndrome.

The epidemiological transition from acute, unequivocal injuries to slow onset, multifactorial disorders like carpal tunnel syndrome has emerged as one of the fundamental challenges to North American workers' compensation systems. Carpal

tunnel syndrome has an indistinct etiology: a variety of contributing factors and conditions can effect the median nerve in the carpal tunnel. Susceptibility to developing carpal tunnel syndrome varies with anatomic structure, body mass index, gender, age, genetic predisposition and psychosocial factors. Systemic conditions and pathologies also contribute to the causation of carpal tunnel syndrome. Carpal tunnel syndrome can have a spontaneous or idiopathic onset.

Carpal tunnel syndrome is a condition that certainly effects workers, but it is not necessarily a condition that is caused by work. The risk depends on the interaction of person and task, and not all cases of carpal tunnel syndrome potentially related to work are in fact directly related to physical activities performed in the workplace. There is some evidence that force, either alone or combined with repetition, is associated with carpal tunnel syndrome, as is vibration: a caveat here is that causal thresholds have not been adequately quantified. Tasks characterized by high frequency but low force (like computer keyboarding) do not appear to be important precipitating factors. There is insufficient evidence of association between other putative occupational risk factors and carpal tunnel syndrome.

Work may be only one contributor to carpal tunnel syndrome, but carpal tunnel syndrome (whatever its cause) can, if poorly managed, have a devastating effect on a person's ability to work. In the majority of cases, a course of appropriate conservative management is the first step in treatment, except where there is evidence of thenar wasting. If there is evidence of wasting, expedited medical and surgical assessment is required due to the risk of progressive and permanent neurological damage.

Concluding his seminal address "The environment and disease: association or causation?" Sir Austin Bradford Hill observed that:

> *all scientific work is incomplete - - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.*[47]

The intent of this investigation is to establish a foundation of current, clinically valid, important and applicable evidence on the diagnosis, causation and treatment of carpal tunnel syndrome. Good decisions can be based upon the existing evidence.

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[47] Hill (1965). In his "President's Address" to the Section of Occupational Medicine of the Royal Society of Medicine (delivered on January 14, 1965), Sir Austin Bradford Hill outlined what would become known as *Hill's Criteria* for inferring causation from epidemiologic associations.

APPENDICES

APPENDIX A. Down a dark (carpal) tunnel

Down a dark (carpal) tunnel

Researchers at the University of Pennsylvania who reviewed online resources for patients with carpal tunnel syndrome have concluded that the information available online "is of limited quality and poor informational value."

The study was conducted by typing "carpal tunnel syndrome" into 5 popular search engines. Using established clinical practice as their guideline, the researchers assessed the first 50 sites named by each search engine.

Of the 250 sites, 75 were duplicates. Of the remaining 175, the researchers found that 14% provided misleading content, 9% offered "unconventional" information and 31% had content that was based only on opinion or sales pitches.

"Internet users are unlikely to encounter complete, unbiased and conventional information," states Dr. Pedro Beredjiklian, an assistant professor of orthopedic surgery at the university's medical school and the lead author.

His paper, "Evaluating the source and content of orthopaedic information on the Internet: the case of carpal tunnel syndrome," was published in the November 2000 issue of the *Journal of Bone and Joint Surgery* (OReilly 2001).

APPENDIX B. The Moore-Garg Strain Index: a potential risk assessment tool

The Moore-Garg Strain Index was proposed by Moore and Garg as a means to assess jobs for risk of work-related musculoskeletal disorders (WRMSDs) of the distal upper extremities (hand, wrist, elbow) (Moore 1995).

Professor Thomas E. Bernard (University of South Florida School of Public Health) subsequently proposed the rating process and form that follow. These and other assessment tools may be found on his ergonomics website: http://hsc.usf.edu/~tbernard/

Dr. Bernard explains:

> *Divide a job into tasks. For each task and for each hand, assess the six job risk factors by assigning it to a category. The data sheet that follows provides a format for this process. For each category, note the rating. The Strain Index is the product of the six ratings.*

Table 10 of this background paper includes a study that evaluates the predictive value of the strain index (Rucker 2002).

Moore-Garg Strain Index

Task	Analyst
	Date / /

Strain Index	Find rating for each risk factor and multiply them together.	SI < 3: Safe SI between 3 and 5: Uncertain SI between 5 and 7: Some Risk SI > 7: Hazardous			
Risk Factor	Rating Criterion	Observation	Ratings	Left	Right
Intensity of Exertion [Borg Scale values in brackets]	Light	Barely noticeable or relaxed effort [0-2]	1		
	Somewhat Hard	Noticeable or definite effort [3]	3		
	Hard	Obvious effort; Unchanged expression [4-5]	6		
	Very Hard	Substantial effort; Changed expression [6-7]	9		
	Near Maximal	Uses shoulder or trunk for force [8-10]	13		
Duration of Exertion (% of Cycle)	< 10%		0.5		
	10-29%		1.0		
	30-49%		1.5		
	50-79%		2.0		
	> 80%		3.0		
Efforts Per Minute	< 4		0.5		
	4 - 8		1.0		
	9 - 14		1.5		
	15 - 19		2.0		
	> 20		3.0		
Hand/ Wrist Posture	Very Good	Perfectly Neutral	1.0		
	Good	Near Neutral	1.0		
	Fair	Non-Neutral	1.5		
	Bad	Marked Deviation	2.0		
	Very Bad	Near Extreme	3.0		
Speed of Work	Very Slow	Extremely relaxed pace	1.0		
	Slow	Taking one's own time	1.0		
	Fair	Normal speed of motion	1.0		
	Fast	Rushed, but able to keep up	1.5		
	Very Fast	Rushed and barely/unable to keep up	2.0		
Duration of Task Per Day (hours)	<1		0.25		
	1 - 2		0.50		
	2 - 4		0.75		
	4 - 8		1.00		
	> 8		1.50		

APPENDIX C. Study designs

Studies may be classified into three broad groups by study design: experimental studies, observational studies and exploratory studies.

- **Experimental studies**, also known as intervention studies or clinical trials, are studies in which conditions are under direct control of the investigator. These are prospective studies involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical intervention. A population is selected for a planned trial of a regimen whose effects are measured by comparing the outcome of another regiment in a control group. To avoid bias, members of the experimental and control groups should be comparable except in the regimen that is offered them. Ideally, allocation of individuals to experimental or control groups is by randomization. In a Randomized Controlled Trial (RCT) individuals are randomly allocated.

  The outcome of a well designed clinical trial involves objective measurements whenever possible, using predetermined outcome measures or “endpoints.” The success or failure of the trial is measured by criteria established in a written protocol before the start of the trial. The trial should include a sufficiently large number of subjects to provide statistically significant differences in outcome measures between placebo and drug-treated groups.

