Relationship of Ultrasonographic Physiologic Changes to Personal Factors and Psychosocial Stressors in the Development and Diagnosis of Carpal Tunnel Syndrome

DISSERTATION

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By

Shawn Christopher Roll, M.S.

Graduate Program in Health and Rehabilitation Sciences

The Ohio State University

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Dissertation Committee:

Kevin D. Evans, Advisor

Jane Case-Smith

Carolyn M. Sommerich

Miriam L. Freimer
Abstract

Carpal tunnel syndrome (CTS) is diagnosed in nearly 12,000 workers every year and may occur in up to 6% of the population. CTS limits individual functional performance and can be costly for employees and employers due to medical expenses and lost productivity. While psychosocial, physical, and personal stressors have all been identified as potential risk factors for carpal tunnel syndrome, little research has been conducted to evaluate the interrelationships and combined effects of each of these factors to identify the most salient stressors. Additionally, due to a lack of efficient and cost-effective technology, few research studies have investigated acute physiologic changes in the upper extremity and median nerve due to such stressors. Instead, studies measure secondary, often chronic, changes in the nerve conduction of symptomatic individuals. In order to move toward interventional techniques that effectively reduce salient risk factors for carpal tunnel syndrome, relationships between risk factors should be better understood and novel tools and methodologies could be investigated to study acute physiologic changes.

Together, a systematic review of literature and a cohort study provided evidence to support the use of sonography as a screening tool for CTS. Standardized methods and measures identified in the systematic review were used to obtain the sensitivity and specificity of sonographic measurements compared to electrodiagnostic testing (EDX).
Cross-sectional area (CSA) of the median nerve within the carpal tunnel had the highest diagnostic accuracy and multiple additional sonographic measures showed high correlation to EDX. Utilizing these measures an exploratory binary logistic regression indicated that CSA of the median nerve as measured by sonography combined with body mass index and level of education could predict the presence of subjective complaints of discomfort or decreased functional tolerances, typical of median nerve pathology.

The preliminary regression analysis in this study provided guidance in completion of further research to understand the constellation of physical, psychosocial, and personal factors that contribute to CTS. These studies were limited by a small sample size, recruitment of subjects from a convenient sample, and some limitations in the measurement techniques. The combined effects of all of these factors, as they relate to physiological changes, require continued research within larger, longitudinal studies.

The effective prevention or remediation of median nerve pathology in the working population is reliant upon understanding the relationship of these factors to physiological changes over time. Refinement of sonographic measurements and techniques is required to identify valid and precise physiologic measures. Further research is needed to combat work-related musculoskeletal disorders, such as CTS, by determining the impact of comprehensive, multidisciplinary interventions. Comprehensive interventions may mediate an individual’s stress through the culture
and values of the organization, psychosocial demands and job control, work styles and workstation positioning, and individual coping mechanisms and cognitive processing.
Dedication

To my peers who seek knowledge and understanding.

To my parents for being excellent role models and for supporting my inquisitive nature.

*I do not think much of a man who is not wiser today than he was yesterday.*

– Abraham Lincoln
Acknowledgments

A man only learns in two ways, one by reading, and the other by association with smarter people.  
– Will Rogers

I must take a moment to acknowledge all the individuals that provided support, guidance, and encouragement along my path.  I have been exceptionally fortunate to have been surrounded by an abundance of scholars in all aspects of my life throughout this process.

One must be convinced to convince, to have enthusiasm to stimulate the others.

– Stefan Zweig

A sincere thank you to my advisor, Dr. Kevin Evans, for involving me in this exciting and innovative line of inquiry.  I am grateful for the master training that I received, both in the practice and application of sonography, and in life.  Thank you to Dr. Evans for not becoming frustrated and continuing to work with me despite the innumerable times I professed a lack of conviction throughout the process.  The great care and concern for my training has lead to full confidence to carry the process forward in an enthusiastic, yet always vigilant, manner.  I will always be thankful to have Dr. Evans as a mentor, teacher, and friend.
A round man cannot be expected to fit in a square hole right away.
He must have time to modify his shape. – Mark Twain

Whenever there may have been uncertainty that I would be a good fit, Dr. Jane Case-Smith always believed in my ability to achieve. While my diverse background and goals were not always a clear fit, without the steady encouragement and support from Dr. Case-Smith my success and forward progress would have been impeded.

Tell me and I’ll forget; show me and I may remember;
involve me and I’ll understand. – Chinese Proverb

I am grateful to Dr. Carolyn Sommerich for allowing me to participate in numerous varied experiences that have helped to strengthen my foundational knowledge, skills, and expertise. The vast knowledge and experience that was imparted through words and actions was always supported by full inclusion and immersion in the process.

Energy and persistence conquer all things. – Benjamin Franklin

I cannot be more thankful for the passion of an extraordinary role model and mentor, Dr. Karen Jacobs. Her energy is unmatched by anyone I know and Dr. Jacobs’ positive determination continually motivates me to do, and be, more.
A day without laughter is a day wasted. 
— Charlie Chaplin

Whether it was a day for data collection or merely a brief encounter, I was able to maintain my positive outlook due to Dr. Miriam Freimer and her staff, Rob Colgan, Paige Williamson and William Hardy. I am grateful for being welcomed into the office and for the ease of data collection in such a supportive environment. While some data collection days were less than productive, these amiable, relaxed, and relentlessly humorous individuals were a blessing during a demanding time.

We can’t help everyone, but everyone can help someone. 
— Ronald Reagan

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Learn from yesterday, live for today, hope for tomorrow. 
— Albert Einstein
Vita

September 20, 1979........................................Greenville, Ohio

2002.......................................................B.S. Allied Medical Professions, Magna Cum Laude with Distinction in Occupational Therapy, The Ohio State University

2002.......................................................Award of Merit, School of Allied Medical Professions, The Ohio State University

2006.......................................................M.S. Allied Medical Professions, The Ohio State University

2009.......................................................Kenneth R. Gottesfeld Award, Society of Diagnostic Medical Sonographers

2010.......................................................Outstanding PhD Graduate Student, School of Allied Medical Professions, The Ohio State University

2003 to Present........................................Program Coordinator, WorkLife at Fairfield Medical Center

2007 to Present........................................Graduate Research Associate, School of Allied Medical Professions, The Ohio State University

Publications


Fields of Study

Major Field: Health and Rehabilitation Sciences

Graduate Interdisciplinary Specialization: College and University Teaching
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<td>°C</td>
<td>degrees Celsius</td>
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<tr>
<td>APB</td>
<td>abductor pollicis brevis</td>
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<td>BCTQ</td>
<td>Boston carpal tunnel questionnaire</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>cm</td>
<td>centimeter</td>
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<td>CMAP</td>
<td>compound muscle action potential</td>
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<td>CSA</td>
<td>cross-sectional area</td>
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<td>carpal tunnel syndrome</td>
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<tr>
<td>df</td>
<td>degrees of freedom</td>
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<td>DML</td>
<td>distal motor latency</td>
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<td>DSL</td>
<td>distal sensory latency</td>
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<td>EDX</td>
<td>electrodiagnostic</td>
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<td>EMG</td>
<td>electromyography or electromyographic</td>
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<td>FCR</td>
<td>flexor carpi radialis</td>
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<td>FPL</td>
<td>flexor pollicis longus</td>
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<td>FR</td>
<td>flattening ratio</td>
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<td>HCU</td>
<td>hand-carried ultrasound</td>
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JCQ     job content questionnaire
kg      kilogram
LCS     longitudinal compression sign
MCV     motor conduction velocity
MHz     megahertz
mm      millimeter
MN      median nerve
MNL     mixed nerve latency
MRI     magnetic resonance imaging
NCS     nerve conduction study
PMA     persistent median artery
Pis     pisiform
RB      retinacular bulge or retinacular bowing
ROC     receiver operating characteristic
Sca     scaphoid
SCV     sensory conduction velocity
SNAP    sensory nerve action potential
SPL     sensory peak latency
UE      upper extremity
US      ultrasonography or ultrasound
WRMSD  work-related musculoskeletal disorder
Chapter 1: General Introduction

The incidence of repetitive strain musculoskeletal disorders are increasing at an alarming rate of 5 to 7% each year.\textsuperscript{1} In the United States, workers’ compensation costs for repetitive strain disorders total more than $6.5 billion with an average claim costing $5000 to $8000.\textsuperscript{2} Additionally, lost work-related musculoskeletal disorders are a significant cause of declining productivity,\textsuperscript{3} increased lost time and sick days,\textsuperscript{4} and increased work disability in the working population.\textsuperscript{5-8}

The prevalence of carpal tunnel syndrome in general population samples is as high as 3.0-5.8\% of females and 0.6-2.1\% of males,\textsuperscript{10} and the etiology of upper extremity musculoskeletal disorders (UE WRMSD) frequently relates to occupational exposures. Occupations requiring repetitive forearm and hand motions, gripping actions, or precise use of the fingers are up to 2.5 times more likely to experience symptoms in the upper extremities than the general population.\textsuperscript{11,12} Manual labor occupations accounted for forty percent of all newly reported cases of carpal tunnel syndrome in 2007 (Table 1.1).\textsuperscript{9}
Table 1.1 Occupational categories ranked by number of reported cases of carpal tunnel syndrome in 2007

Since carpal tunnel syndrome is cumulative, some instances may not fall under recordable standards, and an even higher number may go unreported. Additionally, up to 66% of work-related upper extremity disorders may persist longer than a year.⁶

1.1 Pathophysiology

Carpal tunnel syndrome, the most frequently occurring of all compression neuropathies, occurs with compression of the median nerve in the carpal tunnel that leads to sensorimotor deficits.⁴,¹³ Several models describe pathogenesis of carpal tunnel syndrome, all ultimately lead to compression of the nerve.¹⁴ Injury to the median nerve at connective tissue, vascular, or cellular levels is caused by the pressure overload on the nerve and ultimately the decreased blood supply, or problems with transmission of motor or sensory signals (Figure 1.1).¹⁵

Figure 1.1 Clinical examples of peripheral nerve structure and alteration
While injury may occur in any region, chronic compression involved in the initial stage of overload leads to capillary damage (e.g., leakage and edema), which obstructs arteries and decreases blood flood, all having an additive effect on the secondary dysfunction of signal conduction at the cellular level.\textsuperscript{16} This progression of nerve injury is classified into stages or grades based on the amount of damage at the cellular level, with differing deficits at each stage.\textsuperscript{13,17} In initial stages myelin is displaced and in more severe cases degeneration of the axon occurs, leading to denervation.\textsuperscript{13}

To successfully identify important physiological changes and diagnose carpal tunnel syndrome, clinical and research evaluation techniques and tools must be able to assess for problems in these areas. Unfortunately, most of the current diagnostic techniques evaluate secondary dysfunction at the cellular level, typically occurring in late or chronic stages of injury. An evaluation technique that is able to identify early changes in connective tissue and vascular flow may be a more useful tool in preventing significant injury or nerve damage that occurs in late or chronic stages that affect the cellular level.

1.2 Clinical Evaluation & Diagnosis

Historically, evaluation and diagnosis of carpal tunnel syndrome has relied on patient reports of symptoms, clinical provocative tests, magnetic resonance imaging (MRI) and electromyography/nerve conduction studies. Positive symptoms of carpal tunnel syndrome involve motor, sensory, and autonomic nerve impairment\textsuperscript{18}
characterized by numbness and tingling in the median nerve distribution of the hand, hypotrophy of the thenar musculature, dropping of items, and decreased sweat function in the hand, with symptom exacerbation at night and after frequent or repetitive use of the wrist and hand.\textsuperscript{13, 18-21} Clinical and epidemiological diagnosis of carpal tunnel syndrome is reliant upon both symptoms and positive clinical tests combined with positive electromyographic results.\textsuperscript{21}

To assess physiologic changes due to interventions aimed at prevention of future pathology or effective treatment of current pathology in an effective manner, it is imperative that the evaluation and diagnostic tests and measures are useful as well as reliable and valid. Each of the techniques and tools for diagnosing carpal tunnel syndrome vary on utility and quality criteria, and all diagnostic measures remain controversial.\textsuperscript{22}

\textbf{1.2.1 Clinical Provocative Tests}

The initial method of evaluating for carpal tunnel syndrome is through provocative tests, including Phalen’s\textsuperscript{23} and Reverse Phalen’s, Tinel’s,\textsuperscript{24} and carpal tunnel compression tests. These tests are utilized clinically to elicit symptoms of numbness in the median nerve distribution of the hand. In theory, these tests cause symptoms of secondary dysfunction of nerve transmission translated through overload or low blood flow scenarios. While positive tests are indicative of possible carpal tunnel syndrome, a high positive predictive value compared to gold-standard evaluation is not always realized\textsuperscript{21} and overall sensitivity and specificity are generally poor.\textsuperscript{19, 25} Additional
concerns in reliability and validity of these tests arise due to significant variability noted in the method of application across evaluators. A general paucity of studies examining the reliability of these tests places validity of the tests in jeopardy. Only one study reported inter- and intra-rater reliabilities for these provocative tests as satisfactory, however, skewing of the reliability results is possible because of a poor study design utilizing two expert raters with a subject population with low rate of pathology. Other studies report reliability that is considerably lower than satisfactory for these tests, usually due to the lack of a well-designed methodology.

With overall reliability and validity in question, the utility of these tests may be limited. Because of the poor quality criteria, these tests may be best suited for screening the presence or absence of possible carpal tunnel syndrome symptoms. Studying the relationship of these test results to all variables involved in the development of musculoskeletal pathology may result in a better interpretation for positive results. Accuracy of these tests may be relative to severity or chronic nature of the pathology. It is also possible that instead of directly indicating secondary dysfunction, these measures might be assessing other pathology that contributes to carpal tunnel syndrome symptoms, e.g. tenosynovitis.

1.2.2 Electrodiagnostic Testing

While provocative testing is the clinical standard for initial evaluation of carpal tunnel syndrome, electromyographic (EMG) and nerve conduction testing has long been considered the diagnostic gold standard. These tests can confirm neuropathy in the
median nerve as an underlying cause of the secondary symptoms reported with provocative tests. These tests can identify the severity of nerve pathology, provide baseline measures, and can rule out other neurological conditions (e.g. C6-C7 lesions, brachial plexus injury, general polyneuropathy). As pathology progresses and demyelination of the median nerve increases, conduction velocities measured by surface electromyography in both motor and sensory pathways within that nerve will be slowed or may fail entirely. Needle electromyography (EMG) can be used to determine the extent of damage that has occurred in the nerve by investigating specific muscle activations innervated by the median nerve. Needle EMG measures the size, shape, and patterns of motor unit potentials.

Intraoperative studies have confirmed nerve conduction results in carpal tunnel subjects when directly localized to the median nerve under the transverse carpal ligament, giving credibility and validity for the use of nerve conduction tests as a gold standard for diagnosing carpal tunnel syndrome. In a group of symptomatic individuals, sensitivity for nerve conduction testing has ranged between 40% and 80% with specificity being 95%-100%, indicating a good use of nerve conduction for ruling in carpal tunnel syndrome.

1.2.3 Magnetic Resonance Imaging

With a relatively high sensitivity and specificity achieved by combining provocative clinical tests with EMG, few other evaluation techniques are utilized. Magnetic resonance imaging (MRI) is primarily used as an imaging technique for carpal
Because MRI does not evaluate symptoms, it is better suited as a technology to understand underlying physiologic changes that may be related to carpal tunnel syndrome and has been useful in contributing to epidemiological studies. Using MRI, changes in the area of the carpal tunnel in various wrist positions can be quantified as well as the direction of movement of the structures within the carpal tunnel based on various wrist positions. MRI is therefore useful in identifying the amount of compression or changes in relative size of the median nerve based on these positions, as well as due to any other inflammation or edema of the structures within the carpal tunnel. However, similar to provocative testing, variations in methodologies and specific measurement sites have lead to variable levels of reliability in evaluation of the carpal tunnel and significant discrepancies in measures. Whereas previous techniques were reliant on secondary dysfunction, MRI can identify acute changes; however, this tool has significant limitations including lack of portability, patient discomfort, inability to complete dynamic imaging, and cost that dramatically reduce utility as a research tool in large-scale, prospective longitudinal research studies.

1.2.4 Ultrasonography

Beginning around 1990, ultrasonography was proposed as an alternative means for evaluating carpal tunnel syndrome and within the past decade, research on diagnostic measurements of the size and location of the median nerve has become increasingly prevalent.
Figure 1.2 provides a sample of the high-quality images with well-defined structures, resulting in valid measures between multiple researchers of anterior-posterior diameter, cross-sectional area, and anterior transverse carpal ligament bulge. The carpal tunnel is visualized at the level of the scaphoid (Sca) and pisiform (Pis) bones. The median nerve (arrowhead in right image) is positioned anterior to the flexor pollicis longus (FPL), flexor digitorum superficialis (S) and profundus (P) tendons and posterior to the transverse carpal ligament (arrowheads in left image, curved arrow in right image). The flexor carpi radialis (FCR) lies laterally and the ulnar artery and nerve lie in Guyon’s canal medial to the carpal tunnel.

Studies comparing ultrasonography results to nerve conduction testing in the elbow and wrist have shown positive correlation between ultrasonographic measures of nerve cross sectional area and decreased nerve conduction. Ultrasonography can successfully identify nerve compression and other pathologic changes due to
tendonosis, edema, and other swelling in the carpal tunnel leading to the secondary
dysfunction in the median nerve\textsuperscript{22, 47} evaluated by nerve conduction testing. Four
methods that have become increasingly prevalent for ultrasonographic diagnoses of
carpal tunnel syndrome:\textsuperscript{45}

(1) Increase in cross-sectional area at the level of the pisiform bone

(2) Increase in the cross-sectional area at the level of the pisiform bone
    compared with the cross-sectional area at the level of the distal radius
    (swelling ratio)

(3) Increase in the flattening ratio at the level of the hook of the hamate

(4) Palmar bowing of the flexor retinaculum

Each of these diagnostic methods has been compared to the gold standard of
nerve conduction testing, but none has been determined as the most specific and
sensitive, nor predictive of carpal tunnel syndrome\textsuperscript{48} and there is considerable variability
in overall diagnostic results across all studies.\textsuperscript{49} Bowing of the flexor retinaculum has
shown moderate diagnostic and predictive ability\textsuperscript{50} with a cut-off distance of > 4.0
mm.\textsuperscript{51} Suggested use of a flattening ratio of > 3 in the distal carpal tunnel as a
diagnostic indicator of carpal tunnel syndrome\textsuperscript{51} has not been confirmed by other
researchers.\textsuperscript{52} Instead, most notable changes in the nerve are in the proximal region of
the carpal tunnel.\textsuperscript{43, 45, 52} Carpal tunnel syndrome appears to become more prevalent
when cross-sectional area at the level of the pisiform increases beyond a minimum
threshold of 9.0\textsuperscript{53}, 10.0\textsuperscript{55}, or 11.0\textsuperscript{43} mm\textsuperscript{2}; however, research has indicated diagnostic
threshold measures of up to 15 mm$^2$.\textsuperscript{56} Calculating change scores in cross-sectional areas between multiple points has improved sensitivity and specificity of diagnostic criteria. Initially this change was calculated between the area at the pisiform and the distal radius with moderate success. Recent studies reported improved sensitivity and specificity to near 100\% by modifying this method to determining the change between CSAs at the proximal carpal tunnel and the forearm.\textsuperscript{56, 57}

Research protocols for evaluation of median nerve pathology using gold-standards have been restricted to clinical application due to equipment restrictions; however, cutting edge processing technology packaged in smaller units is continually increasing the prevalence of hand-carried ultrasound units (HCU) for mobile diagnosis and treatment.\textsuperscript{58} Research and clinical use of HCUs has been focused primarily in cardiography with mixed results regarding the benefits and ability to accurately diagnose patients.\textsuperscript{59-61} Anecdotal use of HCU for musculoskeletal purposes has been reported;\textsuperscript{58} however, there is a general paucity of literature describing the successful use and limitations of current HCU technology for musculoskeletal evaluation.