- **Observational studies** are epidemiological studies that do not involve any intervention, experimental or otherwise. Such a study may be one in which nature is allowed to take its course, with changes in one characteristic studied in relation to changes in other characteristics. Analytic epidemiologic methods, such as cross-sectional, case control and cohort study designs, are properly called observational epidemiology, because the investigator is observing without intervention (other than to record, classify, count, and statistically analyze the results).

- **Exploratory studies** generate hypotheses for further and scientifically rigorous investigation. Case series and case reports, which look at individuals who manifest a particular health problem, are part of this category.

The concept of a "hierarchy of evidence" is fundamental to evidence-based medicine. A "hierarchy of evidence" is a schema for grading the scientific evidence (original research studies) based on the tenet that different grades of evidence (study designs) vary in their predictive ability (see Appendix D).

Higher grades of evidence are more likely to reliably predict outcomes. Inferences about therapy, for example, may be very strong if the results come from a systematic review of well designed, methodologically strong RCTs with consistent results. They are somewhat weaker if they are made based on a single RCT, unless it is very large and has enrolled a diverse patient population. Because observational studies may under (or more typically over) estimate treatment effects in an unpredictable fashion, their results are far less trustworthy than those of RCTs. Unsystematic clinical observations (case series and case reports) provide the weakest inferences about treatment effects. Much of the evidence regarding the harmful effects of a therapy comes from observational studies (Guyatt 2000).

Several features of study design have an impact on the ability of a study to generate causal inferences.

- Case control (retrospective) studies divide the study population into groups with the disease (cases) and those without the disease (controls) and compare the rate of exposure to the agent within those groups. If the rate of exposure among the diseased is higher than the rate of exposure among the non-diseased, then a causal link is suggested. This design has potentially significant exposure classification problems.

- Cohort studies and case-control studies have a moderate ability to demonstrate causation, because when well-designed, bias and confounding can be minimized.

- Cross-sectional studies perform the measurement of exposure and outcome at the same time for a case population. The prevalence of disease among the exposed is compared to the prevalence of disease among the unexposed. One problem with this design is that it is often unclear whether the temporal requirement of exposure preceding outcome is met. It may be difficult to make sure that the members of the case population have been exposed long enough to develop the disease and that the latency period has elapsed, which leads to underestimation of risk. Cross-sectional studies have a weak ability to demonstrate causation because they can provide no evidence of a temporal relationship. Only a longitudinal study can do so.

- The best evidence of causation would come from intervention or experimental studies. Well designed Randomized Controlled Trials (experimental studies) provide the highest level of evidence (Level 1). There are ethical constraints, however, on experimental research in humans, and it is not acceptable to expose subjects deliberately to potentially serious hazards. This limits the application of experimental methods in the investigation of disease etiology. Studies of disease causation must be observational and are more susceptible to bias and confounding. Because studies of disease causation cannot be experimental, Level 2 is the highest level of evidence these studies can provide (although it may be possible to evaluate preventive strategies experimentally).

More information on study designs is found in the glossary (Appendix M).

APPENDIX D. Levels of Evidence Summary

Levels of Evidence summary for Therapy Harm or Causation

Grade of Recommendation	Level of Evidence	Type of Study	Study characteristics
A	1a	Systematic review (with homogeneity) of RCT	A systematic summary of the medical literature that uses quantitative methods to summarize the results
	1b	Single RCT with narrow Confidence interval	Randomized controlled trial. A group of patients is randomized to either experimental or control groups, which are followed for the variables or outcomes of interest
	1c	All-or-none case series	Where all patients die or fail without intervention and some survive or succeed with it
B	2a	Systematic review (with homogeneity) of cohort studies	
	2b	Cohort study or poor quality or underpowered RCT (e.g. < 80% follow-up)	Identification of 2 groups of patients, one of which did receive exposure of interest and one which did not and following these cohorts forward in time for the outcome of interest
	2c	Outcomes research	Observation of a defined population at a single point in time or time interval. Exposure and outcome are determined simultaneously
	3a	Systematic review (with homogeneity) of case-control studies	
	3b	Case control study	Study where one identifies patients who have the outcome of interest (cases) and a control group of patients who have not had the outcome of interest, and looking retrospectively to see if they had the exposure of interest.
C	4	Case-series	A report on a series of patients with an outcome of interest. No control group involved.
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research	

Homogeneity means that a systematic review is free of heterogeneity in the directions and degrees of results between individual studies. Systematic reviews with statistically significant heterogeneity should be marked with a (-) sign on their grade.

A minus sign may also be added to grades of studies that are inconclusive due to wide enough confidence interval associated with point estimates so that is not possible to include or exclude real differences.

Source:
Evidence-Based Acute Medicine
Sharon E. Straus, Stephen I-Hong Hsu, Christopher M. Ball, Robert S. Phillips, Churchill Livingstone, Robert Phillips
Paperback / Churchill Livingstone / 15 January, 2002 / 0443064113

APPENDIX E. Comprehensive reviews

Within the last five years, four panels of scientific and medical experts have released major evidence-based reports on the subject of musculoskeletal disorders. They are described below in descending chronological order.

Diagnosis and Treatment of Worker-Related Musculoskeletal Disorders of the Upper Extremity. Evidence Report/Technology Assessment Number 62. (Prepared by ECRI Evidence-based Practice Center under Contract No. 290-97-0020). AHRQ Publication No. 03-EO38. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services. May 2003. Chapell R, Turkelson CM, Coates V.

This report is a systematic evaluation of the evidence pertaining to a broad range of issues related to the diagnosis and treatment of worker-related upper extremity disorders. For the purposes of this report, "worker-related" is defined as a disorder that affects workers, not as a disorder necessarily caused by work. The report focuses on four disorders: carpal tunnel syndrome, cubital tunnel syndrome, epicondylitis, and de Quervain's disease. The Evidence-based Practice Center assessed the published literature describing the effects of these disorders on workers, both before and after treatment, by examining and answering 13 key questions. Eleven of these questions were condition specific and two were not.

The authors do not draw general conclusions regarding carpal tunnel syndrome. Rather, they answer a set of very specific questions about its diagnosis and treatment.

(Cited as: Chapell 2003)

National Research Council and Institute of Medicine. Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities. Panel on Musculoskeletal Disorders and the Workplace. Commission on Behavioral and Social Sciences and Education. Washington, DC: National Academy Press. 2001.

The Panel on Musculoskeletal Disorders and the Workplace was established by the National Research Council and the Institute of Medicine in January 1999 to conduct a two-year study of the contribution of workplace physical and psychosocial factors to the occurrence of musculoskeletal disorders of the low back and upper extremities and to examine the effectiveness of various prevention strategies. The panel conducted a comprehensive review of the scientific literature describing the biological responses to load on tissue; biomechanical models of static, dynamic, and repetitive motion and the effects of various forces and loads on the body; the relationships among the occurrence of musculoskeletal disorders and physical work, social and organizational factors, activities outside the workplace, and individual differences; changes in the workplace or the addition of workplace programs designed to reduce the risks for the occurrence of musculoskeletal disorders, and trends in workplace characteristics and their implications for musculoskeletal disorders in the future.