While research relative to the utility and validity of diagnostic techniques for carpal tunnel syndrome is extensive, research that investigates these techniques in early detection, prevention, and remediation of pathology is lacking. Because provocative tests and nerve conduction studies rely on evaluation of secondary dysfunction, the use of MRI and ultrasonography are better choices for preventative and interventional research. Due to the portability, subject comfort, ease of use and other benefits (i.e.
low cost), the latter has many advantages over the former. Therefore, research protocols utilizing ultrasonographic techniques to identify early changes in the upper extremity biomarkers may indicate progression of pathology and may be more useful than all other current research tools. Additional research is necessary to validate the use of ultrasonography as a new method for measures of acute physiological changes related to the risk factors and stressors linked to UE WRMSD.

1.3 Risk Factors

Many personal, environmental, behavioral, ergonomic, and an unending list of unknown factors combine together to increase risk of WRMSDs. The most significant personal factor is gender. Research indicates that the prevalence of musculoskeletal disorders is twice as high in females as in males and in certain working populations, the prevalence of carpal tunnel syndrome may be up to as much as 4.4 times more in females. Age, years of work, and overall negative work exposures show an expected positive relationship to upper extremity complaints in the working population. Additionally, a significant body of literature relates psychosocial factors, especially job demands, control, and social support to work related upper extremity disorders. Unfortunately, even with the large number of studies on all of these factors, the relative importance and dose-response relationships of physical, psychosocial, and personal factors remains unknown.
1.3.1 Psychosocial Stressors and Risk Factors

Psychosocial stressors have been related to neck\textsuperscript{67} and upper extremity\textsuperscript{68} symptoms and must be closely considered as risk factors in studies of upper extremity disorders.\textsuperscript{69} While the risk is greatest when both physical and psychological exposures are high, epidemiological research indicates that regardless of the extent of physical exposure, an increase in exposure to psychological stressors is related to an increase in wrist and hand symptoms.\textsuperscript{68} Of the numerous psychosocial stressors, psychological demands, job control, supervisor and co-worker support, have been linked to changes in health status\textsuperscript{70} and have a fundamental impact on health related quality of life.\textsuperscript{71}

A widely cited measure of job stress in current literature is the interaction of two of these factors, the demands made on a worker and his or her control over those demands.\textsuperscript{72} The resulting job strain model (Figure 1.3)\textsuperscript{72} of the interaction of these factors provides four quadrants of job styles that can be used to classify and theoretically predict adverse health effects in workers. Along the strain line, high demands and low control (decision latitude) occurring simultaneously create high psychological strain, whereas, low demands and high decision latitude results in low psychological strain. Along a second line, stress associated with active jobs, high demands and high control, is desirable stress that increases motivation and promotes learning in workers. Conversely, passive jobs requiring minimal psychological demands and low control over the work encourages stagnation of the worker.
Figure 1.3 Job demand-control model

UE WRMSD research can, and has, used the categories of the job strain model to describe the psychosocial impact of work on employee health. Machine-paced operative work that requires little variation in the work tasks but requires close attention to be paid to the quality and safety of the work, has been identified as high-strain work. On the other hand, passive work that may continue to be monotonous, but has no standards or repercussions, such as piecework, also correlates to increased musculoskeletal symptoms. Research has shown that office and clerical jobs are more likely to fall into the passive or high-strain quadrants than other job titles, that may be an indication of a link for psychosocial stressors to musculoskeletal disorders in these
populations. While numerous research studies have observed psychosocial factors in cross-sections of working populations, only one research study has looked prospectively at the interaction of psychosocial factors and UE WRMSD. Furthermore, no current studies have accurately described the relative relationship of the multiple psychosocial factors to UE WRMSD.

1.3.2 Physical Stressors and Risk Factors

While psychosocial stress factors are still somewhat unknown, there is a plethora of research on physical stressors and risk factors that contribute to upper extremity work related musculoskeletal disorders, specifically to median nerve pathology. Physical and environmental stressors that contribute to increased compression of the median nerve include extreme positions (flexion/extension/deviation), repetitive movements, pinching/gripping, direct pressure, and vibration. Animal models have been used to show physiological changes due to forces and frequency of use of the hand/wrist in repetitive or awkward positions. Compression on the median nerve has since been studied in multiple rabbit models, all indicating a disruption of nerve conduction due to direct compression and direct compression was found to have a relationship to changes in vascular flow within the nerve.

Animal models have evaluated the effect of both acute and chronic entrapment due to direct compression, but none of these methods relate directly to external loads that are more clinically relevant. Some animal studies have shown that highly repetitive work activities, even with negligible forces can lead to changes in the
pathological presentation of the median nerve, especially increased fibroses caused by collagen up regulation in the epineurium. These changes lead to decreased nerve conduction velocities and have been replicated in monkeys using a combination of repetitive wrist flexion and moderate force through pinching. Human studies have observed similar outcomes with increased pinching and loading of the fingertips causing pressure on the median nerve to be increased.

With evidence of compressive forces and exposure to repetitive or awkward postures leading to nerve pathology in animal models, further research has identified specific forearm, wrist, finger postures that increase carpal tunnel pressure and contribute to carpal tunnel syndrome. Forearm movement into either pronation or supination can cause increased pressure on the median nerve and the carpal tunnel. Wrist flexion and extension have both been observed to reduce the area within the carpal tunnel, but due to the anterior traveling flexor tendons with wrist flexion, the greatest compression of the median nerve occurs when the wrist is in flexion. Additionally, pressures within the median nerve increase during wrist flexion due to the traction of the nerve. In carpal tunnel syndrome patients with restricted excursion of the nerve, this traction is even further increased, causing additional pressure and decreased function of the nerve. Finally, greater ulnar deviation has been associated with higher prevalence of carpal tunnel syndrome symptoms in a working population.
Prolonged exposure to highly repetitive and forceful hand-wrist tasks is commonly acknowledged as a primary physical risk factor for carpal tunnel syndrome.\textsuperscript{77} Within minutes, the pressure on the nerve due to these non-neutral positions can cause changes in myelination and affect median nerve function. Repetitive short durations of compression applied for 2-hour periods can cause increased symptoms and decreased function due to significant pathological changes.\textsuperscript{79} Keyboarding and mouse activity are typical highly repetitive activities involving static non-neutral postures and increased fingertip pressures. This encompasses numerous physical risk factors for carpal tunnel syndrome that contributes to an increased incidence rate.\textsuperscript{85}

### 1.3.3 Personal Stressors and Risk Factors

Similar to physical factors, there is an overwhelming number of research studies on personal factors that lead to etiology and pathophysiology of carpal tunnel syndrome, such as gender, wrist ratios/anthropometry, and co-morbidities.\textsuperscript{86} Of the numerous factors studied, no studies have identified any one factor having a direct relationship to the development of carpal tunnel symptoms. Instead, it is likely that a combination of factors can increase an individual’s risk for developing median nerve pathology. In current research, data indicate that gender and anthropometric measures are the two most likely relevant personal factors in the etiology of carpal tunnel syndrome.

Many studies relating the incidence of work-related injuries and disorder to gender indicate no significant difference between males and females.\textsuperscript{87, 88} However,
studies that focus on upper extremity disorders show a striking effect of gender, with females being much more likely to have symptoms in hand/wrist.\textsuperscript{74,87-91} In fact, females may be as much as twice as likely to experience disorders of the upper extremity,\textsuperscript{91} which in turn can lead to females also being twice as likely to report decreased productivity.\textsuperscript{88} The reasons for this increased risk in females is unknown, but an interaction with the exposure to different physical and psychosocial factors in the work environment may be directly responsible for differences in the occurrence of musculoskeletal symptoms by gender.\textsuperscript{87} This relationship has been shown in motor unit activation in the upper trapezius, with a significant increase in women when negative psychological stress is reported,\textsuperscript{92} but has yet to be closely assessed in median nerve pathology.

Additionally, anthropometric measures and physiologic compositions may be different based on gender. Female flexor tendons tend to occupy more space within the carpal canal.\textsuperscript{93} Similarly, while gender differences are not known, the lumbricals from the hand tend to become space-occupying muscles within the carpal canal during certain movements and activities.\textsuperscript{94,95} Together these two factors can lead to increased pressure on the median nerve if adequate space is not available within the carpal tunnel. The space that is available within the carpal tunnel may be directly related to the individual wrist ratio. Wrist ratio, calculated as the anterioposterior dimension divided by mediolateral dimension, is a primary factor in predicting the development of carpal tunnel syndrome.\textsuperscript{96-98} More than seventy-five percent of all individuals with carpal
tunnel syndrome have a square-shaped wrist (ratio > .70) and a more significant rate of association was noted as the ratio increased (> .75). There is good sensitivity and specificity for diagnosing carpal tunnel syndrome in symptomatic patients when applying this ratio rule to gold-standard diagnostic techniques.

1.4 UE WRMSD Research Models

While research has identified a myriad of factors that mediate the development of upper extremity disorders, current research literature is inconclusive as to any one factor having a direct causal relationship to UE WRMSD. This creates significant challenges for developing a model of UE WRMSDs and very little empirical support exists for any one framework of pathways. A complex theoretical model for describing the influence of these factors has been developed, from which focused models for studying UE WRMSDs must be designed and tested to understand etiology.

Many models have been created in an attempt to describe and predict the interactions of a variety of factors thought to lead to upper extremity disorders in low impact work, and research trends have grouped the factors that can lead to WRMSD into three categories: biomechanical exposure, psychosocial stressors, and personal risk factors. Of the numerous theoretical models that have been developed, the work style model (Figure 1.4) attempts to capture the interaction of both psychological and physical factors in the work environment by describing the relationship to multiple dimensions of the individual work style, that is, how the worker performs his or her task. The resulting changes in behavioral, cognitive, and
physiological components of the individuals’ work style can influence the individual’s work-related symptoms, disorders, and eventual work disability.\textsuperscript{104} It is imperative to note that work style is not personality driven, but “a learned and reinforced strategy for completing, responding to, or coping with increased job demands that may affect musculoskeletal health.”\textsuperscript{84}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{workstyle_model.png}
\caption{Workstyle model\textsuperscript{104}}
\end{figure}

The inclusion of both physical and psychosocial factors in UE WRMSD research models studying etiology, preventative interventions, and rehabilitation is appropriate, as an interaction between these factors does exist.\textsuperscript{68} Numerous additional personal factors influence both the physical and psychosocial aspects of UE WRMSD etiology, and
a lack of control for all the confounding variables is a frequent limitation in this line of research.62 Since reduction of disorders and work disability is the primary goal of WRMSD research, the work style model provides a framework for investigating psychosocial, ergonomic/physical, and other personal risk factors needed to develop appropriate interventions and reduce UE WRMSD. What is known and what lacks validation regarding these stressors, carpal tunnel syndrome diagnosis, and interventions follow in a concise review that provides a rationale for this much-needed research.

1.5 Research Aims

Carpal tunnel syndrome continues to have a significantly high rate of occurrence in the working population, limiting individual functional performance and participation, and can be costly due to medical expenses and lost productivity. While psychosocial, physical, and personal stressors have all been identified as potential risk factors for carpal tunnel syndrome, little research has been conducted to evaluate the interrelationships and combined effects of each of these factors to identify the most salient stressors. Additionally, due to a lack of efficient and cost-effective technology, little research has investigated acute physiologic changes in the upper extremity and median nerve due to such stressors. Instead, studies measure secondary, chronic changes in nerve conduction of symptomatic individuals. In order to move toward intervention techniques that effectively reduce salient risk factors for carpal tunnel syndrome continues to have a significantly high rate of occurrence in the working population, limiting individual functional performance and participation, and can be costly due to medical expenses and lost productivity. While psychosocial, physical, and personal stressors have all been identified as potential risk factors for carpal tunnel syndrome, little research has been conducted to evaluate the interrelationships and combined effects of each of these factors to identify the most salient stressors. Additionally, due to a lack of efficient and cost-effective technology, little research has investigated acute physiologic changes in the upper extremity and median nerve due to such stressors. Instead, studies measure secondary, chronic changes in nerve conduction of symptomatic individuals. In order to move toward intervention techniques that effectively reduce salient risk factors for carpal tunnel syndrome.
syndrome, relationships between risk factors must be better understood and novel tools and methodologies must be established to study acute physiologic changes.

Advances in ultrasonography have positioned this imaging technology as a novel tool for investigating acute physiologic changes in work related musculoskeletal disorder research. With a validated tool to measure these changes, the ability to study physiological changes over time can promote a better understanding of salient risk factors in the development of disorders and increase the quality of prospective research designs. Studies have begun to explore novel approaches using ultrasonography and the investigation of multiple various risk factors in undiagnosed populations. These preliminary studies provide evidence that ultrasonography is a valid tool for studying median nerve, but methodologies and measurements require further study and comparison to gold standards (Figure 1.5).
Data on various stress factors can be collected and related to carpal tunnel syndrome using subjective questionnaires, observational methods, and physiologic measures for informing preventative interventions. However, studies investigating the effects of various factors on the development of upper extremity disorders tend to lack comparison of risk factors to acute physiological changes (Figure 1.6).
It is hypothesized that, given a standardized protocol, ultrasonography can be a valid, non-invasive screening tool for investigating physiologic and morphologic changes related to the development and diagnosis of carpal tunnel syndrome. The following research goals are proposed to test this hypothesis and lay a foundation for future high-quality, longitudinal studies:

1. Evaluate various methodologies and measurement protocols to determine clinical guidelines for using ultrasonography as a clinical and research tool for investigating median nerve pathology. (Chapter 2)
2. Determine the diagnostic accuracy of ultrasound measures as compared to the current gold standard of electrodiagnostic testing. (Chapter 3)

3. Investigate the relationship of physiologic ultrasound measurements to salient factors related to carpal tunnel syndrome in the working population. (Chapter 4)
1.6 References


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78. Diao E, Shao F, Liebenberg E, Rempel D, Lotz JC. Carpal tunnel pressure alters median nerve function in a dose-dependent manner: a rabbit model for carpal tunnel syndrome. *J Orthop Res.* Jan 2005;23(1):218-223.


Chapter 2: Diagnostic accuracy of ultrasonography versus electromyography in carpal tunnel syndrome: A systematic review of literature

Carpal tunnel syndrome (CTS) is characterized by motor, sensory, and autonomic nerve impairment resulting in numbness and tingling in the median nerve distribution of the hand, atrophy of the thenar musculature, dropping of items, and decreased sweat function in the hand, with symptom exacerbation at night and after frequent or repetitive use of the wrist and hand.\textsuperscript{1-5} Historically, clinical diagnosis of CTS is reliant upon a combination of these patient reported symptoms with positive clinical provocative tests and positive electrodiagnostic (EDX) results.\textsuperscript{3, 6} Positive predictive values and overall sensitivity and specificity have been generally poor for provocative tests.\textsuperscript{1, 7} Furthermore, while specificity may be high for EDX testing, significant variability in sensitivity and moderate rates of false-negatives exist.\textsuperscript{8, 9}

In response to the variability of these tests, new methods continue to be developed and tested. Of these new methods, ultrasonography has gained traction as a possible tool for use in clinical evaluation and research on median nerve pathology. Because ultrasonography is pain-free, relatively inexpensive, allows for dynamic evaluation and is becoming more portable, this tool is perfectly situated as a diagnostic tool for musculoskeletal and neurological impairments.\textsuperscript{10, 11} Researchers have
investigated the diagnostic ability of ultrasonography for carpal tunnel syndrome; unfortunately, similar to provocative tests and EDX, each of the ultrasonographic techniques and tools suggested for diagnosing CTS varies on utility and quality criteria. Therefore, diagnostic measures remain controversial and standard measurement techniques have not been determined.

As the use of ultrasonography for evaluation of the median nerve in CTS increases, periodic syntheses of the research evidence can provide direction to research and standardize methods and measures. The first such review of literature on the topic synthesized results of 7 studies published between 1991 and 2001 and was reported in 2003. While the review indicated that sonography was a promising tool for the diagnosis of CTS in place of EDX, standardization of techniques and determination of specific diagnostic values was needed to improve utility. Furthermore, these studies did not compare ultrasonography measures to EDX, did not differentiate carpal tunnel severity and did not establish cut-off values.

A second review of literature was completed that compared results of 13 studies completed between 1999 and 2006 (three of the articles were included in the earlier review). Similar to the previous review, Seror indicated the lack of convincing evidence for a specific cut-off value to be problematic for the diagnostic utility of sonography, both in the variability across all studies and the method by which the cut-points were calculated. This, along with numerous other arguments, resulted in a conclusion in contrast to the previous review, which indicated that ultrasonography was
not an acceptable alternative to EDX, but at most complementary. While sonography can identify morphological changes, entrapment and/or lesion of the median nerve, it has limited utility for differential diagnosis in idiopathic CTS.

Despite the review by Seror, research reports continue to be published promoting the use of sonography in the diagnosis of CTS. Furthermore, while both reviews indicated that the diagnostic utility of sonography was limited by inconsistency of methods and a lack of identification of specific diagnostic cut-points, it is not clear that current research has moved toward resolution of these issues. Because disagreement exists between previous reviews, discrepancies continue to exist in current research, three years have elapsed since the last review and methodology of previous reviews is not consistent with a full systematic search of literature, a full systematic review of published literature is needed to establish the current utility of ultrasonography in the diagnosis of CTS.