On the subject of carpal tunnel syndrome, the report concludes that collectively, a pattern emerges demonstrating that risk is associated with specific aspects of the workplace; that biomechanical studies have shown that extraneural pressures in the

carpal tunnel is increased with hand loading and non-neutral wrist postures; that basic science studies demonstrate how extraneural pressures lead to intraneural edema and fibrosis, demyelination, and axon degeneration; and that these changes cause loss of nerve function.

The report is followed by a dissent by panel member Robert Szabo who argues, among other things, that "the association of carpal tunnel syndrome with work-related risk factors is a recurring theme of causation among workers, ergonomists, lawyers and physicians. The majority of the literature that tries to establish this as a causal association fails to meet the appropriate standards of epidemiological validity."

The panel responds that "Dr. Szabo uses the case of carpal tunnel syndrome with regard to low-force, high repetition exposures (primarily the use of computer keyboards) as the causal factor to suggest that the relationship of musculoskeletal disorders to work exposure may not be sound. The panel has recognized that the evidence for low-force, high repetition exposures is weaker than for other relationships among risk factors and musculoskeletal outcomes . . . keyboard work was not a major consideration or focus of the report."

(Cited as: NRC&IOM 2001)

Work-Related Musculoskeletal Disorders: A Review of the Evidence. Steering Committee for the Workshop on Work-Related Musculoskeletal Injuries: The Research Base. Committee on Human Factors, Commission on Behavioral and Social Sciences and Education, National Research Council. National Academy Press, Washington DC. 1998.

This document is based on the evidence presented and discussed at the two-day Workshop on Work-Related Musculoskeletal Injuries: Examining the Research Base, which was held on August 21 and 22, 1998. In designing the workshop, the steering committee chose not to have the presentations focus on specific parts of the body and associated musculoskeletal disorders. Rather, the examination of the evidence was organized to elucidate the following sets of relationships and factors that potentially contribute to musculoskeletal disorders: (1) biological responses of tissues (muscles, tendons and nerves) to biomechanical stressors, (2) biomechanics of work stressors, considering both work and individual factors, as well as internal loads; (3) epidemiological perspectives on the contributions of physical factors; (4) non-biomechanical (e.g. psychological, organizational and social) factors; and (5) interventions to prevent or mitigate musculoskeletal disorders, considering the range of potentially influential factors.

The authors chose not to focus on specific parts of the body and associated musculoskeletal disorders, hence they did not reach any specific conclusions on the subject of carpal tunnel syndrome.

(Cited as: NRC 1998)

Musculoskeletal Disorders and Workplace Factors. A Critical Review of the Epidemiologic Evidence for Work-Related Musculoskeletal Disorders of the Neck, Upper Extremity, and Low Back. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH). July 1997. Bruce Bernard, Editor.

The National Institute for Occupational Safety and Health published this extensive review of the literature describing the epidemiology of musculoskeletal disorders of the back and upper extremities. The review focused on the results of research projects designed to examine the link between physical activities in the workplace and musculoskeletal disorders; in addition, one section was devoted to an assessment of psychosocial factors such as workload, social support, job control, and activities outside the workplace.

On the subject of carpal tunnel syndrome, the authors concluded:

- there is **evidence** of a positive association between highly repetitive work alone or in combination with other factors and CTS based on available epidemiologic data.
- there is **evidence** of a positive association between forceful work and CTS.
- there is **insufficient evidence** of an association between CTS and extreme postures.
- there is **evidence** of a positive association between work involving hand/wrist vibration and CTS.
- there is **strong evidence** of a positive association between exposure to a combination of risk factors (e.g., force and repetition, force and posture)

(Cited as: Bernard 1997)

APPENDIX F. Search Syntax

MEDLINE Search Syntax (Diagnosis)

Database: MEDLINE <1966 to April Week 2 2003>
Search Strategy:
---

1 exp Carpal Tunnel Syndrome/ (4320)
2 exp "Sensitivity and Specificity"/ (137094)
3 exp Diagnostic Errors/ (53462)
4 (sensitivity or false positive or false negative or predict$ or observer$ with variation$).mp. (548020)
5 2 or 3 or 4 (636824)
6 (blind$ or mask$ or compar$).mp. (2169011)
7 5 and 6 (235002)
8 1 and 7 (165)
9 exp Carpal Tunnel Syndrome/di, ra, us (1450)
10 exp Cohort Studies/ (454388)
11 exp Case-Control Studies/ (226561)
12 (cohort$ or case control$).mp. or 10 or 11 (662489)
13 9 and 12 (212)
14 limit 9 to (clinical trial or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) (62)
15 13 or 14 (246)
16 15 not 8 (199)
17 8 or 15 (364)
18 limit 17 to (all adult <19 plus years>)

EMBASE Search Syntax (Diagnosis)

Database: EMBASE <1988 to 2003 Week 16>
Search Strategy:
---

1 exp Carpal Tunnel Syndrome/ (3201)
2 exp "Sensitivity and Specificity"/ (8312)
3 exp Diagnostic Error/ (8836)
4 (sensitivity or false positive or false negative or predict$ or observer$ with variation$).mp. (399441)
5 2 or 3 or 4 (409500)
6 (blind$ or mask$ or compar$).mp. (1113076)
7 5 and 6 (131768)
8 1 and 7 (125)
9 exp Carpal Tunnel Syndrome/rt, di [Radiotherapy, Diagnosis] (1151)
10 exp Cohort Studies/ (14109)
11 exp Case-Control Studies/ (7789)
12 (cohort$ or case control$).mp. or 10 or 11 (70522)
13 9 and 12 (16)
14 8 or 13 (138)
15 limit 14 to (human)

MEDLINE Search Syntax (Causation)

Database: MEDLINE <1966 to June Week 3 2003>
Search Strategy:
---
1 exp Carpal Tunnel Syndrome/ (4401)
2 exp cohort studies/ (464793)
3 exp case-control studies/ (232926)
4 (cohort$ or case-control$).mp. or 2 or 3 (678802)
5 1 and 4 (671)
6 limit 1 to (clinical trial or controlled clinical trial or
meta analysis or multicenter study or randomized controlled trial) (234)
7 5 or 6 (801)
8 exp probability/ (412057)
9 (risk$ or cohort$ or follow-up or predict$ or case-control$).ti,ab,sh. (1131277)
10 (cause$ or causat$ or causing or causal$ or etiol$ or aetiol$).ti,ab,sh. (918217)
11 exp case-control studies/ (232926)
12 8 or 9 or 10 or 11 (2028123)
13 1 and 12 (1363)
14 7 or 13 (1674)
15 limit 14 to all adult <19 plus years> (1208)

EMBASE Search Syntax (Causation)

Database: EMBASE <1988 to 2003 Week 25>
Search Strategy:
---
1 exp Carpal Tunnel Syndrome/ (3244)
2 exp cohort studies/ (14882)
3 exp case-control studies/ (8033)
4 (cohort$ or case-control$).mp. or 2 or 3 (72205)
5 1 and 4 (54)
6 exp probability/ (8646)
7 (risk$ or cohort$ or follow-up or predict$ or case-control$).ti,ab,sh. (815170)
8 (cause$ or causat$ or causing or causal$ or etiol$ or aetiol$).ti,ab,sh. (603191)
9 exp case-control studies/ (8033)
10 6 or 7 or 8 or 9 (1314849)
11 1 and 10 (1142)
12 11 or 5 (1142)
13 limit 12 to adult <18 to 64 years> (653)

MEDLINE Search Syntax (Treatment)

Database: MEDLINE <1966 to June Week 4 2003>
Search Strategy:
---

1 exp Carpal Tunnel Syndrome/ (4404)
2 exp cohort studies/ (465658)
3 exp case-control studies/ (233485)
4 (cohort$ or case control$).mp. or 2 or 3 (680187)
5 1 and 4 (672)
6 limit 1 to (clinical trial or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) (235)
7 5 or 6 (802)
8 clinical trial.pt. (361379)
9 ((clinical or control$ or compar$) adj (trial$ or study or studies)).ti,ab,sh. (234305)
10 8 or 9 (529646)
11 random$.ti,ab,sh. or randomized controlled trial.pt. (356585)
12 multicenter study.pt. (52392)
13 12 or (multicenter$ or multicentre$ or multi-centre$ or multi-center $).ti,ab,sh. (68533)
14 11 or 13 (395669)
15 10 and 14 (229044)
16 (blind$ or mask$ or placebo$).ti,ab,sh. (181312)
17 16 and 10 (109556)
18 17 and 14 (78281)
19 1 and 18 (43)
20 19 or 7 (805)
21 limit 20 to all adult <19 plus years> (667)

EMBASE Search Syntax (Treatment)

Database: EMBASE <1988 to 2003 Week 26>
Search Strategy:
---

1 exp Carpal Tunnel Syndrome/ (3249)
2 exp cohort studies/ (14985)
3 exp case-control studies/ (8063)
4 (cohort$ or case-control$).mp. or 2 or 3 (72479)
5 1 and 4 (54)
6 ((control$ or compar$) adj (trial$ or study or studies)).ti,ab,sh. (86041)
7 random$.ti,ab,sh. (221298)
8 multicenter study.pt. (0)
9 (blind$ or mask$ or placebo$).ti,ab,sh. (133364)
10 6 or 7 or 8 or 9 (342673)
11 1 and 10 (252)
12 11 or 5 (285)
13 limit 12 to adult <18 to 64 years> (181)

APPENDIX G. Worksheets for evaluating studies of diagnosis

Diagnostic Test Data Abstraction Worksheet

Validity

1. Was there an independent, blind comparison of the test with a reference ("gold") standard? [ ] Yes [ ] No [ ] Can't Tell

   - Was an acceptable Reference standard used?
   - Were both reference standard and test applied to all patients?
   - Was there an explicit description of how blinding was done?

2. Did the patient sample include an appropriate spectrum of (symptomatic) patients to whom the diagnostic test will be applied in clinical practice?
   [ ] Yes [ ] No [ ] Can't Tell

   Patients assessed in the study should have symptoms. The inclusion of large numbers of asymptomatic patients in a trial can inflate the specificity of the test

3. Did the results of the test being evaluated influence the decision to perform the reference ("gold") standard? Verification" or "work-up" bias?
   [ ] Yes [ ] No [ ] Can't Tell

4. Was the definition of the test, and description of how to perform the test of sufficient clarity and detail to permit replication?
   [ ] Yes [ ] No [ ] Can't Tell

   - Preparation of patient? Performance of test? Analysis & interpretation of results?

Clinical Importance (construct 2X2 table)

1. Are likelihood ratios for the test results presented or data necessary for their calculation provided?

   - How big or small is this LR?
   - Confidence intervals

Applicability

1. Will the reproducibility of the test result and its interpretation be satisfactory in my setting?[ ] Yes [ ] No [ ] Can't Tell

2. Are the results applicable to WCB patients? [ ] Yes [ ] No [ ] Can't Tell

   - Similar distribution of disease severity?
   - Similar distribution of competing diseases?
   - Is the test risk or test cost acceptable?

Level of Evidence for Diagnostic studies

First Author Journal Year

Study design

N=

Consecutive Non-consecutive

Prospective Retrospective Cohort Case-Control

What Reference standard was used?

Sample table

Calculator:
http://www.cebm.utoronto.ca/practise/ca/statscal/

	Reference standard (+)	**Reference standard (-)**
Test positive		
Test Negative		

Sensitivity=
Specificity=
LR (+) =
LR(-) =

1	Independent, blind comparison with reference standard Appropriate spectrum of consecutive patients OR Clinical diagnostic rule or model that has been validated in an independent test set
2	Independent, blind comparison with reference standard Nonconsecutive patients or narrow spectrum of study patients OR Clinical diagnostic rule or model that has **not** been validated in an independent test set
3	Independent, blind comparison with reference standard Appropriate spectrum of consecutive patients But Reference standard was not applied to all study patients
4	Reference standard not applied independently or blindly*
5	Expert opinion without explicit critical appraisal Or Based on physiology, bench research or first principles

* If the paper does not **explicitly state** that the test was compared to a reference standard in an independent and blinded fashion, then it is assumed that the comparison was **NOT** done in that manner.

APPENDIX H. Worksheets for evaluating studies of causation

Causation evidence Assessment Guide Nov 2003

	Yes	No	?
Inclusion Criteria (All 3)			
1. Population studied had symptoms, **And** 2. CTS diagnosis confirmed by NCS or by trained clinician using well described, well recognized reproducible, objective sign, **And** 3. Exposure preceded outcome			
Study results are Valid			
1. Clearly identified comparison groups that were similar with respect to important determinants of outcome, other than the one of interest? (RCT, cohort, case-control, etc)			
2. Other known prognosis factors or co-morbidities similar or adjusted for? (Include diabetes, renal disease)			
3. Outcomes and exposures measured in same way in groups being compared (objective or blinded assessment)?			
4. Exposure opportunity similar? Recall bias? Interviewer bias?			
5. Follow-up sufficiently long and complete? a. Reasons for incomplete follow-up? Risk factors similar in those lost and not lost to follow-up?			
Study results are important			
1. Magnitude: OR $\geq$ 2 with narrow confidence intervals			
2. Strength of association present a. Demonstrated dose-response gradient? b. Risk of outcome increases with quantity or duration of exposure? c. Dechallenge-rechallenge study done? d. Association consistent from study to study? e. Association has pathophysiological plausibility?			
Study results are applicable to WCB population			
1. Popluation studied in trial similar enough to a WCB population so that results may be extrapolated?			