Therefore, the initial purpose of this study was to complete a full meta-analysis of high-quality research to determine accuracy and specific cut-points of sonographic measures for diagnosing carpal tunnel syndrome as compared to electrodiagnostic testing. Diagnostic parameters evaluated by the analysis included: (1) cross-sectional area at the pisiform bone, (2) swelling ratio of cross-sectional area at the pisiform bone compared with area at the distal radius, (3) flattening ratio at the level of the hook of the hamate and (4) palmar bowing of the flexor retinaculum.16 Due to a lack of consistency in design and methods within the included studies, we could not statistically
combine individual study results. Therefore, this report presents a full systematic synthesis of the utility of ultrasound, both for the aforementioned measures and other diagnostic criteria, relative to EDX in diagnosing carpal tunnel syndrome.

2.1 Methods

Three search methods were used to ensure a full systematic review of both published and unpublished literature, including (1) database search, (2) hand-search, and (3) contact with authors. Database searches for studies were conducted using PubMed for MEDLINE, CINAHL, Cochrane, BIOSIS Previews, Health Source Nursing/Academic, PsychINFO, SPORTDiscus, and ProQuest Dissertation Abstracts. Standardized search terms included any combination of ‘median neuropathy’ or ‘carpal tunnel’ and ‘ultrasonography’, ‘ultrasound’, or ‘sonography’. Search results were limited to studies published in the past 10 years (i.e. 2000-2009); however, studies of any methodological designs and of any language were included in the original searches. Figure 2.1 details the inclusion process for this review.
Following initial search of all databases, 495 abstracts were obtained. A secondary hand-search occurred by searching bibliographies of review and key articles as well as a hand-search through results obtained from a world wide web search through Google Scholar. The secondary search resulted in the addition of 87 abstracts. Duplicates were removed and 407 abstracts were screened for inclusion in the review.
To eliminate bias, the first and third authors screened all abstracts. Each screener independently read each abstract to determine the possible fit of the article with the systematic review. The screeners marked any abstracts that included diagnostic ultrasonography and a reference to carpal tunnel syndrome or median nerve pathology. All abstracts that were marked for inclusion by either screener were moved forward for review of the full text; therefore, no method was required for reconciliation between results of the two independent screeners. Based on the screening of abstracts, the full-text reports of 135 articles were obtained for rating and final determination of inclusion in the review.

Prior to reviewing the full-text articles, inclusion criteria were discussed by the authors and the methodology for rating the articles was agreed upon. Inclusion criteria included:

(1) Sonographic measurements of the median nerve for one or more of the following: cross-sectional area, swelling ratio (radius to pisiform or forearm to pisiform), flattening ratio, or palmar bowing of the retinaculum;

(2) At least one electrodiagnostic (EDX) measure for comparison to sonography or classification of CTS;

(3) Linear array ultrasound transducer with frequency of $\geq 10$ MHz;
(4) Clearly described ultrasound and EDX methodologies consistent with all literature;

(5) Research designs that included: a detailed description of subject inclusion and exclusion criteria to ensure idiopathic CTS; adequate sample size for statistical power (e.g. no case study reports); detailed methodological protocols allowing for replication; and data analysis that reported variability and used statistical tests relevant to the level of data collected.

The first and third authors reviewed the full-text of all 135 articles based on these criteria. Each rater tracked responses to the inclusion criteria and made a final recommendation for inclusion or exclusion of the article. Disagreement between raters was settled through consensus and the second author was available to review articles when consensus by the two primary raters could not be reached. For any articles with limited data or unclear methods, attempts were made to contact authors to ensure all data were available for final inclusion in this review. Following rating of all full-text, 23 articles were included into the final review process. The primary reason for article exclusion was due to methodological limitations that did not meet inclusion criteria or for a lack of data reporting comparative results. Articles that were methodologically sound but did not include EDX testing (n = 10) or researched the median nerve in
specific diagnoses other than idiopathic carpal tunnel syndrome (n = 19) were excluded from the aggregate, but were maintained for purpose of enhancing the discussion in this review.

Data were extracted from all included articles for methods, measures and outcomes of the studies. During data extraction, the type of extracted data and comparative Tables were continually modified such that a valid interpretation and synthesis of the included articles could be completed based on variations in the studies. Data extraction was completed by the first author and random reliability checks were completed by the third author to ensure data had been extracted completely and correctly. All final data Tables are referenced within the results section of this systematic review.

Important research design components extracted from the studies were patient and equipment information, reference standards, and quality control within the study. The age, gender, and total number of individual wrists within the patient and control subject groups were determined and the type of ultrasound equipment and transducer were recorded. Studies were classified based on the use of clinical symptoms and/or EDX as the reference standard. Finally, data were extracted relative to reported quality assurance of equipment and standardization of measurement protocols to ensure reliability and validity of results within the articles.

Both ultrasonographic and EDX measurements chosen by the authors within each study were recorded. While the studies often collected numerous ultrasound and
EDX measurements, only those measurements that were used in final comparative analysis were extracted for purposes of this review. For each of the measures, the reference standard used within the study was recorded and ultrasound measures were further classified based on how the authors had derived the standard (i.e., previous literature, calculated by ROC curves, or control mean+2 S.D.). Finally, data were extracted relative to the determination of the use of EDX to create dichotomous or severity classifications within subjects and/or for independent diagnostic accuracy based on clinical symptoms.

Once all methodological and measurement data were extracted, articles were reviewed for statistics relative to diagnostic accuracy or of a comparative nature. Sensitivity and specificity were extracted from each article and sorted according to the test measures and reference standard utilized. When these statistics were not reported, but adequate data were available in the article, sensitivity and specificity were calculated. Because the purpose of this review was to determine the utility of ultrasound as compared to EDX, correlation and comparative statistics between control and patient groups were not recorded. However, articles that reported comparative statistics between ultrasound and EDX measures were recorded when deemed relative to the synthesis of data within this review.

2.2 Results

The findings include a description of the study populations, number of subjects, methodology of diagnostic criteria measured (ultrasonography and reference standard),
and comparison results (sensitivity and specificity) from each of the 23 studies. A summary of these data follows.

2.2.1 Subjects

Studies with similar inclusion and exclusion criteria were used for analysis. Exclusion criteria included pregnancy, history of previous CTS surgery, and presence of known neurological or systemic disorder that could contribute to CTS (e.g. diabetic neuropathy, thyroid disorders, and other polyneuropathies). Additionally, all studies indicated that subjects with anatomical abnormalities such as bifid median nerve and persistent median artery were excluded. Case reports and studies with less than 20 subjects in the patient group were excluded from the review to ensure appropriate power was achieved within each individual study report. One study varied from these inclusion criteria as recruitment included only those subjects with CTS symptoms but negative EDX results.\textsuperscript{17} Methodological characteristics of all studies included in this review are included in Table 2.1.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subject/Wrists (age, % female)</th>
<th>Control/Wrists (age, % female)</th>
<th>Subject diagnostic classification system (n)</th>
<th>US machine/transducer</th>
<th>US measures (dx threshold)</th>
<th>EDX measures (dx threshold)</th>
<th>Quality control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayrak et al. 2007</td>
<td>27/47 (43.6 yrs, 78%)</td>
<td>20/40 (37.5 yrs, 65%)</td>
<td>Normal (6)</td>
<td>Toshiba PowerVision 7000 / 10 MHz liner</td>
<td>CSAw</td>
<td>Z scores calculated based on a reference value not provided.</td>
<td>EDX-US within 1 week</td>
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<td></td>
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<td>Minimal (8)</td>
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<td>CSAp</td>
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<td>Mild (6)</td>
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<td>CSAh</td>
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<tr>
<td>Hobson-Webb et al. 2008</td>
<td>44/44 (52.4 yrs, 77%)</td>
<td>18/18 (39.2 yrs, 44%)</td>
<td>-</td>
<td>Philips HDI 5000 / 15-7 MHz linear</td>
<td>CSAw (&gt;10mm²)</td>
<td>DML (&gt;4.4ms)</td>
<td>EDX-US on same day</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CSAw-f Ratio (&gt;1.4)</td>
<td></td>
<td>Skin temp 34°C</td>
</tr>
<tr>
<td>Hobson-Webb and Padua 2009 Site 1</td>
<td>46 / 46 (52.6 yrs, -)</td>
<td>-</td>
<td>0-5</td>
<td>Philips HDI 5000 / 7-14 MHz linear</td>
<td>CSAw (&gt;14mm²)</td>
<td>DML (&gt;4.4 ms)</td>
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<td>CSAf @ 12 cm</td>
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<td></td>
<td>CSAw-f Ratio (&gt;1.5)</td>
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<td>Site 2</td>
<td>50 / 50 (52.8 yrs, -)</td>
<td>-</td>
<td>0-5</td>
<td>BK Medical Falcon Pro Focus 2202 / 5-12 MHz linear</td>
<td>CSAw (&gt;10mm²)</td>
<td>SCV thumb-wrist (&gt;42 m/s)</td>
<td>EDX-US within 1 week</td>
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<td>CSAf @ middle 1/3</td>
<td>SCV palm-wrist (&gt;37 m/s)</td>
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<td>CSAw-f Ratio (&gt;1.5)</td>
<td>DML (&gt;4.0 ms)</td>
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<td>-</td>
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<td>Karadag et al. 2009</td>
<td>54 / 96 (43.3 yrs, 93%)</td>
<td>-</td>
<td>Normal (49)</td>
<td>Esaote MyLab 70 / 6-18 MHz linear</td>
<td>CSAp</td>
<td>SCV</td>
<td>EDX-US within 2 days</td>
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<td>Mild (22)</td>
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<td>DML</td>
<td>Skin temp 32° - 34°C</td>
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<td>Moderate (15)</td>
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<td></td>
<td>Severe (11)</td>
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<tr>
<td>Kele et al. 2003</td>
<td>77 / 110 (52 yrs, 77%)</td>
<td>33 / 55 (44 yrs, 60%)</td>
<td>-</td>
<td>GE Logiq 500M / 11 MHz linear</td>
<td>Compression Sign</td>
<td>SCV</td>
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<td></td>
<td>CSAw (&gt;11mm²)*</td>
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<td></td>
<td>-</td>
<td>&gt;70 yrs: &lt;40 m/sec</td>
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<tr>
<td>Kleuser et al. 2009</td>
<td>68 / 100 (57.9 yrs, 76%)</td>
<td>58 / 93 (55.1 yrs, 72%)</td>
<td>Mild-Moderate (41)</td>
<td>Esaote MyLab90 / 8-14 MHz or 6-18 MHz linear</td>
<td>CSA – maximum within tunnel (&gt;10, 11, or 12mm²)</td>
<td>SCV</td>
<td>EDX-US within 2 weeks</td>
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<td>CSAf</td>
<td>DML</td>
<td></td>
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<td>Koyuncuoglu et al. 2005</td>
<td>43 / 59 (43 yrs, 91%)</td>
<td>15 / 30 (40.7 yrs, 87%)</td>
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<td>CSAp (&gt;10.5mm²)</td>
<td>DML (&gt;4.2ms)</td>
<td>EDX-US within 1 week</td>
</tr>
</tbody>
</table>

Table 2.1 Characteristics and study design for all studies included in the analysis (listed alphabetically)
Table 2.1 Continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subject/Wrists (age, % female)</th>
<th>Control/Wrists (age, % female)</th>
<th>Subject diagnostic classification system (n)</th>
<th>US machine/transducer</th>
<th>US measures (dx threshold)</th>
<th>EDX measures (dx threshold)</th>
<th>Quality control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurca et al. 2008</td>
<td>37/74 (56 yrs, 76%)</td>
<td>25/50 (51 yrs, 72%)</td>
<td>-</td>
<td>Esaote Megas CVX / 10 MHz linear</td>
<td>CSAp (&gt; 0.1cm²)*</td>
<td>DML (&gt;4.6 ms) DSL (&gt;3.8 ms)</td>
<td>Skin temp &gt; 30°C</td>
</tr>
<tr>
<td>Kwon et al. 2008</td>
<td>29/41 (53.0 yrs, 86%)</td>
<td>29/41 (53.0 yrs, 86%)</td>
<td>-</td>
<td>Philips HDI 5000 / 12-5 MHz liner</td>
<td>CSAp (&gt;10.7mm²)*</td>
<td>Sensory Amp (&lt;15uv) DSL (&gt;3.5ms) DML (&gt;4.0ms)</td>
<td>EDX-US within 1 week Skin temp &gt; 30.5°C</td>
</tr>
<tr>
<td>Mallouhi et al. 2006</td>
<td>151/206 (58 yrs, 71%)</td>
<td>-</td>
<td>-</td>
<td>Philips HDI 5000 / 7-15 MHz linear</td>
<td>Nerve Edema (hypoechoic signal) Max CSA w-h (&gt;0.11cm²) FR (&gt;3) RB (&gt;2mm) Hypervascularization (presence of intraneural vessel)</td>
<td>SCV (&lt; 62m/s) DML (&gt;3.9ms)</td>
<td>Retrospective Case Analysis</td>
</tr>
<tr>
<td>Mondelli et al. 2008</td>
<td>85/85 (46.8 yrs, 82%)</td>
<td>(controls used only for creating reference values)</td>
<td>0 (28) 1 (11) 2 (37) 3 (9) 4 (0) 5 (0)</td>
<td>Esaote Technos Mp / 5-10 MHz linear</td>
<td>CSAw (&gt;10.5mm²) CSAp (&gt;12.2mm²) CSAh (&gt;10.1mm²) SCV (&lt;45.2m/s) DML (&gt;4.4 ms)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Naranjo et al. 2007</td>
<td>68/105 (47.0 yrs, 82%)</td>
<td>-</td>
<td>Normal (25) Mild (13) Moderate (30) Severe (37)</td>
<td>GE Logiq 5 Pro / 12 MHz liner</td>
<td>CSAw (&gt;10.1 mm²)* CSAp (&gt;9.7 mm²)* CSAh (&gt;11.5mm²)* FRH (&gt;2.77)* RB (&gt;2.76mm)*</td>
<td>DML (&gt;3.4ms) DML (?)</td>
<td>-</td>
</tr>
<tr>
<td>Padua et al. 2008</td>
<td>54/54 (53.3 yrs, 80%)</td>
<td>-</td>
<td>Negative (3) Minimal (12) Mild (13) Moderate (9) Severe (12) Extreme (5)</td>
<td>BK-Medical Falcon Pro Focus 2202 / 12-5 MHz linear</td>
<td>CSAp (&gt;10mm³)</td>
<td>SCV DML</td>
<td>EDX-US on same day</td>
</tr>
<tr>
<td>Pastare et al. 2009</td>
<td>66 / 97 (51 yrs, 72%)</td>
<td>9 / 18 (31 yrs, 56%)</td>
<td>Negative Minimal Moderate Severe</td>
<td>GE E Logiq book / 12 MHz liner</td>
<td>CSAp (&gt;0.09 cm³)</td>
<td>SPL (&gt; 3.3 ms) DML (&gt; 4.0 ms)</td>
<td>EDX-US on same day Skin temp &gt;31°C</td>
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</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subject/Wrists (age, % female)</th>
<th>Control/Wrists (age, % female)</th>
<th>Subject diagnostic classification system (n)</th>
<th>US machine/transducer</th>
<th>US measures (dx threshold)</th>
<th>EDX measures (dx threshold)</th>
<th>Quality control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saracgil et al. 2009</td>
<td>54/100 (55 yrs, 100%)</td>
<td>25/45 (50 yrs, 100%)</td>
<td>-</td>
<td>/ VFX 13.5 MHz linear</td>
<td>CSAw (&gt;14mm²)*</td>
<td>DML (&gt;4ms)</td>
<td>Skin temp &gt; 32°C</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>CSAP (&gt;14mm²)*</td>
<td>DSL (&gt;3.41 m/sec)</td>
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<td></td>
<td>CSAH (&gt;14mm²)*</td>
<td>SCV (&lt;35.9 mm/sec)</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>FRw (&gt;4)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>FSp (&gt;4)</td>
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<td></td>
<td></td>
<td></td>
<td>FRH (&gt;4)*</td>
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<td></td>
<td></td>
<td></td>
<td>CSAP/CSAw (&gt;1.5)*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RB (&gt;3.5mm)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swen et al. 2001</td>
<td>63 (52 yrs, 70%)</td>
<td>20 (49 yrs, 75%)</td>
<td>-</td>
<td>Aloka SSD 2000 / 10 MHz linear</td>
<td>CSAP (&gt;10mm²)*</td>
<td>DML (&gt;3.6ms)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>DSLu-DSLm (&gt;0.4ms)   DML (&gt;4.3ms)</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>SCV (&lt;49 m/sec)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>SCV &lt;49 m/sec)</td>
<td></td>
</tr>
<tr>
<td>Visser et al. 2008</td>
<td>168/168 (52 yrs, 77%)</td>
<td>137/137 (46 yrs, 61%)</td>
<td>Normal (26)</td>
<td>Philips HDI 5000 / 5-12 MHz linear</td>
<td>CSAw (&gt;0.1cm²)*</td>
<td>DML (&gt;4.2 ms)</td>
<td>Skin temp &gt; 32°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimal (28)</td>
<td></td>
<td>CSAP (&gt;9.875mm²)</td>
<td>DSL (&gt;3.5 ms)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild (11)</td>
<td></td>
<td>RB (&gt;2.11mm)</td>
<td>DML (&gt;4.5ms)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate (53)</td>
<td></td>
<td>LCS (&gt;1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe (40)</td>
<td></td>
<td>CSAp (&gt;11mm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2008</td>
<td>37/61 (44.0 yrs, 92%)</td>
<td>20/40 (43.7 yrs, 75%)</td>
<td>-</td>
<td>Acuson Sequoia 512 / 8-15 MHz linear</td>
<td>CSAP (&gt;9.785mm²)</td>
<td>SCV &lt;41 m/s</td>
<td>EDX-US within 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RB (&gt;2.11mm)</td>
<td>DSL (&gt;3.5 ms)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LCS (&gt;1.5)</td>
<td>DML (&gt;4.1 ms)</td>
<td></td>
</tr>
<tr>
<td>Wiesler et al. 2006</td>
<td>26/44 (56 yrs, 81%)</td>
<td>43/86 (36 yrs, 47%)</td>
<td>-</td>
<td>Philips HDI 5000 / 12/5 MHz linear</td>
<td>CSAp (&gt;11mm²)</td>
<td>DML (&gt;3.5ms)</td>
<td>Skin temp &gt; 32°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DML (&gt;4.5ms)</td>
<td></td>
</tr>
<tr>
<td>Wong et al. 2004</td>
<td>120/95 (49 yrs, 82%)</td>
<td>-</td>
<td>-</td>
<td>Siemens Sonoline Elegra / 13-5 MHz linear</td>
<td>CSAW (&gt;10mm²)</td>
<td>DML Media-Ulnar (&gt;0.4ms)</td>
<td>EDX-US within 1 week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CSAH (&gt;12mm²)</td>
<td>DML (&gt;4.0 ms)</td>
<td></td>
</tr>
<tr>
<td>Yesildag et al. 2004</td>
<td>86/148 (49.8 yrs, 88%)</td>
<td>45/76 (42.7 yrs, 87%)</td>
<td>-</td>
<td>Philips ATL 1500 /12 MHz linear</td>
<td>CSAP (&gt; 10.5 mm²)*</td>
<td>SCV &lt;50 m/s</td>
<td>EDX-US within 1 week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FR</td>
<td>DML (&gt;4.2ms)</td>
<td></td>
</tr>
<tr>
<td>Ziswiler et al. 2005</td>
<td>74/104 (51 yrs, 65%)</td>
<td>-</td>
<td>1 – Certainly Normal (26)</td>
<td>Philips ATL 3500 / 5-12 MHz linear</td>
<td>Largest CSA from inlet to outlet (&gt;10mm²)*</td>
<td>SCV &lt;41-53 m/s</td>
<td>Skin temp &gt; 33°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 – Probably Normal (0)</td>
<td></td>
<td></td>
<td>DML (&gt;3.9-4.1 ms)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 – Mild CTS (30)</td>
<td></td>
<td></td>
<td>SNAP (&lt;5mV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 – Moderate CTS (27)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5 – Severe CTS (24)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

CTS, carpal tunnel syndrome; CSAf, cross-sectional area at the distal forearm; CSAh, cross-sectional area at the carpal tunnel outlet/hamate bone; CSAp, cross-sectional area at the proximal carpal tunnel/pisiform bone; CSAw, cross-sectional area at the wrist/tunnel inlet/radioulnar joint; DML, distal motor latency; DSL, distal sensory latency; EDX, electrodiagnostics; FR, flattening Ratio; LCS, longitudinal compression sign; MCV, motor conduction velocity; MNL, mixed nerve latency; RB, retinacular bowing; SCV, sensory conduction velocity; SPL, sensory peak latency; US, ultrasonography
Seventeen studies deemed wrists to be independent of the subject factors for statistical analysis, whereas the remaining six studies completed statistical analysis at the level of the individual, only using data from either the dominant hand or the most severely affected hand. Sixteen of the studies utilized a control group. One study recruited only female subjects whereas the remaining studies included both male and female participants. The percentage of females in each of these studies ranged from 65% to 93% for patient groups and 56% to 87% in control groups. The mean age range for patients was 43 years to 58 years whereas the mean age for controls was 31 years to 55 years.

2.2.2 Ultrasonography Equipment and Methods

Ultrasonography equipment varied greatly across all studies, but subject positioning was noted to be standard. Equipment manufacturers included: Acuson, Aloka, BK Medical, Diasonics, Esaote, General Electric (GE), Philips, Siemens, and Toshiba. To ensure adequate image resolution to obtain valid and reliable measures, transducer frequency of at least 10 MHz was required for a study to be included. All transducers used in the included studies were linear array and upper limits of frequencies ranged from 10 MHz to 18 MHz. Subjects were all sitting with their forearm supinated and resting on a surface, the wrist in a relaxed, neutral position and the fingers in a relaxed, semi-flexed position.
Reports of quality control of equipment and standardization of methods varied greatly across the included studies. No studies reported quality control measures or calibration of the ultrasonography equipment. Half of the studies (12 of 23) reported timing of the delay between data collection with ultrasonography and EDX data collection varying from the same day up to two weeks. The remaining studies did not report the timing between data collection for each measurement. Similarly only eleven of the studies reported controlling for skin temperature of subjects during EDX data collection, reporting temperatures between 30°C and 34°C.

Ultrasonographic images were collected at various anatomical locations, primarily in a transverse plane. While the majority of studies collected images at multiple locations, only those locations that were used in comparative or diagnostic statistical analysis were recorded for the studies. The primary site of image collection was at the level of the pisiform (61%). In addition to being documented as the level of the pisiform, this level was alternatively described by authors as the ‘proximal carpal tunnel’ or ‘the distal wrist crease.’ Nine studies (39%) obtained a longitudinal image at the radio-ulnar joint of the wrist also described as the ‘carpal tunnel inlet’ or ‘proximal to the carpal tunnel.’ Five studies (21%) obtained images at the level of the hook of the hamate, also described as the ‘carpal tunnel outlet’ and ‘distal carpal tunnel.’ Three studies evaluated the entire region from the proximal tunnel through the distal tunnel and obtained an image in which the median nerve was perceived to have the largest cross-sectional area. Two studies obtained a cross-sectional image of the median nerve
in the distal one-third of the forearm (6cm from wrist crease) and one study at the middle one-third of the forearm (12 cm from wrist crease) as a comparative measure. Longitudinal images of the median nerve within the carpal tunnel region were obtained in two studies for qualitative analysis of the median nerve.\textsuperscript{19,20}

The utility of EDX within the study design as a comparative measure or grouping mechanism was not consistently reported and measurements and thresholds varied greatly across all studies. At a minimum, all studies utilized sensory conduction velocity (SCV) and distal motor latency (DML) as comparative measurements. Diagnostic thresholds for these measurements varied, but were referenced to previous literature or standardized laboratory values. One study modified diagnostic criteria based on the age of the subjects.\textsuperscript{19} Recent studies utilized EDX results to create diagnostic groups by severity (i.e. negative, mild, moderate, and severe); whereas, older studies categorized EDX results into dichotomous groups (i.e. negative or positive).

2.2.3 Ultrasonography Measurements

For valid interpretation and comparison of diagnostic statistics, methods for measuring the median nerve were reviewed in each study. Because the outer edge of the epineurium of the median nerve can at times be challenging to determine, only those studies that completed measurements along the inner hyperechoic border of the median nerve were included. Some studies completed each measure only one time while other studies completed measurements multiple times and used the mean or median measure. The most extensive methodology encountered among the studies
involved completing five measurements, the highest and lowest measures were eliminated, and the remaining three measures were averaged.\textsuperscript{21}

At least one cross-sectional area (CSA) measure was obtained in every study included in this analysis. Two studies\textsuperscript{13, 22} calculated CSA by an indirect method using a mathematical ellipsoid formula and all other studies completed a direct trace to obtain CSA of the median nerve. The most recent studies published in 2008 and 2009 use a combination of multiple CSAs to evaluate the swelling of the nerve through a ratio or absolute value change score. Ratios were calculated between the wrist and forearm\textsuperscript{13, 23} and between the pisiform and wrist.\textsuperscript{18} The absolute difference between the maximum CSA within the carpal tunnel region and the CSA in the distal forearm was used as a diagnostic measure in one study.\textsuperscript{24}

Additional measurements primarily collected in study reports between 2000 and 2007 include flattening ratio of the median nerve at multiple levels and anterior bowing of the flexor retinaculum. The flattening ratio was measured in five studies, calculated by dividing the medio-lateral diameter (major axis) by the anterior-posterior diameter (minor axis) of the median nerve. Retinacular bowing, measured in five studies, was calculated by measuring the distance from the apex of the retinaculum to a point perpendicular to a straight line connected the insertion points on the trapezium and hook of the hamate.
In addition to the quantitative data, three studies utilized qualitative measures as an indicator for a diagnosis of CTS (Table 2.2). Two studies evaluated longitudinal images of the median nerve at the carpal tunnel region for signs of compression. Both studies scored the longitudinal images based on observations of a uniform appearing median nerve versus flattened or enlarged appearing nerves. The third study reviewed images for signs of edema within the carpal tunnel and recorded the presence of hypervascularization within the median nerve. In this retrospective study, the authors recorded hypervascularization as any Doppler images with evidence of flow.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Qualitative Analysis</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kele et al. 2003</td>
<td>Longitudinal Compression</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Compression &amp; Cross Sectional Area</td>
<td>89.1%</td>
<td>98%</td>
</tr>
<tr>
<td>Mallouhi et al. 2006</td>
<td>Evidence of Hypervascularization</td>
<td>95%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Edema in the Carpal Tunnel</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td>Wang et al. 2008</td>
<td>Longitudinal Compression</td>
<td>50%</td>
<td>95.8%</td>
</tr>
</tbody>
</table>

Table 2.2 Diagnostic accuracy of various qualitative analyses of grey-scale ultrasound images

2.2.4 Diagnostic Accuracy of Ultrasonography

Although similar ultrasonographic measurements were used, the calculation of diagnostic accuracy of ultrasonography measurements across all studies was confounded by methodologies utilizing different reference standards and calculations of diagnostic thresholds. Correlations between ultrasonographic measures and EDX were
mild to moderate (Table 2.3) and accuracy statistics (i.e. sensitivity and specificity) varied greatly across all the studies. The methods utilized and reported statistics for all quantitative measurements are included in Table 2.4 and Table 2.5.
<table>
<thead>
<tr>
<th>Study</th>
<th>Flattening Ratio</th>
<th>Retinacular Bulge</th>
<th>Cross-Sectional Area Wrist</th>
<th>Cross-Sectional Area Pisiform</th>
<th>Cross-Sectional Area Hamate</th>
<th>CSA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yesildag et al. 2004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.025</td>
<td>-</td>
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<tr>
<td>Koyuncuoglu et al. 2005</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziswiler et al. 2005</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wiesler et al. 2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bayrak et al. 2007</td>
<td>r: [0.089-0.403]</td>
<td>r: 0.317</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mondelli et al. 2008</td>
<td>-</td>
<td>-</td>
<td>r: 0.46</td>
<td>r: 0.25</td>
<td>r: 0.26</td>
<td>-</td>
</tr>
<tr>
<td>Padua et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Visser et al. 2008</td>
<td>-</td>
<td>-</td>
<td>Spearman ρ: 0.41</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hobson-Webb and Padua 2009</td>
<td>-</td>
<td>-</td>
<td>r: 0.40</td>
<td>-</td>
<td>-</td>
<td>r: 0.35</td>
</tr>
<tr>
<td>Karadag et al. 2009</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cohen’s K: 0.619</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pastare et al. 2009</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Spearman ρ: [0.635 - 0.714]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Saracgil et al. 2009</td>
<td>r: [-0.096 - 0.077]</td>
<td>r: [-0.258 - 0.323]</td>
<td>r: [-0.174 - 0.369]</td>
<td>r: [-0.092 - 0.360]</td>
<td>r: [-0.129 - 0.416]</td>
<td>r: 0.240</td>
</tr>
</tbody>
</table>

Table 2.3 Correlation of ultrasound measures to electrodiagnostic testing (EDX)
<table>
<thead>
<tr>
<th>Study</th>
<th>Flattening Ratio</th>
<th>Retinacular Bulge</th>
<th>CSA Wrist</th>
<th>CSA Pisiform</th>
<th>CSA Hamate</th>
<th>CSA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swen et al. 2001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>Kele et al. 2003</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>48.2%</td>
<td>96.1%</td>
</tr>
<tr>
<td>Koyuncuoglu et al. 2005*‡</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30.5%</td>
<td>96.7%</td>
</tr>
<tr>
<td>Naranjo et al. 2007</td>
<td>65.4%</td>
<td>47.8%</td>
<td>79%</td>
<td>52%</td>
<td>86.3%</td>
<td>48%</td>
</tr>
<tr>
<td>Visser et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>78%</td>
<td>91%</td>
</tr>
<tr>
<td>Kurca et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>Kwon et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>66%</td>
<td>63%</td>
</tr>
<tr>
<td>Pastare et al. 2009</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>62%</td>
<td>100%</td>
</tr>
<tr>
<td>Saracgil et al. 2009*</td>
<td>2%-6%</td>
<td>2%</td>
<td>19%</td>
<td>-</td>
<td>33%</td>
<td>-</td>
</tr>
</tbody>
</table>

Calculated diagnostic threshold values using sensitivity analysis, receiver operating characteristic curves, or other regression statistics.

Calculated diagnostic threshold values based on characteristics of a control group (e.g. 2 standard deviations).

*Statistics calculated based on presented data in report.

‡ Subjects with symptoms and negative EMG only.

Table 2.4 Sensitivity and specificity of various quantitative grey-scale ultrasonography measures for carpal tunnel syndrome with symptoms as reference standard. Diagnostic thresholds (Table 2.1) were selected based on published literature, calculated based on a deviation from a control group or statistically determined based on the data collected within the study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Flattening Ratio</th>
<th>Retinacular Bulge</th>
<th>CSA Wrist</th>
<th>CSA Pisiform</th>
<th>CSA Hamate</th>
<th>CSA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yesildag et al. 2004</td>
<td>37.2%</td>
<td>85.5%</td>
<td>-</td>
<td>-</td>
<td>89.9%</td>
<td>94.7%</td>
</tr>
<tr>
<td>Wong et al. 2004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>86%</td>
<td>74%</td>
</tr>
<tr>
<td>El Miedany et al. 2004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[96.6%-98.4]</td>
<td>[96.8%-100]</td>
</tr>
<tr>
<td>Ziswiler et al. 2005†</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>82%</td>
<td>87%</td>
</tr>
<tr>
<td>Mallouhi et al. 2006</td>
<td>60%</td>
<td>76%</td>
<td>65%</td>
<td>68%</td>
<td>91%</td>
<td>47%</td>
</tr>
<tr>
<td>Wiesler et al. 2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>91%</td>
<td>84%</td>
</tr>
<tr>
<td>Wang et al. 2008</td>
<td>-</td>
<td>-</td>
<td>77%</td>
<td>75%</td>
<td>82%</td>
<td>87.5%</td>
</tr>
<tr>
<td>Padua et al. 2008*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>72.5%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Hobson-Webb et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mondelli et al. 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>56.7%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Klauser et al. 2009†</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[94%-100%]</td>
<td>[57%-95%]</td>
</tr>
<tr>
<td>Hobson-Webb and Padua 2009</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>37% False-Negative</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>32% False-Negative</td>
<td>-</td>
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<tr>
<td>Site 2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Calculated diagnostic threshold values using sensitivity analysis, receiver operating characteristic curves, or other regression statistics
Calculated diagnostic threshold values based on characteristics of a control group (e.g. 2 standard deviations)
*statistics calculated based on presented data in report
†used maximum CSA between wrist and hamate levels

Table 2.5 Sensitivity and specificity of various quantitative grey-scale ultrasonography measures for carpal tunnel syndrome with electrodiagnostic tests (EDX) as reference standard - Diagnostic thresholds (Table 2.1) were selected based on published literature, calculated based on a deviation from a control group or statistically determined based on the data collected within the study.
Overall, diagnostic accuracy for the various ultrasonographic measurements varied significantly. Sensitivity was noted to be as low as 2% and as high as 100%, with specificity ranging between 47% and 100%. Accuracy ratings were consistently low for measurement of flattening ratios (sensitivity <65.4%) and retinacular bulging (sensitivity <79%). Accuracy statistics for measurements of median nerve swelling (i.e. ratio or change) were not well analyzed in the studies included in this review. Furthermore, the methodologies utilized by these studies interrogating nerve swelling varied and are not able to be easily combined. The most consistent and best sensitivity and specificity are reported for various measures of CSA. The largest portion of the studies measured CSA within the mid portion of the carpal tunnel at the level of the pisiform. This measurement was noted to have the highest overall accuracy statistics. CSA measurements within the mid portion of the carpal tunnel have a sensitivity of 29.4% to 100% and specificity of 47% to 100%.

Studies were subdivided into categories based on the reference standard and based on the methodology by which the diagnostic thresholds were determined. For CSA at the pisiform level, studies that used symptoms of CTS as the reference achieved sensitivity of 30.5%-93% versus 29.4%-100% for those utilizing EDX or a combination of the two references (specificity of 48%-100% and 57%-95% respectively). Studies that set diagnostic thresholds based on previous literature report sensitivity of 30.5%-100% and specificity of 57%-100%. Those studies utilizing data from a control group to determine diagnostic thresholds report sensitivity of 29.4%-93% and specificity of up to
96%. The least variability for diagnostic accuracy was noted when thresholds were statistical calculated utilizing ROC curves or regression within the collected data (sensitivity of 66%-91% and specificity of 47%-87%).

2.3 Discussion

Results of this systematic review of literature expose significant limitations with current research to document a clear understanding of the application of ultrasonography to diagnose carpal tunnel syndrome. There is vast agreement from all the studies that ultrasonography is valuable for detecting anomalies, such as bifid median nerves and persistent median arteries, as well as secondary pathologic findings that may contribute to carpal tunnel syndrome, such as tenosynovitis, crystal or amyloid deposits, ganglia, and tumors. Furthermore, ultrasonography is noted to be less time consuming and better tolerated by patients than EDX. While numerous benefits set ultrasonography apart from EDX, a direct link to ultrasonography and specific diagnostic measures for CTS have yet to be documented. Determination of this diagnostic utility of ultrasonography has been confounded by a lack of standardization in research methodologies/designs and variability in evaluation and measurement protocols. Results of previous and future research require improved association to pathology and clinical practice.

2.3.1 Limitations in Reviewed Research

Inclusion criteria for this review were discussed at length such that studies were only included which met quality standards; however, significant limitations are noted in
the methods reported in many of these studies that could draw question to the results.

The most notable of these limitations is a lack of reporting of quality control testing for the equipment utilized in any of the studies. Quality assurance measures are frequently cited and have become appropriate practice when utilizing ultrasonography for image guided treatments. With diagnostic accuracy studies, precision of measurement is imperative and quality assurance testing of equipment should be completed on a regular basis, especially with studies that collected data over multiple years.

Even if data are collected through a valid and reliable measure, the inherent limitation of diagnostic criteria for CTS must not be overlooked. The foundation of CTS diagnosis is a subjective report of symptoms, without a specific universally accepted diagnostic reference or threshold. Utilizing EDX as a reference standard in combination with symptoms is most often the process for clinical diagnosis; however, the rate of false-negatives with EDX can be as high as 20%. Knowing this, any false-positives that may be reported with ultrasonographic measurements may in fact be a result of error due to EDX. Interpretation of the results obtained in these studies should be done with caution based on the limitations of applying a specific diagnostic criterion. Despite these limitations, EDX continues to be a clinically acceptable means for diagnosis and therefore is a plausible reference standard.