Article About Causation or Harm from Evidence Based Medicine Working Group

Citation: _____

Grade/level of evidence:

Are the Results of the Study Valid? (yes/no/cannot tell)

1.Were there clearly identified comparison groups that were similar with respect to important determinants of outcome, other than the one of interest? (RCT, cohort, base-control? Other known prognosis factors similar or adjusted for?)

2. **Were the outcomes and exposures measured in the same way in the groups being compared?** (Recall bias? Interviewer bias? Exposure opportunity similar?

3.**Was follow-up sufficiently long and complete? (**Reasons for incomplete follow-up? Risk factors similar in those lost and not lost to follow-up?)

4. Is the temporal relationship correct? (Exposure preceded outcome?)

5. Is there a dose-response gradient? (Risk of outcome increases with quantity or duration of exposure?)

6. Overall, are the results of the study valid?

What are the Results?

1. **How strong is the association between exposure and outcome?** RR's or OR's?
2. **How precise is the estimate of risk? (**Confidence intervals?)

Are results applicable to WCB Patients?

1. Are the results applicable? Patients similar for demographics, morbidity and other prognostic factors? Are treatments and exposures similar?

2.What is the magnitude of the risk? Absolute risk increase (and its reciprocal)?

3.On the basis of this, should one attempt to stop the exposure?

Strength of evidence? Magnitude of risk? Adverse effects of reducing exposure?

APPENDIX I. Worksheet for evaluating studies about therapy

Articles about Therapy: From Evidence Based Medicine Working Group

Citation:

Grade/level of evidence:

Are the results valid? (yes/no/cannot tell)

- Was the assignment of patients to treatment randomized?
- Were all patients who entered the trial properly accounted for and attributed at its conclusion?

  Was **follow-up** complete? Were patients analyzed in the groups to which they were randomized ? **Intention to treat analysis** used**?**

- Were patients, their clinicians and study personnel 'blind' to treatment?
- Were the groups similar at the start of the trial?

Baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced? If different, were these adjusted for?

- Aside from the experimental intervention, were the groups treated equally?

  Co-intervention? Contamination? Compliance?

What are the results?

- How large is the treatment effect?

  Absolute risk reduction? Relative risk reduction?

- How precise is the estimate of the treatment effect?

  Confidence intervals?

Will the results help in patient care?

- Can the results be applied to WCB patients?

  Patients similar for demographics, severity, **co-morbidity** and other prognostic factors? Compelling reason why they should not be applied?

- Were all clinically relevant outcomes considered?

Are substitute endpoints valid?

- Are the benefits worth the harms and costs?

NNT for different outcomes?

APPENDIX J. The likelihood ratio

Test information is only valuable if it changes the probability of disease enough to alter treatment or diagnosis.

The likelihood ratio (LR) is a statistical expression that describes how a test result modifies the probability that a disease or condition is present

A likelihood ratio of 1 means that the post-test probability is exactly the same as the pre-test probability. LRs greater than 1 increase the probability that the target disorder is present, and the higher the LR the greater the increase. Conversely, LRs less than 1 decrease the probability of the target disorder, and the smaller the LR, the greater the decrease in probability and the smaller its final value.

As a rough guide:

- LRs >10 or <0.1 generate large, and often conclusive changes from pre- to post-test probability.
- LRs of 5-10 and 0.1 – 0.2 generate moderate shifts in pre- to post-test probability.
- LRs of 2-5 and 0.5 – 0.2 generate small (but sometimes important) changes in probability; and
- LRs of 1-2 and 0.5-1 alter probability to a small (and rarely important) degree.

LRs are calculated using the reported sensitivity and specificity. The LR for a positive result (positive likelihood ratio or LR+) = sensitivity/(1-specificity). The LR for a negative result (negative likelihood ratio or LR-) = (1-sensitivity)/specificity.

The LR+ tells us how much to increase the probability of disease if the test is positive, while the LR- tells us how much to decrease it if the test is negative. The LR+ corresponds to the clinical concept of "ruling in" disease. The LR- corresponds to the clinical concept of "ruling out" disease.

Source: Jaeschke 1994

APPENDIX K. How to update this background paper

Systematic review of the literature revealed that scientific knowledge about carpal tunnel syndrome is incomplete. The results of future original research studies will undoubtedly provide the evidence necessary to answer currently unanswerable questions about the diagnosis, causation and treatment of carpal tunnel syndrome.

This report should be updated periodically. As the results of new studies become available, their level of evidence should be determined, and the validity of their results, including clinical importance and applicability to Alberta's injured workers, should be critically appraised.

Insofar as possible, preparation of this evidence report was designed to be a deliberate, systematic and reproducible process. That process is described in detail in the section entitled "Assessing the Scientific Evidence." In addition, Appendix N includes a list of important evidence-based medicine background resources, and the MEDLINE and EMBASE syntax we used for the literature searches on diagnosis, causation and treatment of CTS are found in Appendix F.

Application of the methodology described to the results of future literature searches (using identical databases and search syntaxes) will lay the foundation for an accurate evidence-based update of this background paper.

APPENDIX L: Articles that were retrieved, reviewed and excluded

The studies below were retrieved and reviewed but did not meet the inclusion criteria based on diagnostic method, and/or did not meet the domain-specific inclusion criteria, and/or did not meet the inclusion criteria based on study design, and/or did not meet the inclusion criteria based on clinical relevance, and/or were not subsequently identified for use as references for specific pieces of information about carpal tunnel syndrome anatomy, pathophysiology, comorbidities, etc.

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APPENDIX M: Glossary

Aging of the population: a demographic term, meaning the increase over time in the proportion of older persons in the population. It does not necessarily imply an increase in life expectancy.

Algorithm: any systematic process that consists of an ordered sequence of steps with each step depending on the outcome of the previous one.

Anecdotal evidence: evidence derived from descriptions of cases or events (as opposed to systematically collected data that can be submitted to statistical tests). Anecdotal evidence is considered weak evidence and must be viewed with caution. It is sometimes useful to generate hypotheses. See *case study*.

Applicability: the degree to which the results of an study hold true in other settings or in other populations.

Association: statistical dependence between two or more events, characteristics or other variables. An association may be fortuitous or may be produced by various other circumstances; the presence of an association does not necessarily imply a causal relationship.

Bias: deviation of results from the truth, or processes leading to such deviation. A synonym for bias is *systematic error*. In studies of the effects of health care bias can arise from systematic differences in the groups that are compared (selection bias), the care that is provided, or exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into the study (attrition bias) or how outcomes are assessed (detection bias). Bias does not necessarily carry an imputation of prejudice, such as the investigators' desire for particular results and so differs from conventional use of the word in which bias refers to a partisan point of view.

Blinded study: (Syn: *masked study*) a study in which observers and/or subjects are kept ignorant of the group to which subjects are assigned in an effort to eliminate bias. When both observers and subjects of a study are blinded, it is referred to as a double blind study.

Body Mass Index (BMI): a ratio of weight to height squared.

Case control study: retrospective comparison of exposures of persons with the disease (cases) to those of persons without the disease (controls). The relationship of an attribute (intervention, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and controls. Case-control studies are sometimes described as being retrospective studies as they are always performed looking back in time.

Case series: an uncontrolled observational study involving an intervention and outcome for more than one person; report of a number of cases of disease.

Case study: (synonyms: *anecdote, case history, single case report*). An uncontrolled observational study involving an intervention and outcome for a single person.

Clinical signs: physical findings that a physician determines by a physical examination; indicators of disease that are obvious to someone other than the patient. These signs cannot be considered objective diagnostic tools since they are dependent on patient performance and patient report.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study): follow-up of exposed and non-exposed groups, with a comparison of disease rates during the time covered. An observational study in which a defined group of people (the cohort) is followed over time and outcomes are compared in subsets of the cohort who were exposed or not exposed, or exposed at different levels, to an intervention or other factor of interest. Cohorts can be assembled in the present and followed into the future (a "concurrent cohort study"), or identified from past records and followed forward from that time up to the present (a "historical cohort study"). Because random allocation is not used, matching or statistical adjustment must be used to ensure that the comparison groups are as similar as possible.

Co-morbidity: coexistence of a disease or diseases in a study participant in addition to the index condition that is the subject of the study.

Comparison group: any group to which the index group is compared. Usually synonymous with control group.

Confidence interval (CI): the range of numerical values in which we can be confident (to a compared probability, such as 90% or 95%) that the population value being estimated will be found. Confidence intervals indicate the strength of the evidence; where the confidence intervals are wide, they indicate less precise estimates of effect. The larger the trial's sample size, the larger the number of outcome events and the greater the confidence that the true relative risk reduction is close to the value stated. Confidence intervals represent the probability of random errors but not systematic errors (bias).

Confounding variable, confounder: a variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation. A confounding variable may be due to chance or bias. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of the factor(s) being studied, and the measure of the effect of an intervention or exposure is distorted because of the association of exposure with other factor(s) that influence the outcome under study.

Control: in clinical trials comparing two or more interventions, a control is a person in the comparison group that receives a placebo, no intervention, usual care or another form of care. In case control studies a control is a person in the comparison group without the disease or outcome of interest. In statistics control means to adjust for or take into account extraneous influences or observations.

Control group: any group to which the index group is compared. Usually synonymous with comparison group.

Critical appraisal: the fair and systematic assessment and interpretation of research, typically as reported in published articles, including its contribution to scientific knowledge, the validity of its results and any cause and effect inferences, as well as its relevance. The application of the rules of evidence to a study.

Cross-over trial: A type of clinical trial comparing two or more interventions in which, upon completion of one course of treatment, the participants are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this design is that the effects of the first treatment may carry over into the period when the second is given.

Cross-sectional study (synonym: prevalence study): a study that examines the relationship between diseases (or other health related characteristics) and other variables of interest as they exist in a defined population at one particular time. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.

Dose-response relationship: a relationship in which change in amount, intensity or duration of exposure is associated with a change (either an increase or a decrease) in risk of a specified outcome.

Double blind: Neither the participants in a trial nor the investigators (outcome assessors, who might also be care providers) are aware of which intervention participants are given. The purpose of blinding the participants (recipients and providers of care) is to prevent bias.

Electrogoniometer: a device that is positioned across a joint and puts out a continuous electrical signal describing the angle of the joint.

Epidemiology: the study of the distribution of disease within a defined population. Epidemiological studies are used to evaluate whether specific exposures are risk factors for the development of a specific disease. Epidemiology does not establish causation between an individual's exposure and his or her disease, but helps in identifying and understanding risk factors that may have an inference of association with the disease.

Etiology: the science of causes, causality; in common usage, cause.

Evidence-based medicine toolkit (EMB toolkit): a collection of tools for identifying, assessing and applying relevant evidence for better health care decision-making. The appraisal tools are adapted from the Users' Guides series prepared by the Evidence Based Medicine Working Group and originally published in JAMA. The Evidence Based Medicine Toolkit is found at www.med.ualberta.ca/ebm/ebm.htm.

Experimental study. a study in which conditions are in direct control of the investigator. In epidemiology, a study in which a population is selected for a planned trial of a regimen whose effects are measured by comparing the outcome of another regimen in a control group. Also known as intervention studies.

FTEs: Full Time Equivalents.

Healthy Worker Effect: The results of epidemiological studies depend on the comparisons made between the cases and control groups used. If the groups are not well matched, the results will not be meaningful. For this reason cases and control groups may be matched for age, sex and race, as well as lifestyle factors like smoking and alcohol consumption. Occupational groups very often have lower total mortality than the general population as the latter includes people unable to work due to illness or disability. In other words, any group of workers is likely to be more healthy than the population as a whole, a phenomenon known as the "healthy worker effect."

Hill's criteria of causation: the first complete statement of the epidemiologic criteria of causal association is attributed to the British medical statistician Austin Bradford Hill (1897-1991). Hill's criteria include consistency, strength, specificity, dose-response relationship, temporal relationship, biological plausibility, coherence, and experiment.

Idiopathic: unknown cause.

Incidence: the probability of developing a disease within a specified time period. Incidence is calculated by dividing the number of people who developed the disease in a time period by the number of people in the study population at the beginning of the time period.

Intention-to-treat analysis: a procedure in the conduct and analysis of randomized controlled trials. All patients allocated to each arm of the treatment regimen are analyzed together as representing that treatment arm, whether or not they received or completed the prescribed regimen. Failure to follow this step defeats the main purpose of random allocation and can invalidate the results.

-itis: state of inflammation. The word ending "itis" denotes inflammation on the part indicated by the word stem to which it is attached.

Kappa: measures the relation between the test result and the reference standard result. The closer kappa is to 1, the stronger the correlation between the test and the reference standard.

Likelihood ratio (LR): a statistical expression that describes how a test result effects the probability that a disease or condition is present. The likelihood ratio for a test compares the likelihood of that result in patients with disease to the likelihood of that result in patients without the disease. LRs are calculated using sensitivity and specificity.

Negative Likelihood Ratio (LR-): indicates how much to decrease the probability of disease if the test is negative; it corresponds to the clinical concept of "ruling out" disease. The LR for a negative result (negative likelihood ratio or LR-) = (1-sensitivity)/specificity.

Negative study: A term used to refer to a study that does not have "statistically significant" (positive) results indicating a beneficial effect of the intervention being studied. The term can generate confusion because it refers to both statistical significance and the direction of effect, studies often have multiple outcomes, the criteria for classifying studies as "negative" are not always clear and, in the case of studies of risk or undesirable effects, "negative" studies are ones that do not show a harmful effect.