A common problem with staging research is controlling extraneous variables. These variables can usually be addressed through careful design and recruitment methods. One of the most critical mediators for valid EDX results is temperature. As
the temperature of the extremity increases the conduction velocities will also increase and latencies will decrease.\textsuperscript{29} Only half of the reports indicate having controlled this factor. The minimum skin temperature variability between 30°C and 34°C may have led to variability in the results, and should be questioned in the studies that did not report a standard measure of skin temperature. In order to make a valid comparison of the EDX results to ultrasonographic measurements, the research should be designed so that the time duration between measurements is as short as possible. Only three of the studies collected the data on the same day, two studies collected the data within 2-3 days, six studies collected data within a week, one study reported collecting data within two weeks, and the remaining studies did not report the timing of data collection.

Hobson-Webb et al.\textsuperscript{23} and Pastare et al.\textsuperscript{30} were the only studies reviewed to report appropriate control of skin temperature and short lapse between data collection. However, each of these studies was further limited by differences that may be attributed to variability in the comparison group. Having a comparison group that tended to be younger and more male\textsuperscript{23} as well as being of very small size\textsuperscript{30} could have easily influenced the results. This was a common problem with comparison groups across all studies, with controls often being younger and a higher proportion male. Both age and gender have been suggested as correlates to the development of CTS. The study designs with subjects and controls matched on age and gender may be more valid than studies with group differences in these variables.
2.3.2 Ultrasonography Scanning and Measurement Protocols

Combining the data from each of the studies in the review was difficult due to variations in the description of scanning protocols and process for selection of variables and thresholds for data analysis. These factors even varied within studies because clinical practice protocols were well established and non-conformant between sites, creating difficulty in collapsing data and comparing results. Variability in these factors was widespread across studies throughout the ten-year period and successful future research will require standardization of protocols to ensure collection of valid and reliable data that can be generalized and translated to clinical practice.

The advancement of technology allows for refined image collection, analysis and measurement. Measurement capabilities have become very efficient and more precise, which can increase the sensitivity of comparing these measurements to diagnostic criteria. The ability to magnify images in post-processing without losing quality can improve the ability of obtaining a precise measure of a small median nerve. Indirect calculation of the cross-sectional area (CSA) of the median nerve utilizing the ellipsoid formula was completed by Hobson-Webb and Padua and Swen et al. This work has been shown to be unreliable as the nerve has a tendency to become displaced by surrounding tissues and does not always take on a perfectly ellipsoid shape. Therefore, calculation with ellipsoid formula can result in poor diagnostic accuracy. For similar reasons, the moderate correlations between ultrasonography and EDX reported by Bayrak et al. may have been affected by the use of an automatic ellipse to measure
CSA. Utilization of a direct trace around the inner hyperechoic border of the median nerve as utilized in the majority of the studies appears to be the most reliable and precise method of measurement.

Variability within a measurement can be reduced by calculating an average of repeated measurements. While multiple studies only collected one measurement for analysis, the majority of studies utilized protocols that based comparisons on the average of multiple measures meant to reduce error. The most extensive application of this process attempted to reduce error by collecting five measurements, deleting the highest and lowest values and averaging the remaining three measures. Wiesler et al. approached the measurement from a conservative standpoint and retained the smallest of three measurements for further analysis. The former methodology seems to account for the fact that human error may persist even in the most highly trained and skilled sonographer. Elimination of the highest and lowest measures reduces the chance of measurement error due to outliers. This could be especially important in the analysis of images that may be of low quality or in patients that are difficult to scan. During the active scanning process, visualization of the smallest CSA of the nerve within one image will ensure that the probe is placed in the most perpendicular plane to obtain the true CSA of the nerve instead of an oblique view. However, the strict reliance on the smallest measure has the potential to underestimate disability and reduce diagnostic accuracy.
Standardization of ultrasonography scanning protocols relies on very clear descriptions of anatomical landmarks. The primary inconsistency among the studies in this review is how the spatial orientation of the carpal tunnel is defined by anatomical landmarks. As noted by Mondelli et al., the distal edge of the radial-ulnar joint is considered to be the inlet to the carpal tunnel, whereas some studies describe the inlet of the tunnel as defined by the location of the pisiform bone. While the pisiform is considered a bone within the proximal row of carpal bones, the arching of these bones tends to place the pisiform slightly distal. With the median nerve passing through the central portion of the tunnel, at the level of the pisiform it will have already crossed under the transverse ligament. Therefore, the carpal tunnel region may be best described as the inlet on the proximal side at the edge of the radial-ulnar joint, the mid carpal tunnel at the level of the pisiform, and the distal tunnel outlet at the hamate bone.

Standardization of these descriptions will be helpful in discussion of research and clinical results, but clinical significance of various types of measurements at each point requires investigation. Measurement of CSA in the distal portion of the carpal tunnel has low diagnostic accuracy (sensitivity [18%-65%]). These low statistics may be a result of the challenge of obtaining reliable images in this region due to poor signal quality created by the curved palm and flat transducer and the deep oblique path of the nerve. The ability to accurately visualize and measure the nerve in this region has been reported to be as low as 42%, indicating that this measure is not reliable.
Retinacular bulge measures are taken on images at this same location, which may be the cause for lower sensitivity of this measure as well. Studies that measured CSA immediately proximal to the carpal tunnel at the inlet had improved diagnostic sensitivity, but still slightly lower accuracy statistics than those measuring CSA within the carpal tunnel at the pisiform level.

Measurement of CSA within the carpal tunnel, at the level of the pisiform, appears to be the most widely referenced and most accurate measure. Across these studies, three methods were used for determining diagnostic thresholds: (1) previous literature/lab standards, (2) control group comparison, and (3) statistical calculation. Because this review and all previous literature reviews indicate that no specific thresholds have been determined, referencing previous literature to set a specific threshold is erroneous and may lead to invalid statistical analysis. Studies that calculated thresholds based on a control group utilized thresholds that tended to be higher and more conservative than other studies. Determination of thresholds based on control group data is logical; however, due to the idiopathic state of CTS, it is challenging to determine a true, non-pathologic control group that is 100% matched to the patient group on all possible risk factors (e.g. age, gender, BMI, wrist ratio). Furthermore, because of the precision of the measurements and the small changes that are being documented in mild cases of CTS, calculation of two standard deviations from a control group mean as a threshold may not correctly capture CTS cases of all severities. Clinical severity skewed toward mild cases in Mondelli et al.\textsuperscript{33} and lack of accounting for severity
in Saracgil et al. may explain low sensitivity [29.4%-33%] with calculated respective thresholds of 12mm² and 14mm² for CSA. Further limits in the later study include measurements completed in cm that were extrapolated to mm for statistical analysis and admitted lack of experience of those collecting data.

Statistical calculation of thresholds based on the data collected in both a patient and control group, accounting for severity of CTS, had the best accuracy results. Calculation of thresholds utilizing ROC curve analysis or other regression methods resulted in thresholds that ranged from 9.7mm² to 11mm². Utilizing a standard threshold within these levels resulted in an average sensitivity of 81% and specificity of 70%. Two studies that accounted for the severity of CTS in these results indicated that instead of one threshold, multiple thresholds could be utilized to better rule in or rule out CTS. Naranjo et al. noted that 100% sensitivity could be achieved by raising the threshold to 13mm² and Ziswiler et al. suggest that CSA within the carpal tunnel smaller than 8mm² had adequate power to rule out CTS and measures larger than 12mm² had sufficient power to rule in CTS. These results further support the importance of pathologic severity and support the concept that one diagnostic threshold may not be clinically useful.

Anthropometry is an additional important component in development and classification of many musculoskeletal disorders and may be a component to consider when diagnosing CTS. Comparison of these CSA to current diagnostic standards continues to present with limitations that could be due to variability that exists across
the subjects and not necessarily attributed to the measurements. Factors such as body mass index and wrist size may influence the nerve, not only in pathology, but in a normal state. Measuring the naturally occurring status of the individual’s median nerve for comparison may provide a more reliable measurement of pathology. While only three studies have evaluated this relationship of CSA in the forearm to size of the median nerve in the carpal tunnel, these studies show promising results. Klauser et al.\textsuperscript{24} indicate that the calculation of the absolute value change has been shown to improve accuracy over the singular measurement. Calculation of a ratio for these two measures may be an alternative methodology that has only been preliminarily tested.\textsuperscript{13, 23}

Another promising new method that requires further investigation involves the use of Doppler to interrogate the vascular structure of the nerve. It has been suggested that the odds of a correct diagnosis of CTS may be 16 times better utilizing Doppler over other grey-scale measurements.\textsuperscript{36} The authors noted that color Doppler was present within the nerve for those patients with CTS symptoms, even when the nerve did not show signs of swelling or compression. This may indicate pathologic intraneural vascularization within and around the nerve before other swelling and edema. Because this study was completed as a retrospective case analysis, conclusions that have been drawn regarding the use of Doppler must be interpreted cautiously. Data collection and equipment settings were not under direct control or planned through the research methods, which could have introduced error in the results. However, as ultrasonographic technology continues to improve and be utilized for diagnosis of CTS,
further interrogation of the intraneural vasculature of the nerve is appropriate and Mallouhi et al.\textsuperscript{36} provide good points for consideration in developing protocols.

2.3.3 Clinical Utility

The primary etiology of idiopathic carpal tunnel syndrome is believed to be due to compression of the median nerve either by direct flattening or by indirect reduction of space within the carpal tunnel. Qualitative observation of compression of the median nerve may provide useful information for prevention of CTS in pre-pathological or very acute stages. Low correlations\textsuperscript{20} and low sensitivity among studies in this review provide no evidence to support measurement of flattening of the nerve for clinical diagnosis. Similarly, qualitative evaluation of edema and other pathology within the carpal tunnel region leading to compression of the median nerve may be useful in identifying etiology. However, measurement of bulging of the flexor retinaculum due to such swelling is limited by the ability to obtain consistent images in the distal portion of the carpal tunnel.\textsuperscript{19,34} Moderate accuracy statistics do not support the utility of the measure for clinical diagnosis of CTS.

Cross-sectional area of the median nerve had the most stable measures of sensitivity, but the location of CSA measurement requires further standardization in clinical practice. The progression of median nerve swelling and its relationship to the stage of CTS development is not well known. Therefore, it may be erroneous to assume that this swelling will occur at the same specific location within all individuals and instead may occur at multiple levels.\textsuperscript{28} Most literature has concluded that this swelling
occurs within the tunnel at the level of the pisiform. However, if the carpal tunnel is not sufficiently large to allow for swelling of the nerve or other anthropometric or individual factors exist, excess swelling may occur immediately proximal to the tunnel. Multiple studies in this review suggested that measurement of the largest CSA within the entire carpal tunnel region may be a more accurate measure than focusing specifically at the level of the pisiform.\textsuperscript{24, 26, 36} Instead of standardization of the data collection protocol to include measurement at specific bony landmarks, these landmarks could provide end points for a range of interrogation. Visualization of the largest CSA of the median nerve could be determined during completion of a dynamic scan through the region bordered by the radial-ulnar joint proximally and the hamate bone distally. Additional recommendations for this scanning protocol are needed to ensure that true cross-sections are being visualized and oblique scans are not being obtained.\textsuperscript{21}

Conclusions by Wiesler et al.\textsuperscript{31} that a rigid diagnostic threshold for ultrasonography measurements does not appear to be appropriate or valuable in the clinical setting are well supported by the results of this review. The size of the median nerve and swelling occur on a continuum, and therefore diagnostics cannot be easily related to specific cut-off values.\textsuperscript{28} This continuum may shift based on individual factors or clinical differences leading to different outcome measures. Evaluating probabilities based on variations in these factors may lead to a sliding scale of flexible cutoffs to be applied to various situations, thereby improving clinical diagnosis.\textsuperscript{26}
The severity and stage of disorder progression appear to be the primary factors to consider when utilizing ultrasonography to make a clinical diagnosis. Although one clear cut-off was not identified, as the severity of CTS increases CSA increases, producing a positive correlation of ultrasonography and EDX measures. Statistical analysis indicates that diagnostic accuracy increases as the CSA continues to increase beyond $10\text{mm}^2$. In mild or relatively acute cases that tend to be closer to this statistically calculated threshold, more variability is noted in the data and diagnostic accuracy declines. One study has attempted to gain better understanding of this phenomenon, noting increased swelling in the median nerve of up to 30.5% of individuals with mild symptoms but negative EDX, which still leaves a significant portion of symptomatic individuals without diagnosis.

Proponents of EDX indicate that a tool that measures functions of the nerve will be the best indicator of the severity of any nerve dysfunction, and therefore be better than a physiologic measure of nerve size or shape. In clinical practice, nerve conduction studies continue to serve a purpose for ruling out other pathological conditions such as cervical radiculopathy, brachial plexopathy, polyneuropathy, or other focal mononeuropathies. Unfortunately, EDX evaluates the results of secondary nerve injury that typically occurs in late or chronic stages of CTS injury. By measuring damage to the large nerve fibers, EDX can be negative in early stages of CTS leading to substantial false-negative rates.
An evaluation technique such as ultrasonography that is able to identify early changes in connective tissue and vascular flow may be a more useful tool. When EDX testing is normal, ultrasonography may still indicate swelling in individuals who have not yet developed secondary dysfunction or damage of the nerve fibers but have become symptomatic. Early identification of these changes can allow for intervention to prevent nerve damage that occurs in late or chronic stages. While data reported by Koyuncuoglu et al. indicates that sensitivity may remain low for the ultrasonography measures in this population, further study is required. Because increased CSA is related to symptoms and declining hand function, individuals with large CSA, such as greater than 12mm or 13mm, may be diagnosed with mild or acute CTS that has not yet become pathologic based on EDX.

The evidence does not suggest that ultrasonography is an acceptable alternative to EDX for diagnosis of CTS. Furthermore, combining ultrasonography and EDX may not always improve diagnostic accuracy, but the two evaluation procedures may be complementary when utilized appropriately. Ultrasonographic evaluation of the median nerve may be best used as a screening tool in the first step of individuals with suspected CTS. Based on the largest threshold in this review, individuals with CSA greater than 14mm could be spared the time, expense, and discomfort of EDX. Only those individuals with mild cases and smaller CSA would require further evaluation.
2.4 Conclusions

Continued future research is necessary to better understand the utility of ultrasonography for diagnosing CTS. Initial recommendations for research focus on implementing research designs that adequately control all mediating factors to ensure that error is reduced. Prospective research designs should involve regular quality assurance checks on ultrasonography equipment and appropriate control of measurement error due to skin temperature. For accurate comparison, data collection for ultrasonographic measures and EDX should be completed on the same day and controls should be age and gender matched.

Similarly, future research should focus on standardization of ultrasonographic protocols and measurement techniques. Collection of grey-scale images for the calculation of flattening of the median nerve or bulging of the flexor retinaculum does not appear to provide clinically useful information. While CSA measurements of the median nerve show moderate to good correlation and potential for providing diagnostic information, clarity in the anatomical locations of data collection is needed to improve consistency in research and clinical reports. It is possible that enlargement of the median nerve may occur at various locations both proximal to and within the carpal tunnel. Studies that have utilized the largest CSA within the entire wrist region have accuracy statistics that are the most stable. Therefore, it is likely that measuring the largest CSA within the entire region may be the most appropriate technique for future research and clinical practice. With standardization of CSA measurements as a
foundation, other novel ultrasonographic measures should continue to be investigated. Utilization of the CSA at the forearm as an internal control for observing swelling of the median nerve has potential to be a more precise indicator and requires further investigation through well-designed studies.

In addition to swelling, ultrasonographic measures related to other aspects of pathology require further research and protocol development. Qualitative observations of compression, waist-line effects or other observations of non-linear longitudinal appearance may also be valuable information for future research. Edema and fluid retention, both within the nerve and in the surrounding regions can be observed as increased hypoechoic signals altering the appearance of the nerve. The inflammatory process may additionally be qualitatively or quantitatively measured utilizing Doppler techniques to identify changes in intraneural vasculature. Finally, since ultrasound allows for dynamic visualization of structures, observation of general mobility patterns of the median nerve may be a potentially useful parameter.

Despite the lack of solid research evidence for diagnostic utility of ultrasonography in this review, screening with ultrasonography appears to enhance current diagnostic techniques. As the CSA of the nerve increases to a severe stage, the accuracy of diagnosis increases, which indicates that as a first step in evaluation, patients with severe swelling would not require the more expensive, uncomfortable, and invasive EDX. Further investigation is required for the best combination of ultrasonography and EDX for individuals with mild cases that appear as false-negatives.
on EDX as well as following false-positive subjects as indicated by ultrasonography develop CTS.²⁸

This review may be limited by only considering studies that included EDX for comparative or classification purposes within the same population. Correlation studies that used clinical diagnosis as the reference standard in patients and controls without EDX may provide additional valid information relative to the diagnostic utility of ultrasonography for CTS. Additionally, this review focused on idiopathic CTS and therefore did not include studies in subject populations with specific diagnoses. A detailed methodology was utilized to ensure a complete, unbiased review occurred.³⁹
2.5 References


Chapter 3: Screening for carpal tunnel syndrome using ultrasonography

The use of ultrasonography for investigation and diagnosis of musculoskeletal pathology has been rapidly increasing over the past few decades. Advances in the quality and portability of ultrasound have well positioned this technology as the tool of choice for research and clinical application in orthopedics, neurology, and other musculoskeletal practice settings.\(^1\) Full integration of ultrasound into clinical and research application requires convincing diagnostic standards.

Evidence supporting this use of ultrasonography as a diagnostic tool for median nerve pathology, specifically carpal tunnel syndrome (CTS), is inconsistent. There is a lack of convincing evidence to support the use of diagnostic thresholds measured with ultrasonography.\(^2\) The significant conflicting evidence in previous studies may be a result of variable methodologies and techniques, and overall positive correlations to diagnostic gold standards continues to show promise of ultrasonography as a screening tool for CTS.\(^3\)

Flattening ratio of the median nerve, anterior bowing of the flexor retinaculum, and measurement of the cross-sectional area of the median nerve are the three most common diagnostic measures that have been investigated. Of these, measurement of cross-sectional area (CSA) of the median nerve within the carpal tunnel at the level of
the pisiform is the most consistent measure in previous research literature. Studies that have attempted to take indirect measures of CSA area using the ellipsoid formula have shown lower diagnostic accuracy.⁴,⁵ Due to the irregular shape the median nerve frequently takes, the majority of literature indicates that measurement of the CSA is best completed through a direct trace.⁶,⁷ Similarly, a few studies have included the hypoechoic epineurium in the CSA measurement;⁸-¹⁰ however, there is consensus in the literature that more precise measurement of the CSA should be taken along the inner hypoechoic border.

Diagnostic accuracy continues to vary across research studies utilizing CSA at the pisiform; therefore, measurement of the swelling of the median nerve has been suggested as a refined methodology.¹¹ Anthropometry may cause natural variation in the size of the median nerve among individuals of different genders and body compositions. Therefore, comparison of the CSA of the median nerve in the carpal tunnel region to an unaffected site (i.e. forearm) may provide more accurate information regarding changes within a specific individual.