Null hypothesis: the statistical hypothesis that one variable has no association with another variable or set of variables, or that two or more population distributions do not differ from one another. In simplest terms, the null hypothesis states that the results observed in a study, experiment or test are no different from what might have occurred as a result of the operation of chance alone. Test hypothesis is a synonym for null hypothesis.

Observational study: epidemiologic study that does not involve any intervention, experimental or otherwise. Changes or differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. Analytic epidemiologic methods such as case-control and cohort study designs are properly called observational epidemiology because the investigator is observing without intervention other than to record, classify, count, and statistically analyze results. Also known as a non-experimental study. There is a greater risk of selection bias in observational studies than in experimental studies.

Odds Ratio (OR): when the odds (not risk) of occurrence of an event or disease is compared between two groups (exposed and unexposed), the result is an Odds Ratio (OR). An OR is usually computed in a case control study where it is not possible to get the true risk (incidence). Odds are the ratio of the number of people in a group with an event to the number without an event. Thus, if a group of 100 people had an event rate of 0.20, 20 people had the event and 80 did not, and the odds would be 20/80 or 0.25. An odds ratio of 1 indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome. When the event rate is small, odds ratios are very similar to relative risks.

-osis: abnormal condition. The word ending "osis" denotes a condition, usually abnormal, of the part indicated by the word stem to which it is attached.

P (probability) value: the probability that a test statistic would be as extreme as or more extreme than observed if the null hypothesis were true. The letter P, followed by the abbreviation n.s. (not significant) or by the symbol < (less than) and a decimal notation such as 0.01, 0.05, is a statement of the probability that the difference observed could have occurred by chance if the groups were really alike, i.e., under the null hypothesis. Investigators may arbitrarily set their own significance levels, but in most biomedical and epidemiologic work, a study result whose probability value is less than 5% ($P<0.05$) or 1% ($P<0.01$) is considered sufficiently unlikely to have occurred by chance to justify the designation "statistically significant."

Pathogenesis: the development of the disease of the sequence of events involved in the tissue changes.

Pathophysiology: the interruption of, or interference with, normal physiological and developmental processes or structures.

Placebo, placebo effect: an inert medication or procedure. The placebo effect (usually but not necessarily beneficial) is attributable to the expectation that the regimen will have an effect, i.e., the effect is due to the power of suggestion.

Positive Likelihood Ratio (LR+): indicates how much to increase the probability of disease if the test is positive; it corresponds to the clinical concept of "ruling in" disease. The LR for a positive result (positive likelihood ratio or LR+) = sensitivity/(1-specificity).

Predictive value: in screening and diagnostic tests, the probability that a person with a positive test is a true positive (i.e. does have the disease) is referred to as the "predictive value of a positive test." The predictive value of a negative test is the probability that a person with a negative test does not have the disease.

Prevalence: the probability of currently having a disease without regard to time of onset. Dividing the number of people who currently have the disease by the number of people in the study population yields the prevalence.

Primary study: "original research" in which data is first collected. The term primary research is sometimes used to distinguish it from "secondary research" (reanalysis of previously collected data), meta-analysis, and other ways of combining studies.

Prospective study: study design where one or more groups (cohorts) of individuals who have not yet had the outcome in question are monitored for the number of such events which occur over time. A study in which people are divided into groups that are exposed or not exposed to the intervention(s) of interest before the outcomes have occurred. Randomized controlled trials are always prospective studies and case control studies never are. Concurrent cohort studies are prospective studies, whereas historical cohort studies are not, although in epidemiology a prospective study is sometimes used as a synonym for cohort study.

Protocol: the plan or set of steps to be followed in a study.

Psychosocial: pertaining to mental or psychological as well as social aspects. Commonly recognized psychosocial factors include non-biophysical aspects of the work environment or social milieu.

Randomized controlled trial (RCT): An experiment in which investigators randomly allocate eligible people into treatment and control groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups. If the sample size is large enough, this study design avoids problems of bias and confounding variables by assuring that both known and unknown determinants of outcome are evenly distributed between treatment and control groups.

Relative risk (RR): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes a RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

Reliability: refers to the degree to which results obtained by a measurement procedure can be replicated. Lack of reliability can arise from divergences between observers or measurement instruments, or instability in the attribute being measured.

Retrospective study: a study in which the outcomes occurred to the participants before the study commenced. Case control studies are always retrospective, cohort studies sometimes are, randomized controlled trials never are. A study design in which cases where individuals who had an outcome event in question are collected and analyzed after the outcomes have occurred.

Risk factor: an aspect of personal behavior or life-style, an environmental exposure, or an inborn or inherited characteristic, which on the basis of epidemiologic evidence is known to be associated with a health-related condition considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings. 1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as occurrence of a disease. Not necessarily a causal factor. A risk marker. 2. An attribute or exposure that increases the probability of occurrence of disease or other specified outcome. A determinant. 3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk marker.

Risk Ratio (RR): the ratio of incidence among exposed and incidence among unexposed. A Risk Ratio is an extremely powerful measure of association and the greater the RR, the more the strength of the observed association. An RR of 10 implies a much stronger association than an RR of 2, an RR of 1 implies no association between the two variables. In practice, it is difficult to estimate the RR because true incidence figures are obtained only from studies which have a longitudinal component (cohort study) and such studies are difficult to do.

Selection bias: Error due to systematic differences in characteristics between those who are selected for study and those who are not. In assessments of the validity of studies of healthcare interventions, selection bias refers to systematic differences between comparison groups in prognosis or responsiveness to treatment. Random allocation with adequate concealment of allocation protects against selection bias. Other means of selecting who receives the intervention of interest, particularly leaving it up to the providers and recipients of care, are more prone to bias because decisions about care can be related to prognosis and responsiveness to treatment. Selection bias, confusingly, is also sometimes used to describe a systematic difference in characteristics between those who are selected for study and those who are not. This affects the generalizability (external validity) of a study but not its (internal) validity.

Sensitivity: the proportion of truly diseased persons, as identified by the diagnostic "gold standard" who are identified as diseased by the diagnostic test under study.

Single blind: the investigator is aware of the treatment/intervention the participant is getting, but the participant is unaware.

Specificity: the proportion of truly nondiseased persons, as identified by the diagnostic "gold standard," who are identified as nondiseased by the diagnostic test under study.

Spectrum bias: when the population under investigation does not reflect the general population or the clinically relevant population.

Statistical power: the probability that the null hypothesis will be rejected if it is indeed false. In studies of the effectiveness of healthcare interventions, power is a measure of the certainty of avoiding a false negative conclusion that an intervention is not effective when in truth it is effective. The power of a study is determined by how large it is (the number of participants), the number of events (e.g. strokes) or the degree of variation in a continuous outcome (such as weight), how small an effect one believes is important (i.e. the smallest difference in outcomes between the intervention and the control groups that is considered to be important), and how certain one wants to be of avoiding a false positive conclusion (i.e. the cut-off that is used for statistical significance).

Statistically significant: an estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a P-value. For example, a P-value of 0.049 for a risk difference of 10% means that there is less than a one in 20 (0.05) chance of an association that is as large or larger having occurred by chance and it could be said that the results are "statistically significant" at P = 0.05). The cut-off for statistical significance is usually taken at 0.05, but sometimes at 0.01 or 0.10. These cut-offs are arbitrary and have no specific importance. Although it is often done, it is inappropriate to interpret the results of a study differently according to whether the P-value is, say, 0.055 or 0.045 (which are quite similar values, not diametrically opposed ones). Note the distinction between clinical and statistical significance; clinical significance is the more important. For example, when large numbers of comparisons are made, some differences will be "statistically significant" by chance; i.e. they are meaningless.

Strength of inference: the likelihood that an observed difference between groups within a study represents a real difference rather than mere chance or the influence of confounding factors, based on both p values and confidence intervals. Strength of inference is weakened by various forms of bias and by small sample sizes.

Symptoms: subjective feelings reported by the patient.

Syndrome: a symptom complex in which the symptoms and/or signs coexist more frequently than would be expected by chance on the assumption of independence.

Systematic error: deviation of the results or inferences from the truth, or processes leading to such deviation. A synonym for systematic error is *bias*.

Systematic review: a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

Type II error: the error of failing to reject a false null hypothesis – in other words, declaring that a difference does not exist when in fact it does. In research, a null hypothesis and an alternative hypothesis are specified. Typically, the null hypothesis corresponds to no change. A Type II error is accepting the null hypothesis when the null hypothesis is false. Many studies have small sample sizes that make it difficult to reject the null hypothesis, even when there is a big change in the data. In these situations, a Type II error might be a possible explanation for the negative study results. A Type II error is only an error in the sense that an opportunity to reject the null hypothesis

correctly was lost. It is not an error in the sense that an incorrect conclusion was drawn since no conclusion is drawn when the null hypothesis is not rejected.

Validity: the extent to which a variable or intervention measures what it is supposed to measure or accomplishes what it is supposed to accomplish. The *internal validity* of a study refers to the integrity of the experimental design. The *external validity* of a study refers to the appropriateness by which its results can be applied to non-study patients or populations. Validity is the degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors). Validity has several other meanings, usually accompanied by a qualifying word or phrase; for example, in the context of measurement, expressions such as "construct validity", "content validity" and "criterion validity" are used. The expression "internal validity" is sometimes used to distinguish validity (the extent to which the observed effects are true for the people in a study) from external validity or generalizability (the extent to which the effects observed in a study truly reflect what can be expected in a target population beyond the people included in the study).

Variable: any quantity that varies. Any attribute, phenomenon, or event that can have different values.

Definitions in this glossary are drawn from a number of sources, including the Clinical Epidemiology Glossary found in the University of Alberta's *Evidence Based Medicine (EBM) Toolkit* (2003) and *A Dictionary of Epidemiology* (1995), edited by John Last.

APPENDIX N: Evidence-Based Medicine Resources

This list of evidence-based medicine resources is reproduced from the University of Alberta's Evidence-Based Medicine Toolkit (EBM-Toolkit 2003).

Barratt A. Irwig L. Glasziou P. Cumming RG. Raffle A. Hicks N. Gray JA. Guyatt GH. Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA. 281(21):2029-34, 1999

Bucher HC. Guyatt GH. Cook DJ. Holbrook A. McAlister FA. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA. 282(8):771-8, 1999

Dans AL. Dans LF. Guyatt GH. Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA. 279(7):545-9, 1998

Drummond MF. Richardson WS. O'Brien BJ. Levine M. Heyland D. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 277(19):1552-7, 1997

Giacomini MK. Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 284(3):357-62, 2000

Giacomini MK. Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA. 284(4):478-82, 2000

Guyatt GH. Sackett DL. Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 270(21):2598-601, 1993

Guyatt GH. Sackett DL. Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 271(1): 59-63, 1994

Guyatt GH. Sackett DL. Sinclair JC. Hayward R. Cook DJ. Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA. 274(22):1800-4, 1995

Guyatt GH. Naylor CD. Juniper E. Heyland DK. Jaeschke R. Cook DJ. Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. JAMA. 277(15):1232-7, 1997

Guyatt GH. Sinclair J. Cook DJ. Glasziou P. Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA. 281(19):1836-43, 1999.

Guyatt GH. Haynes RB. Jaeschke RZ. Cook DJ. Green L. Naylor CD. Wilson MC. Richardson WS. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA. 284(10):1290-6, 2000.

Hayward RS. Wilson MC. Tunis SR. Bass EB. Guyatt G. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA. 274(7):570-4, 1995

Jaeschke R. Guyatt G. Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 271(5):389-91, 1994 Feb 2.

Jaeschke R. Guyatt GH. Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA. 271(9):703-7, 1994

Laupacis A. Wells G. Richardson WS. Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA. 272(3):234-7, 1994

Levine M. Walter S. Lee H. Haines T. Holbrook A. Moyer V. Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA. 271(20):1615-9, 1994.

McAlister FA. Straus SE. Guyatt GH. Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group. JAMA. 283(21):2829-36, 2000

McGinn TG. Guyatt GH. Wyer PC. Naylor CD. Stiell IG. Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA. 284(1):79-84, 2000.

Naylor CD. Guyatt GH. Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. The Evidence-Based Medicine Working Group. JAMA. 275(7):554-8, 1996.

Naylor CD. Guyatt GH.Users' guides to the medical literature. XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. JAMA. 275(18):1435-9, 1996.

O'Brien BJ. Heyland D. Richardson WS. Levine M. Drummond MF. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group JAMA. 277(22):1802-6, 1997.

Oxman AD. Sackett DL. Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA. 270(17):2093-5, 1993.

Oxman AD. Cook DJ. Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA. 272(17):1367-71, 1994.

Richardson WS. Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 273(16):1292-5, 1995.

Richardson WS. Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? Evidence Based Medicine Working Group. JAMA. 273(20):1610-3, 1995.

Richardson WS. Wilson MC. Guyatt GH. Cook DJ. Nishikawa J. Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA. 281(13):1214-9, 1999.

Richardson WS. Wilson MC. Williams JW Jr. Moyer VA. Naylor CD. Users' guides to the medical literature: XXIV. How to use an article on the clinical manifestations of disease. Evidence-Based Medicine Working Group. JAMA. 284(7):869-75, 2000

Wilson MC. Hayward RS. Tunis SR. Bass EB. Guyatt G. Users' guides to the Medical Literature. VIII. How to use clinical practice guidelines. B. what are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. JAMA. 274(20):1630-2, 1995

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