Two methodologies for measuring the swelling of the median nerve have been proposed, but neither has been confirmed with extensive research. Swelling calculated as a ratio between CSA at the wrist and pisiform levels was noted to have very low sensitivity (6%), indicating that use of a wrist measurement may not be a good internal comparison.¹² However, measurement of the CSA swelling as a ratio between the forearm and wrist¹³ has been shown to reduce the rate of false-negatives from 37% to
2% over a single measure of CSA at the pisiform.\textsuperscript{14} An alternative measure of swelling calculated as the absolute change in CSA between the forearm and carpal tunnel region has also demonstrated high diagnostic accuracy at 96%-100% sensitivity.\textsuperscript{15}

The objective of this study is to investigate the utility of ultrasonography for diagnosis of CTS compared to the current clinical gold standard of electrodiagnostic (EDX) testing. This study will standardize data collection and measurement techniques based on previous literature, while investigating the accuracy of both previously studied measures and new methods. Previous measurements to be evaluated include flattening ratio, bowing of the flexor retinaculum, and CSA in the carpal tunnel region. Swelling of the median nerve will be evaluated through both absolute change in CSA and ratio of CSA in the carpal tunnel compared to the forearm.

3.1 Materials and Methods

From June through December 2010, all patients that entered the neurodiagnostic clinic at The Ohio State University for nerve conduction study and electromyography (EMG) were screened for entry into the study. The study was explained to the subjects and all subjects provided written consent to participate and permission for the researchers to review test results. This study was approved by the Biomedical Institutional Review Board at The Ohio State University.

3.1.1 Subjects

Only those patients with suspected idiopathic CTS were offered the option to participate in the study. This required a referral that indicated a diagnosis of carpal
tunnel syndrome or with primary symptoms of CTS. Patients were included in the study if they had complaints of numbness or tingling in the median nerve distribution of at least one hand that had lasted at least 3 weeks. Patients were excluded from the study if they had a previous history of trauma to the wrist or hand that included broken bones, if there was a history of previous surgery to the wrist or any permanently placed shunts or objects in the hand or wrist, if there was a known history of other systemic neurological disorders or uncontrolled thyroid disorders, or if the patient was pregnant or within 3-months post-partum. The same exclusion criteria were used to recruit a convenience sample of asymptomatic, non-clinical control subjects. The study was limited to the working adult population 18 to 65 years of age. Subjects with anatomic anomalies observed during EDX or ultrasound data collection were excluded from further analysis (i.e., bifurcated median nerve, Martin-Gruber anastomosis). Subjects with diabetes were not excluded from the study provided diabetic neuropathy was ruled out with EDX. Similarly, subjects with a persistent median artery (PMA) were not excluded provided no other anatomic anomalies or obstruction of the PMA was observed that may have been contributory to symptoms.

Anthropometric and demographic data included age, height, mass, gender, hand dominance, and wrist width and depth. Each subject’s body mass index (BMI) and wrist ratio (wrist depth divided by wrist width) was calculated. Clinical assessment was completed by the researchers on the same date as ultrasound and EDX testing was conducted. The clinical assessment included a subjective report of symptoms including
duration of symptoms, Symptom Severity Scale (SSS) and Functional Severity Scale (FSS),\textsuperscript{17} and clinical provocative tests (Phalen’s, Tinel’s, Durkin’s).

Wrists were evaluated separately and divided into symptomatic and asymptomatic wrists following completion of provocative tests and subjective symptom reports. Both wrists of patients were included in the study provided EDX was ordered by the referring physician and each wrist met all inclusion criteria. The wrists of control subjects who complained of symptoms or had positive provocative tests were excluded.

3.1.2 Electrodiagnostic Testing

Electrodiagnostic studies (EDX) were completed on all symptomatic subjects with a Care Fusion Synergy Tower (Middleton, WI). Nerve conduction studies (NCS) and EMG testing were completed based upon American Association of Electrodiagnostic Technologists (AAET) and American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) guidelines. Skin temperature at the fingers was greater than 34°C for all subjects prior to initiating nerve conduction protocols. Orthodromic sensory responses were obtained by placing stimulating electrodes at the proximal crease of digit II and in the palm, 8cm from the recording site on the ventral forearm at the wrist crease. Distal sensory nerve action potentials (SNAP) were averaged. SNAP amplitude, velocity, and latency were measured for all subjects. Compound muscle action potentials (CMAP) were obtained by placing the recording electrodes over the abductor pollicis brevis (APB) on the thenar eminence. The stimulating electrodes were placed 7cm proximally over the median nerve at the wrist and at the antecubital fossa. Distal
motor latency, distal and proximal CMAP amplitudes and conduction velocity were recorded. Additional nerve conduction on the ulnar nerve were always performed and the comparison to nerve conduction results in the contralateral arm and leg were completed as indicated to determine any underlying polyneuropathy. Needle EMG was completed in the APB and additional muscles were studied to rule out proximal median nerve, brachial plexus or radicular pathology.

NCS results were considered diagnostic of CTS when the sensory conduction velocity (SCV) was less than 50 m/s across the carpal tunnel. Additional abnormalities including SNAP amplitude of less than 10µV, distal motor latency (DML) greater than 4.2ms, CMAP amplitude of less than 4.0mV, and changes recorded by EMG were used to determine the severity of CTS. EMG was recorded as normal or acute and/or chronic. The absence of any electrical diagnostic criterion resulted in classification of the wrist as normal. Reduction in the SCV with normal motor responses and EMG was categorized as mild CTS. Sensory nerve abnormalities combined with prolonged DML but normal EMG was considered to represent moderate CTS. The absence of sensory responses coupled with motor nerve changes and abnormal EMG was categorized as severe CTS.

3.1.3 Ultrasound Imaging

Ultrasound imaging was completed with a GE Healthcare Logiq i ultrasound (Milwaukee, WI) with a 12 MHz linear-array transducer. Ultrasound settings and image acquisition were based on previously published protocol. The subjects sat facing the examiner with the forearm supinated and resting on a flat surface. The hand, wrist and
fingers were in a neutral and relaxed position throughout the evaluation. Longitudinal and cross-sectional images of the median nerve were collected (1) in the distal 1/3 of the forearm 6 cm proximal to the distal wrist crease, (2) proximal to the entrance of the carpal tunnel at the radiocarpal joint, and (3) within the carpal tunnel at the level of the pisiform. One additional cross-sectional image was taken at the distal carpal tunnel to observe the flexor retinaculum between the trapezium and hook of the hamate.

Ultrasound images were collected in wrists of both symptomatic and asymptomatic control subjects. During collection of the images, the researcher annotated the image and placed a mark on the image to identify the median nerve to ensure appropriate structures were analyzed. For symptomatic subjects, ultrasound data was collected on the same-day and within one hour of EDX testing. Researchers obtaining ultrasound images were not blinded to the subject symptom status, but were blinded to the results of EDX testing in symptomatic subjects. Quality assurance checks were completed for grey-scale images on the ultrasound equipment at least monthly throughout data collection to ensure reliability in image collection and processing.

3.1.4 Image Processing

To ensure reliability of measurements, all image processing and measurement was completed by the first author with periodic reliability checks by the second author. During measurement the examiner was blinded to the symptomatic reports of the subject and to the results of EDX testing. Without reducing image resolution, images were magnified to improve precision of measurements along the inner echogenic
border of the median nerve. Each measurement was repeated five times, the highest
and lowest measures were excluded, and the remaining three measurements were
averaged.

Measurements of the anterior-posterior height (mm) and medial-lateral width
(mm) were taken at each of the three locations from the inside edge of the echogenic
borders of the median nerve. Cross-sectional area (CSA) (mm$^2$) was obtained utilizing a
direct trace along the inner rim of the echogenic border of the nerve in each location
(Figure 3.1). The height of the retinacular bulge was measured as the perpendicular
distance from a line connecting the insertion points on the trapezium and hook of the
hamate to the anterior most point of the flexor retinaculum (Figure 3.2).
Figure 3.1 Location of the transducer to obtain cross-sectional image of the median nerve at the radial-carpal joint (a) with sample image of a normal median nerve (b) and measurement of an enlarged median nerve in a symptomatic subject (c)
Figure 3.2 Measurement of the retinacular bulge in an asymptomatic control (a) and a symptomatic patient (b)

Flattening ratio was calculated by dividing the width by the height of the nerve in each of the locations. CSA in the forearm was used as an internal reference for each subject. CSA change scores were calculated as the absolute difference of the CSA at the distal radius and pisiform to the CSA at the forearm. CSA ratio was calculated for each subject as the CSA at the distal radius and pisiform each divided by the CSA at the forearm.
3.1.5 Statistical Analysis

All demographic, anthropometric, and clinical data were compared between the symptomatic patients and asymptomatic controls to identify differences between the two groups on patient level variables. Frequencies, descriptive statistics and distribution statistics for variables within each group were completed. Chi-square testing was completed on all categorical data and independent sample t-tests were completed on continuous data to identify any differences between the two groups (p <0.05).

Data from symptomatic subjects were analyzed based on EDX results. Kendall’s tau-b correlations were calculated for each variable versus the diagnostic group assignment in symptomatic subjects. Pearson correlations were completed between ultrasound measures and the primary EDX measures of SCV and DML within the symptomatic group. Correlation results were used to identify specific ultrasound measures to be further analyzed with receiver operating characteristic (ROC) curve analysis to calculate the sensitivity and specificity of US measurements.

3.2 Results

Ninety-five subjects were consented to participate in the study. Following screening and application of all exclusion criteria, 47 symptomatic patients (83 wrists) and 44 asymptomatic controls (83 wrists) were included in the study. Wrists were excluded prior to the collection of data if the subject reported a history of surgery (n=3) or wrist fracture (n = 3). In symptomatic subjects, data were only included for wrists
with subjective complaints of median nerve pathology in the hands and at least one positive provocative test. Wrists were excluded from analysis for any control subjects who reported symptoms or had positive provocative tests \((n = 4)\). Following ultrasound evaluation wrists were excluded from analysis if bifurcation of the median nerve \((n=7)\) or Martin-Gruber anastomosis \((n=1)\) were visualized. Persistent median artery was documented in 6 wrists \((3.2\% \text{ of the total sample})\), but was not deemed to be a primary exclusion factor. Table 3.1 reports frequencies of all exclusion criteria by group.

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Symptomatic patients ((n = 98 \text{ wrists}))</th>
<th>Asymptomatic controls ((n = 92 \text{ wrists}))</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifurcated Nerve</td>
<td>4 ((4.1%))</td>
<td>3 ((3.3%))</td>
<td>7 ((3.7%))</td>
</tr>
<tr>
<td>Previous Surgery</td>
<td>3 ((3.1%))</td>
<td>0 ((0.0%))</td>
<td>3 ((1.6%))</td>
</tr>
<tr>
<td>History of Wrist Fracture</td>
<td>1 ((1.0%))</td>
<td>2 ((2.2%))</td>
<td>3 ((1.6%))</td>
</tr>
<tr>
<td>Martin-Gruber Anastomosis</td>
<td>1 ((1.0%))</td>
<td>0 ((0.0%))</td>
<td>1 ((0.5%))</td>
</tr>
<tr>
<td>Symptoms Not Matching Group Assignment</td>
<td>6 ((6.1%))</td>
<td>4 ((4.3%))</td>
<td>10 ((5.3%))</td>
</tr>
</tbody>
</table>

**Table 3.1** Number of wrists (percentage of occurrence) excluded by group and across all subjects recruited into the study

Significant differences were noted between the two subject groups in age, mass, BMI, and wrist ratio \((p < .05; \text{ Table 3.2})\). All ultrasound measurements were significantly larger in the symptomatic group versus the asymptomatic group with exception of flattening ratio which was nearly identical between the two groups \((\text{Table 3.3})\). While data for all ultrasound measures were noted to be normally distributed, the variability of data was much wider for the symptomatic group versus the control group on all measures except CSA in the forearm. Because the distribution of data for CSA in the
forearm was similar between groups and the means differed only by 0.50mm², the clinical relevance of this significant difference is questionable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic patients (n=47)</th>
<th>Asymptomatic controls (n=44)</th>
<th>Test-statistic</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.6 (10.6)</td>
<td>40.0 (12.1)</td>
<td>t = 2.355</td>
<td>89</td>
<td>0.021</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>37/10</td>
<td>30/14</td>
<td>χ² = 1.301</td>
<td>1</td>
<td>0.254</td>
</tr>
<tr>
<td>Hand Dominance (r/l)</td>
<td>44/3</td>
<td>37/7</td>
<td>χ² = 2.108</td>
<td>1</td>
<td>0.146</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.0 (8.3)</td>
<td>168.8 (8.5)</td>
<td>t = -1.578</td>
<td>89</td>
<td>0.118</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>88.0 (21.2)</td>
<td>78.0 (19.7)</td>
<td>t = 2.339</td>
<td>89</td>
<td>0.022</td>
</tr>
<tr>
<td>BMI</td>
<td>32.0 (7.4)</td>
<td>27.4 (7.0)</td>
<td>t = 2.980</td>
<td>89</td>
<td>0.004</td>
</tr>
<tr>
<td>Number of Wrists</td>
<td>83</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dominant Wrists</td>
<td>44</td>
<td>42</td>
<td>χ² = .602</td>
<td>1</td>
<td>0.438</td>
</tr>
<tr>
<td>Wrist Ratio</td>
<td>.732 (.041)</td>
<td>.710 (.041)</td>
<td>t = 3.535</td>
<td>164</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 3.2 Descriptive characteristics of symptomatic patients and asymptomatic controls.

<table>
<thead>
<tr>
<th>Ultrasound measurement</th>
<th>Symptomatic wrists (n=83)</th>
<th>Asymptomatic wrists (n=83)</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA in Forearm (mm²)</td>
<td>6.16 (1.28)</td>
<td>5.64 (1.04)</td>
<td>2.841</td>
<td>157.5</td>
<td>0.005</td>
</tr>
<tr>
<td>CSA at Distal Radius (mm²)</td>
<td>10.42 (3.82)</td>
<td>7.95 (1.72)</td>
<td>5.363</td>
<td>114.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA at Pisiform (mm²)</td>
<td>11.36 (4.33)</td>
<td>8.31 (1.89)</td>
<td>5.883</td>
<td>112.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retinacular Bulge (mm)</td>
<td>3.21 (0.55)</td>
<td>2.83 (0.46)</td>
<td>4.873</td>
<td>159.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flattening Ratio at Pisiform</td>
<td>2.97 (0.67)</td>
<td>2.97 (0.67)</td>
<td>-0.003</td>
<td>164</td>
<td>0.998</td>
</tr>
<tr>
<td>CSA Change Radius-Forearm (mm)</td>
<td>4.26 (3.45)</td>
<td>2.31 (1.73)</td>
<td>4.615</td>
<td>120.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA Change Pisiform-Forearm (mm)</td>
<td>5.20 (4.11)</td>
<td>2.67 (1.84)</td>
<td>5.127</td>
<td>113.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA Ratio (Radius/Forearm)</td>
<td>1.71 (0.55)</td>
<td>1.44 (0.35)</td>
<td>3.714</td>
<td>138.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA Ratio (Pisiform/Forearm)</td>
<td>1.88 (0.67)</td>
<td>1.50 (0.36)</td>
<td>4.440</td>
<td>125.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3.3 Comparison of means (SD) of ultrasound measures of the median nerve between symptomatic and asymptomatic wrists.
Prior to analysis of EDX and ultrasound in the symptomatic group, all wrist level data points were compared between the dominant and non-dominant hands across all subjects to ensure that no similarities or correlation occurred between the hands of individual subjects that could influence the data. No patient effect was noted in the data when right and left wrists were compared and wrist data were deemed independent for analysis.

NCS results were used to categorize symptomatic wrists into normal (n = 32), mild (n = 25), moderate (n = 23) and severe (n = 3). Significant moderate to strong correlations were noted between ultrasound measurements and NCS results and the resulting diagnostic categorization of symptomatic wrists (Table 3.4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>DML (r)</th>
<th>SCV (r)</th>
<th>Severity (tau-b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.262</td>
<td>-0.0285</td>
<td>0.208</td>
</tr>
<tr>
<td>BMI</td>
<td>0.226</td>
<td>-0.409**</td>
<td>0.344*</td>
</tr>
<tr>
<td>Wrist Ratio</td>
<td>0.259*</td>
<td>-0.127</td>
<td>0.183*</td>
</tr>
<tr>
<td>CSA in Forearm (mm²)</td>
<td>0.211</td>
<td>-0.249*</td>
<td>0.161</td>
</tr>
<tr>
<td>CSA at Distal Radius (mm²)</td>
<td>0.515**</td>
<td>-0.595**</td>
<td>0.517**</td>
</tr>
<tr>
<td>CSA at Pisiform (mm²)</td>
<td>0.678**</td>
<td>-0.746**</td>
<td>0.595**</td>
</tr>
<tr>
<td>Retinacular Bulge (mm)</td>
<td>0.467**</td>
<td>-0.466**</td>
<td>0.385**</td>
</tr>
<tr>
<td>Flattening Ratio at Pisiform</td>
<td>0.082</td>
<td>0.025</td>
<td>0.021</td>
</tr>
<tr>
<td>CSA Change Radius-forearm (mm)</td>
<td>0.493**</td>
<td>-0.567**</td>
<td>0.509**</td>
</tr>
<tr>
<td>CSA Change Pisiform-forearm (mm)</td>
<td>0.648**</td>
<td>-0.706**</td>
<td>0.582**</td>
</tr>
<tr>
<td>CSA Ratio (Radius/forearm)</td>
<td>0.434**</td>
<td>-0.517**</td>
<td>0.430**</td>
</tr>
<tr>
<td>CSA Ratio (Pisiform/forearm)</td>
<td>0.578**</td>
<td>-0.623**</td>
<td>0.522**</td>
</tr>
</tbody>
</table>

* Significant at $P < .05$; **significant at $P < .001$

Table 3.4 Correlation of measurements to nerve conduction study (NCS) data and categorical severity of carpal tunnel syndrome diagnosis in symptomatic subjects (n=47 subjects/83 wrists)
The strongest correlations were observed for CSA at the pisiform ($r = .678-.746$), absolute change between the CSA at the forearm and CSA at the pisiform ($r = .648-.706$), ratio of CSA in the forearm to CSA at the pisiform ($r = .578-.623$) and to CSA at the radius ($r = .515-.595$). Moderate significant correlation was noted between the retinacular bulge measurement and NCS results. BMI was noted to be moderately correlated to SCV and the classification of diagnosis, but no significant correlation was noted between BMI and DML. In contrast, wrist ratio was mildly correlated with DML and diagnostic classification, but no significant correlation was noted to SCV. Age and flattening ratio showed no significant correlation to NCS results and a mild correlation was noted in CSA of the forearm to SCV.

Based on correlation results, CSA at the pisiform, the absolute change in CSA from the forearm to pisiform and retinacular bulge were further analyzed. A box plot of CSA at the forearm demonstrates the lack of any clear difference among the diagnostic groups, providing support for use of this measure as an internal comparison measure. Additional box plots display the increasing trend in measurement size of the diagnostic ultrasound measures by NCS severity category (Figure 3.3). Distribution of data in the moderate diagnostic group was much wider than other groups. While a general upward trend is noted for the measurement of the retinacular bulge, the distribution of measures is wider across all groups for this variable than is displayed by the other plots. Asymptomatic control measures included in the box plots demonstrate the similarity of measurements between the NCS normal classification and asymptomatic controls.
Figure 3.3 Box plots displaying data for various ultrasound measures (mm or mm$^2$) by diagnostic group
Receiver operating characteristic (ROC) curve analysis was completed based on positive or negative EDX results in the symptomatic subjects. ROC curves were generated for the four ultrasound measurements that previous literature and correlational analysis suggested as significant. ROC curves for CSA at the pisiform, retinacular bulge, CSA change and CSA ratio are presented in Figures 3.4-3.7. Diagnostic thresholds were determined based on ROC curves at 10.3mm², 2.94mm, 4.16mm², and a ratio of 1.70 for each measure respectively (Table 3.5). Sensitivity for each measurement was either 80.4% or 82.4% with variable specificity.

<table>
<thead>
<tr>
<th>Ultrasound measurement</th>
<th>AUC</th>
<th>95% CI</th>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA at Pisiform</td>
<td>0.899</td>
<td>0.833-0.964</td>
<td>10.3mm²</td>
<td>80.4%</td>
<td>90.6%</td>
</tr>
<tr>
<td>Retinacular Bulge</td>
<td>0.759</td>
<td>0.655-0.864</td>
<td>2.94mm</td>
<td>82.4%</td>
<td>59.4%</td>
</tr>
<tr>
<td>CSA Change Pisiform-Forearm</td>
<td>0.886</td>
<td>0.813-0.959</td>
<td>4.16mm²</td>
<td>82.4%</td>
<td>87.5%</td>
</tr>
<tr>
<td>CSA Ratio (Pisiform/Forearm)</td>
<td>0.842</td>
<td>0.756-0.928</td>
<td>1.70</td>
<td>80.4%</td>
<td>81.2%</td>
</tr>
</tbody>
</table>

Table 3.5 Sensitivity and specificity of various ultrasound measures
Figure 3.4 Receiver operation characteristic curves fitting for CSA at the pisiform measures versus electrodiagnostic testing results
Figure 3.5 Receiver operation characteristic curves fitting for retinacular bulge measures versus electrodiagnostic testing results

AUC: .759 (95% CI, .655-.864)
Figure 3.6 Receiver operation characteristic curves fitting for CSA change forearm-pisiform measures versus electrodiagnostic testing results

AUC: .886 (95% CI, .813-.959)
Figure 3.7 Receiver operation characteristic curves fitting for CSA ratio forearm-pisiform measures versus electrodiagnostic testing results
3.3 Discussion

The results of this study confirm findings of previous research indicating CSA of the median nerve at the pisiform as strongly correlated with EDX, the gold standard of diagnosis for CTS. These data also confirm that, while CTS is commonly thought of as a compression neuropathy, flattening ratio is not a useful measurement in diagnosis. More importantly, this study provides support for further investigation of the change in the CSA of the median nerve from the forearm within each individual. Furthermore, more detailed investigation is required to better differentiate various diagnostic severities and refine new techniques to improve the utility of ultrasound in screening for median nerve pathology.

While not as strongly correlated with EDX as a single CSA measure at the pisiform, interrogating the individual change in CSA within each individual shows promising utility in CTS screening. As the data indicate, there was a relationship between BMI and diagnostic measures in our subjects, which may validate the utility of an internal comparison measure. However, it is not clear if enlarged nerves are a pathological result of increased BMI or if the nerve is naturally larger due to the increased overall anthropometric composition of the individual. Researchers have indicated that the calculation of absolute value change in CSA between the forearm and pisiform has the potential to improve diagnostic accuracy. Other studies suggest that calculation of a ratio of these CSA measures provides improved accuracy. The data in this study indicate stronger correlations and increased distribution of data for an
absolute change score than with a ratio score, but both were not as good as the singular measure of CSA at the pisiform. Further cause and effect relationships may need to be studied in normal populations to better understand the impact of anthropometry to validate these comparative type measurements.

Although the single CSA measure at the pisiform stands up throughout the research literature, moderate to strong correlation of the CSA measure immediately proximal to the carpal tunnel at the radial-carpal joint may provide relevant diagnostic information. It is possible that space within the carpal tunnel may be restricted in some individuals due to anthropometry, leading to more significant enlargement of the nerve immediately proximal to or distal to the tunnel itself. Swelling at multiple levels, on a continuum, within the carpal tunnel region is likely.\(^9\) Therefore, by obtaining images and measurements at only one specific anatomic landmark within the carpal tunnel, the largest CSA may not be obtained on every individual, reducing overall diagnostic accuracy.\(^9\) Improved diagnostic accuracy for clinical protocols may occur with measurement of the largest CSA in the entire carpal tunnel region.\(^15,20\)

Calculated diagnostic thresholds are consistent with previous research at approximately 10mm\(^2\) for CSA at the pisiform and a threshold of approximately 3mm for the height of anterior retinacular bowing. The sensitivity of these diagnostic threshold values were moderately high (80%), and specificity was noted to vary among the measures. Because EDX was completed only for symptomatic patients, the extreme variability noted in accuracy of EDX may have influenced the accuracy of the US
measures.\textsuperscript{19, 21-23} Despite the low and possibly unreliable accuracy measures, the moderate to strong correlations of ultrasound measurements to EDX measures requires continued investigation. ROC curve analysis completed based on multiple diagnostic categories may more accurately reflect the trend that is suggested by strong correlations. Furthermore, the results of the current study may be limited due to the assumption of independence of data from wrists in the same individual. Further analysis of these data and similar biomedical research may best be completed by techniques that investigate clustered data instead of assuming independence.

These statistics support previous work, by indicating that the selected ultrasound measures are very good at differentiating normal from severe CTS.\textsuperscript{21} However, ultrasound measurements are not as good at differentiating mild cases from normal cases. This may lead to the use of ultrasound as a screening tool to identify more severe cases that do not require follow-up with EDX.\textsuperscript{22} Additionally, there is a cross-section of symptomatic patients that have normal EDX and are not significantly different from control subjects on ultrasound measures. Because ultrasound has the ability to measure acute changes in physiology, it may aid in identification of physiology involved in symptomatic subjects that have normal EDX. Ultrasound measurement of CSA at the pisiform has previously been reported to help diagnose CTS in patients with EDX negative tests.\textsuperscript{6} However, this conclusion was based on very different accuracy outcomes with sensitivity of 30.5\% and specificity of 96.7\%. Furthermore, the results of
the current study do not show any difference in ultrasound measurements between asymptomatic controls and patients with normal EDX.

Further evaluation of the use of ultrasound for improved screening may lie in the development of additional measures or qualitative evaluation techniques. In this study numerous variations in the morphology were observed in the longitudinal view of the median nerve at the carpal tunnel level. The most convincing observation was of anterior-posterior swelling of the nerve (Figure 3.8). A notch-sign or waistline effect was noted in the longitudinal view of the nerve in other subjects. Previous use of a qualitative scale for observing these changes in the longitudinal view has resulted in reported sensitivity of 50% and specificity of 95.8% to 100%.\textsuperscript{18,24} Combination of this qualitative measure with the quantitative measure of CSA increased sensitivity to 89.1%.\textsuperscript{24}
In addition to specific changes in the median nerve, observation and measurement of the entire wrist and hand region may provide useful information. Differences noted in the wrist ratio between the symptomatic and asymptomatic controls support previous literature. Developing ultrasound techniques to explore the internal measurements of the carpal tunnel may be a more precise measure than external anthropometry. Ultrasound may also be useful in observation of the space occupied by the flexor tendons or excursion of the lumbricals into the carpal canal. Measurement of edema within the carpal tunnel may help to identify a differential diagnosis of tendonitis and guide treatment in a different direction. Similarly, the
investigation of hyperemia or ischemia both within the nerve and in the entire region may assist in identifying pathology, especially in acute or mild cases where EDX is not convincing. It has been suggested that evaluation of other anatomic anomalies may help in diagnosis of CTS and identification of these anomalies can impact the course of treatment. However, bifurcated nerves and persistent median arteries occurred at similar rates in both symptomatic and asymptomatic populations and may not provide valid contribution to diagnosis of pathology.

The primary limitation of this study is the lack of a control group with comparative data. While asymptomatic controls were recruited and utilized to provide a baseline comparison to the symptomatic patients, EDX was not collected on the control subjects, which may have caused artificial significance of diagnostic results from only a patient population. The results of this study may represent a patient population and the comparative data inform future studies. Inherent differences between the groups were noted with the patient population being older and having a larger BMI. However, since age and BMI have both been suggested as contributory factors to the development of CTS, these group differences may not have had considerable impact on comparative outcomes. Future studies may better control these factors by matching control to patient subjects. Finally, while wrists diagnosed in the severe category were notably different in ultrasound measurements from the other groups, the relatively low number of subjects with a severe diagnosis, as compared to other diagnostic outcomes, limits the interpretation of results. Future studies with even distribution across all
diagnostic categories, or recruitment for comparison of specific categories are needed to gain a deeper understanding of diagnostic utility for these ultrasound measures.
3.4 References


Chapter 4: Ultrasonography as a predictor for subjective symptoms of carpal tunnel syndrome

Numerous personal, physical, and psychosocial exposures have been suggested as contributory factors in the development of carpal tunnel syndrome (CTS). Because no one factor has been directly linked to the development of CTS, it is likely that a combination of factors can increase an individual’s risk for developing median nerve pathology. Personal factors, such as age, gender, anthropometry, and co-morbidities, have been tied to CTS. Gender and anthropometric measures are the two most likely relevant personal factors in the etiology of CTS, which are further influenced by psychosocial stressors and physical exposures.

Upper extremity disorder research shows a striking effect of gender, with females being significantly more likely to have symptoms in the hand/wrist. The reasons for this increased risk in females is unknown, but an interaction with the exposure to different physical and psychosocial factors may be directly responsible for differences in the occurrence of musculoskeletal symptoms by gender. Female flexor tendons tend to occupy more space within the carpal canal which could be a cause for increased pathology. When women reported negative psychological stress, a significant increase in motor unit activation in the upper trapezius is noted. Physiological
responses to physical and psychological stress may manifest differently in females than in males resulting in variable expression of median nerve pathology.

Regardless of gender specific differences, anthropometry may contribute to differences in the space that is available within the carpal tunnel. Wrist ratio, calculated as the anterioposterior depth divided by mediolateral width, has been linked to the development of CTS.\textsuperscript{13-15} Wrist ratio has a high sensitivity and specificity for diagnosing CTS in symptomatic patients.\textsuperscript{15-17} More than seventy-five percent of individuals with CTS have a square-shaped wrist (ratio > .70)\textsuperscript{14} and a more significant rate of association was noted as the ratio increased (> .75).\textsuperscript{16} While the shape of the carpal tunnel may naturally restrict space, lumbricals from the hand have also been found to occupy space within the carpal canal during certain movements.\textsuperscript{18,19}

The combination of natural anthropometry and physical movements and stress may contribute to an increased risk of CTS. Research on physical stressors related to CTS focus mainly on increased compression of the median nerve due to extreme positions.\textsuperscript{20} Forearm pronation and supination increase pressure in the carpal tunnel,\textsuperscript{21} wrist flexion and extension can reduce the area within the carpal tunnel,\textsuperscript{22} and prolonged or repetitive ulnar deviation of the wrist\textsuperscript{23} causes lateral compression on the median nerve. Each of these positions has been associated with higher prevalence of CTS symptoms in a working population. Similar to the movement of the lumbricals with hand use, the flexor tendons travel anterior with wrist flexion.\textsuperscript{24} Because more proximal portions of the tendons are naturally larger, this forward movement of tendons along
with natural reduction of the carpal tunnel space with wrist flexion creates the greatest compression of the median nerve.\textsuperscript{25} Vibration and direct compression\textsuperscript{20} as well as prolonged exposure to highly repetitive and forceful hand-wrist tasks are also frequently acknowledged as physical risk factors for CTS.\textsuperscript{26, 27}

Epidemiological research indicates that regardless of the extent of physical exposure, an increase in exposure to psychological stressors is related to an increase in wrist and hand symptoms.\textsuperscript{28} Psychological demands of a job, combined with decision latitude and control of the work tasks have been linked to changes in health\textsuperscript{29} and have a fundamental impact on quality of life.\textsuperscript{30} A significant number of research studies have validated the impact of these factors in different occupations.\textsuperscript{31-33} The interaction of these factors results in a classification of four job styles that can be used to predict adverse health effects in workers (Figure 1).\textsuperscript{34} High demands and low control occurring simultaneously create high strain within a worker, whereas, low demands and high decision latitude results in low psychological strain. Active jobs with high demands and high control increase motivation and promote learning in workers and passive jobs requiring minimal psychological involvement and low control over the work encourages stagnation.\textsuperscript{34}
Ultrasonography has been gaining significant attention in research related to the diagnosis of CTS.\(^\text{35}\) Sonography has been shown to correlate with subjective symptoms\(^\text{36}\) and has been used as a dependent outcome measure following treatment and surgery.\(^\text{37}\) While a plethora of studies have been completed to evaluate the predictive relationship of various personal and physical exposures,\(^\text{4,38-40}\) no studies have specifically evaluated the utility of sonography measures as predictors of subjective symptoms.
Based on current literature, it is apparent that a combination of personal, physical, and psychosocial factors contributes to an increased risk of physiological changes in the median nerve and the incidence of CTS. The objective of this study was to investigate the relationship of previously studied factors and innovative physiologic measures of the median nerve (MN) with grey-scale ultrasonography (US), compared to subjective reports of symptoms and decreased function due to MN pathology.

4.1 Research Design

Data were collected from patients referred to a neurology clinic for evaluation of median nerve pathology and from a convenient sample of non-patient working adults. Recruitment into the study was non-specific, provided individuals met all criteria for participation. This protocol was approved by The Ohio State University Biomedical Institutional Review Board and all subjects provided signed consent to participate.

4.1.1 Subjects

A heterogeneous sample was recruited for participation in this study to maximize the distribution and variability of data for an exploratory regression analysis of various independent variables. Subjects were recruited from both clinical and non-clinical sites and were of working ages, between 18 and 65 years old. Subjects were excluded from participation prior to consent if they had a history of fracture or surgery in their dominant wrist, if they were pregnant or within three months post-partum, or if they had known rheumatic disorder, polyneuropathy, or uncontrolled thyroid disorder. Subjects were excluded following consent when anatomic anomalies, i.e. bifurcated
median nerve or Martin Gruber anastomosis, were discovered during data collection. To ensure statistical power, a minimum of 10 subjects per variable were recruited, i.e. 80 subjects.

4.1.2 Variables

Regardless of physiologic or clinical test results, diagnosis of CTS requires subjective report of symptoms and functional deficits. Since no perfect gold standard of diagnosis exists for CTS, exploration of factors contributing to subjective reports provides a clear grouping mechanism for regression analysis. The Boston Carpal Tunnel Questionnaire (BCTQ) provides a subjective measure of both symptom severity (SS) and functional status (FS) related to median nerve pathology. Subjects were instructed to complete the BCTQ based on the dominant hand. An average was calculated for both the SS and FS scales for each subject. Subjects with average scores greater than 1.0 for either scale were considered to have complaints of median nerve pathology. Those subjects with average scores of 1.0 on both scales were considered to have a lack of symptoms.

Anthropometric and personal measures were collected for each subject. These factors included subject age, gender and hand dominance. Body mass index (BMI) was calculated for each subject based on height (cm) and mass (kg), measured on the date of data collection. Wrist ratio was calculated for the dominant wrist of each subject as the depth (mm) divided by the width (mm) of the wrist.
Questions from the job content questionnaire (JCQ) were utilized to obtain ratings of psychosocial strain in the workplace based on decision latitude (control) and psychological demands (demand).\textsuperscript{31} Scores for control and demand were calculated for each subject and these scores provided categorization of individual subjects into one of four job classifications. Subjects providing scores greater than 30 for both control and demand were considered to have active jobs and those subjects with jobs scoring below 30 on both scales were considered to be in passive occupations. Subjects that indicated having high control but low demands were categorized as having low strain occupations and those occupations with high demands and low control were categorized as high strain.

Additional demographic, work exposure and person data were collected to describe the subjects. Subjects reported their level of education in one of three categories: (1) high school or less, (2) associate or bachelor degree, (3) masters or doctoral degree. Because no objective or observational measurement of work exposure could be obtained, the subjects provided the average number of hours worked per week and their job title. Finally, subjective mental health and physical heath were obtained with the Self-Rated Health Short Form-12.\textsuperscript{42} (Refer to Appendix A for a copy of the complete subject questionnaire.)

A Logiq i hand-carried ultrasound console with a 12-MHz linear array transducer (GE Healthcare Ultrasound, Milwaukee, WI) was used to collect images of the median nerve in every subject. Ultrasonography was completed utilizing a previously published
protocol. Cross-sectional images were obtained in the dominant upper extremity of each subject (1) at the forearm 6 cm from the distal wrist crease, (2) in the middle carpal tunnel at the level of the pisiform, and (3) in the distal carpal tunnel at the hook of the hamate.

Physiologic data were obtained by measuring the MN in the images collected from each subject. Cross-sectional area (CSA) of the median nerve was measured via a direct trace along the inner hypoechoic border of the median nerve in the forearm and at the level of the pisiform. A CSA change score was calculated for each subject by subtracting the CSA at the pisiform from the CSA at the forearm. Anterior bowing of the flexor retinaculum was measured as the perpendicular distance from the outer most edge of the flexor retinaculum to a line drawn from the insertion points on the trapezium and hook of the hamate. All measurements were completed five times, the highest and lowest measures were dropped and the remaining measures were averaged. The researcher completing measurements was blinded to subject complaints and recruitment method.

4.1.3 Statistical Analysis

Descriptive statistics were calculated and comparison between subjects with and without complaints was completed for all variables utilizing t-test or chi-square analysis as indicated. Occupations were categorized based on JCQ results to obtain descriptive grouping for qualitative discussion and comparison between groups based on BCTQ results. All descriptive statistics were completed with SPSS (Version 19).
To evaluate the relationship of personal, physical and psychosocial variables to complaints of median nerve pathology, an exploratory stepwise binary logistic regression analysis was completed. Initial odds ratios were calculated for the contribution of each individual variable to the BCTQ group. Adjustments were made to variables with small units of measure to provide appropriate odds ratios. When a set of variables were noted to be highly correlated, only one variable was included in the final model. Variables were included in the final stepwise regression based on published literature and the results of individual odds ratios. A 0.10 selection criteria was utilized and final odds ratios were calculated for variables that remained in the model following forward and backward stepwise iterations.

4.2 Results

Ninety-five subjects were consented for participation in the study and seven subjects were excluded following consent due to anatomic anomalies. Scores on the BCTQ were calculated for the remaining 88 subjects and 56 subjects (63.6%) reported symptoms or functional limitations in their dominant hand. Statistical averages and frequencies were calculated and compared using t-test or chi-square analysis between the resulting groups for all variables (Table 4.1). No differences were noted between age, gender, hand dominance, height, wrist ratio, or mental health scores between the two groups. Significant differences ($p < .05$) were observed in education, BMI, SF-12 physical health score, and for all sonography measures.
Table 4.1 Characteristics of subjects with and without complaints

<table>
<thead>
<tr>
<th></th>
<th>Complaints (n=56)</th>
<th>No Complaints (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>44.4 (11.5)</td>
<td>40.8 (12.3)</td>
<td>0.163</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>44:12</td>
<td>22:10</td>
<td>0.306</td>
</tr>
<tr>
<td>Hand Dominance (R:L)</td>
<td>51:5</td>
<td>27:5</td>
<td>0.341</td>
</tr>
<tr>
<td>Education (H:C:G)</td>
<td>27:18:11</td>
<td>5:17:10</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.3 (8.4)</td>
<td>169.0 (8.6)</td>
<td>0.155</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>88.5 (21.6)</td>
<td>74.2 (17.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>32.1 (7.7)</td>
<td>26.0 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wrist Ratio</td>
<td>0.726 (0.044)</td>
<td>0.717 (0.044)</td>
<td>0.351</td>
</tr>
<tr>
<td>SF-12 Physical Health</td>
<td>41.0 (10.7)</td>
<td>54.2 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-12 Mental Health</td>
<td>50.3 (10.2)</td>
<td>53.4 (6.0)</td>
<td>0.080</td>
</tr>
<tr>
<td>CSA at Forearm (mm²)</td>
<td>6.06 (1.30)</td>
<td>5.55 (0.94)</td>
<td>0.038</td>
</tr>
<tr>
<td>CSA at Pisiform (mm²)</td>
<td>11.11 (4.01)</td>
<td>8.32 (1.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retinacular Bulge (mm)</td>
<td>3.26 (0.49)</td>
<td>2.86 (0.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>CSA Change Forearm-Pisiform (mm²)</td>
<td>5.06 (3.82)</td>
<td>2.77 (1.62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

F:M, female:male, R:L, right:left, H:C:G, high school:college:graduate, CSA, cross-sectional area

All occupations reported by the subjects are listed in Table 4.2 based on results of the JCQ. The majority of subjects indicated having active (42.0%) or low strain jobs (36.4%), while only nine subjects indicated having high strain or passive jobs. Ten subjects reported being unemployed and were not included in this descriptive analysis. Nearly all subjects having high strain or passive jobs were in the complaint group. Approximately two-thirds of subjects with active jobs fell into the complaint group; whereas, only half of subjects with low strain jobs had complaints. Figure 4.2 provides a graphical display of the distribution of subjects by group within each categorization.
<table>
<thead>
<tr>
<th>Complaints</th>
<th>Active (n=37)</th>
<th>Low Strain (n=32)</th>
<th>High Strain (n=7)</th>
<th>Passive (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative Assistant</td>
<td>2</td>
<td>2</td>
<td>Bus Driver (2)</td>
<td>Personal Banker</td>
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<tr>
<td>Attorney</td>
<td>Babysitter</td>
<td></td>
<td>Registered Nurse (3)</td>
<td>Surgical Technician</td>
</tr>
<tr>
<td>Audiologist</td>
<td>Customer Service Representative</td>
<td></td>
<td>Telemarketing Representative</td>
<td></td>
</tr>
<tr>
<td>Educator/Faculty (5)</td>
<td>Dock Worker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook/Food Service (2)</td>
<td>Fellowship Coordinator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Administrator</td>
<td>Home Health Aide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifeguard</td>
<td>Homemaker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lift Operator</td>
<td>Insurance Broker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Technologist</td>
<td>Janitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse Anesthetist</td>
<td>Physical Therapist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse Assistant</td>
<td>Physical Therapist Assistant</td>
<td></td>
<td>Respiratory Therapist</td>
<td></td>
</tr>
<tr>
<td>Painter/Drywall (Union)</td>
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<td></td>
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<td></td>
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<td>Paramedic</td>
<td>School Librarian</td>
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<tr>
<td>Pharmacist</td>
<td>Therapy Attendant</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Registered Nurse (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheduler</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Service Manager</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprinkler Fitter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Complaints</td>
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<td></td>
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<tr>
<td>Accountant</td>
<td>Administrative Assistant (3)</td>
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<td>Undergraduate Student</td>
<td></td>
</tr>
<tr>
<td>Administrative Assistant</td>
<td>EMG Technician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educator/Faculty (3)</td>
<td>Graduate Student (5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Finance Director</td>
<td>Manager</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Transcriptionist</td>
<td>Occupational/Physical Therapist (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse Case Manager</td>
<td>Physical Therapist Assistant (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered Nurse</td>
<td>Professor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonographer (2)</td>
<td>Speech-Language Pathologist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tax Reporting Manager</td>
<td>Substitute Teacher/EMT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2 Job content questionnaire categorization of occupations reported by subjects with and without complaints (unemployed, n=10)
Figure 4.2 Percent of subjects with and without complaints of symptoms or decreased function on the Boston Carpal Tunnel Questionnaire by job categorization based on the Job Content Questionnaire

Initial odds ratios of each variable for predicting BCTQ complaints are presented in Table 4.3. Of the individual odds ratios, BMI, education, and all US measures were noted to be significant \( (p < .05) \). Units of measure were adjusted for wrist ratio (x100) and retinacular bulge (x10). It was determined that CSA change and CSA ratio scores were highly correlated with CSA at the pisiform and these factors were eliminated from further consideration in the model with the assumption that the variables shared information. Although age, gender, and wrist ratio were not noted to be individually significant, previous literature indicated that these variables should be considered as important when analyzing the full regression model.
Table 4.3 Univariate odds ratios for various characteristic variables for predicting complaints related to carpal tunnel syndrome

A significant stepwise binary logistic regression model was obtained ($r^2=0.281, p=0.002$) with BMI, education, and CSA at the pisiform combining to predict the presence of complaints of symptoms or decreased function in the subjects. For every 1 mm$^2$ increase in CSA at the pisiform, subjects are 1.3 times more likely to complain of symptoms and odds are 1.1 times higher as BMI increases. Based on this exploratory model there is a trend that individuals with a high school education are 3.5 times more likely to complain of symptoms or functional limitations than those with graduate level education. Final odds ratios are listed in Table 4.4.

Table 4.4 Final model for factors predicting complaints related to carpal tunnel syndrome based on stepwise binary logistic regression ($p=0.002$)
4.3 Discussion

This preliminary study indicates that changes in sonographic measures of the median nerve may provide more relevant information for predicting median nerve pathology than other previously studied factors. Gender, BMI, and wrist ratio have previously been noted to be primary personal factors that are related to CTS; however, this analysis indicates a potential significant contribution of level of education and morphological measures of the nerve.

The outcomes of this exploratory analysis are in contrast to results of previous studies exploring the predictability of sonographic measures. Kaymak et al. found that CSA measurements of the median nerve in the carpal tunnel had no correlation to the BTCQ SS and FS scales [-0.04-.18], whereas electrodiagnostic testing results were moderately correlated to subjective reports. The lack of correlation in this previous study interpreted as an inability of sonography to predict carpal tunnel may be limited. Statistical analysis was limited and the study did not include numerous factors that may predict CTS. The regression analysis with sonographic measurements and CTS symptoms as completed in the current study provides a better analysis of predictability.

To demonstrate this predictive relationship, sonographic measurements have been noted to be predictive of subjective reports in subjects prior to and following carpal tunnel release surgery. As in the previous study, no direct correlation was found between sonographic measures and the BCTQ, but a regression analysis indicated a relationship of sonographic measures to subjective reports. For every reduction in
1mm² of CSA following surgery, the odds of individuals being in the non-complaint group based on the BCTQ increased by 20% to 24%. The results of this regression may provide more information relative to the success of surgical intervention than they do to the relationship of sonography to symptoms reports. However, these results provide foundational evidence that can be combined with the results of the current study to promote the continued investigation of sonographic measures.

In addition to the relationship of sonographic measurements to subjective reports, it is important to consider additional factors that may contribute to symptoms and decreased functional tolerances. Research indicates that the prevalence of musculoskeletal disorders is twice as high in females as in males, and may be up to as much as 4.4 times higher in females. Although the prevalence of disorders is higher in females, Mondelli et al indicated that men have up to five times higher probability of reduction of subjective reports following surgical intervention than females. The contradiction in research may indicate that the influence of gender on the physiological state as measured by sonography may be different than the relationship of gender to symptom reports. The initial odds ratios in the current exploratory regression did indicate a trend of difference in subjective reports based on gender. However, these results were not significant when considered alone, and gender was not noted to be a significant predictor when considered in the full regression model with all other variables. The contribution of gender may not have had enough power to adequately
affect the regression due to the disproportionate ratio of female to male subjects in the sample of this exploratory study.

Secondary to gender, anthropometric measures have been shown to have a high correlation to the development of CTS. Of these measures, wrist ratio has been one of the primary factors showing positive relationship to CTS.\textsuperscript{14,15,47} In the current study, wrist ratio was not significantly different between the groups and it was not a predictor of group assignment. Previous studies have reported a relationship of wrist ratio to diagnosis of CTS by electrodiagnostics;\textsuperscript{4,40} whereas, the current study has investigated the relationship of wrist ratio to subjective complaints of possible median nerve pathology. Although wrist ratio was not noted to be a significant predictor of symptoms or decreased function, BMI was a significant predictor. BMI has previously been shown to be different between CTS patients and controls.\textsuperscript{40} For each unit increase in BMI the risk of CTS nearly doubles\textsuperscript{4} and those with BMI greater than 30 are four to nine times more likely to receive surgical intervention for CTS than those with BMI less than 25.\textsuperscript{38} Unlike the lack of correlation to subjective reports noted with wrist ratio, SS and FS scores have been noted to be lower in individuals with lower BMI.\textsuperscript{48} A closer evaluation of the relationship between physiology and anthropometric measures should continue to be investigated.

The significant influence of the level of education on the presence of subjective reports was not an expected outcome, but may have theoretical significance. Less formal education is often required for more physically demanding jobs, while college
and graduate education often lead to less physical occupations. People with blue collar occupations may be up to seven to nine times more likely to have been surgically treated for CTS than white collar jobs. In a study with a homogenous subject population, medical transcriptionists without a college education self-reported more upper extremity symptoms than those with college education. In the current study, subjects with blue collar occupations, that would require less education, typically reported complaints, but numerous subjects with skilled jobs also had complaints. Together these results could indicate that education could be a more important factor than occupational categorization. However, because none of these studies specifically measured physical exposure related to the occupations, the relative importance of educational level and occupational exposure remains unclear.

In addition to the limited analysis of physical and psychosocial factors in this study, it should be noted that this study was limited by a small, heterogeneous sample. The results may be best interpreted as an exploratory analysis of the contribution of various factors to subjective reports. In order to better understand the relationships between this extensive set of variables, a sample of two-times the size may be required. Furthermore, matching subjects for age and gender, between clinical and non-clinical populations, would provide better control of variables in order to explain variance and gain a better understanding of the remaining variables. The exploration of psychosocial and physical exposure factors was limited due to the type of measures chosen as
variables in this study. More precise measurement of these variables or a change in the subject inclusion criteria could enhance the interpretation of these factors.

4.4 Conclusion

This study was successful in exploring the contribution of a variety of suspected contributory factors of CTS, of which sonography may be an important indicator of median nerve pathology. Further research is required to improve the understanding of each of these factors coupled with a more objective outcome measure. Utilizing the CSA of the median nerve as the outcome measure in a linear regression model could provide stronger evidence with regard to the influence of personal, psychosocial, and physical factors as predictors of physiologic changes. While large homogenous participant samples are required to validate these findings, the preliminary data provided suggest continued investigation of sonography as a screening tool for median nerve pathology.
4.5 References


28. Devereux JJ, Vlachonikolis IG, Buckle PW. Epidemiological study to investigate potential interaction between physical and psychosocial factors at work that may increase the risk of symptoms of musculoskeletal disorder of the neck and upper limb. *Occup Environ Med*. Apr 2002;59(4):269-277.


Chapter 5: Research findings and future directions

The objective of this research was to investigate the utility of ultrasonography as a tool for obtaining physiologic data in carpal tunnel syndrome (CTS). To validate this tool, a systematic review of previously published literature was completed to develop data collection and measurement protocols. These protocols were used to collect data for comparison of ultrasonographic measurements to current clinical diagnostic standards and exploration of the relationship of physiological measures to the symptoms of CTS.

5.1 Summary of Findings

In chapter 2, it was discovered that significant variability exists in current research literature regarding the diagnostic accuracy of ultrasonographic measurements as compared to current clinical gold standards. This variability was due in part to a lack of standardization in the description of protocols, quality control, and measurement techniques. The sonographic measurement that demonstrated the most promise was the largest cross-sectional area (CSA) of the median nerve within the carpal tunnel region. Measurement techniques that require further research and standardization include observation of swelling of the median nerve from the forearm to the carpal
tunnel region, qualitative observation of nerve compression or edema, and investigation of changes intraneural vasculature using Doppler techniques.

Utilizing a clear methodological protocol with adequate quality control informed by the systematic review, data were collected to demonstrate a positive relationship between ultrasonographic measurements and electrodiagnostic testing (EDX). Data presented in chapter 3 support the findings of the systematic review, indicating that flattening ratio of the median nerve is not a relevant diagnostic measurement and that CSA of the median nerve within the carpal tunnel had the greatest diagnostic accuracy of all the sonographic measures. Retinacular bowing and swelling of the median nerve had moderate to strong correlation with EDX and provided high sensitivity, suggesting continued investigation of these measurement techniques.

Finally, validated sonographic measures of physiology were compared to various personal, psychosocial and physical factors previously reported to be predictive of CTS. The exploratory logistic regression analysis completed in chapter 4 indicated that sonographic measurements may provide relevant information to predict the presence of symptoms and decreased function due to CTS. These preliminary findings support continued investigation of sonography as a screening tool for median nerve pathology.

5.2 Limitations

The primary limitations of the studies in this report involve the sample size and subject characteristics. Both the comparative analysis of sonography to nerve conduction and the regression analysis were limited by small sample sizes. Because
control subjects and clinical patients were recruited from a convenient sample, differences may exist in the data due to the grouping of subjects instead of being attributed to the variables being studied. Additionally, while the data suggested significant differences in sonographic measures among subjects categorized as having severe CTS based on EDX, this may be an overestimate of the effect due to a very small number of subjects in this diagnostic category.

Although quality control measures and specific methodologies based on the recommendations of the systematic review provided good internal validity for these studies, statistical analysis techniques were limited. A significant limitation in the analysis of diagnostic accuracy of sonographic measurements in this study was the evaluation of data by wrist. Treating the two wrists of the same individual as independent has the potential to cause significant error in the analysis. Furthermore, using EDX as the comparison measure creates difficulty for interpretation of diagnostic accuracy, as EDX is not a perfect gold standard for the diagnosis of CTS.\textsuperscript{1,2}

In addition to improved statistical analysis, multiple measurement techniques require refinement in the investigation of risk factors. Previous equation modeling with a broad focus of job demands factors did not indicate that job demands were adequately related to symptoms; however, the subjective measures of job demands in this previous study did not evaluate specific components of job related stress.\textsuperscript{3} Specific psychosocial data were collected with the Job Content Questionnaire, but these data could not be easily analyzed due to missing information from unemployed subjects.
There was a lack of physical exposure data to adequately assess the contribution of physical risk factors. Additionally, with the exception of anthropometric and physiological measures, data collected in the investigation of risk factors was obtained through subjective questionnaires. Self-reports tend to overestimate risk and may be related to psychological (e.g. anxiety, depression) or other personal factors. More precise and comprehensive measurement of risk factors is required. Collection of a numeric dependent measure instead of categorical data could allow for the completion of more powerful regression techniques in future research.

Due to these limitations, the interpretation of results in these studies was restricted to identifying trends that occurred in the data and informing the methodology of future studies. Future studies will require significantly larger samples with an equal distribution of CTS severity that have age, gender and body type matched controls. Further research using cluster analysis techniques to analyze diagnostic accuracy in data that may not be independent is needed. Finally, future research should be designed with specific measurement tools and techniques in mind to provide valid and reliable data to successfully study the interrelationship of various risk factors for CTS.

5.3 Future Research

Despite limitations, these data indicated that ultrasonography has potential utility for CTS screening and informs additional analyses and future research opportunities. Most epidemiological studies have been cross-sectional or retrospective cohort studies. These studies provided incidence rates and preliminary data on risk
factors, but did not investigate the specific physiological mechanisms. Further investigation is needed to understand and monitor acute changes in physiology and the overall dose-response relationships of factors leading to UE WRMSD. Longitudinal, prospective studies could assist in understanding the relationship of risk factors to specific physiological changes. High quality studies in large populations with varying degrees of exposure to risk factors, adequate follow-up periods, and precise diagnostic procedures are needed to determine the effect of interventions to reduce costs, reduce disability, and increase quality of life in the work force.  

5.3.1 Ultrasonographic Methods

While it has been difficult to show that ultrasonography can be a primary tool for diagnosis of CTS, based on the recommendations of the systematic review and the results of the studies in this report, multiple measurement techniques and research methods require investigation to support the use sonography as a screening tool for work related pathology. In the comparative analysis in this report, measurement of the CSA of the median nerve were collected and analyzed at specific bony landmarks. These data may be better analyzed through identification of the largest CSA within the entire wrist region instead of only obtaining CSA at specific locations. Obtaining a dynamic scan of the entire carpal tunnel region will allow investigators to determine the location of the absolute largest CSA, eliminating the chance that it was not imaged.

Qualitative observations, within the carpal tunnel region, have received preliminary investigation with mixed results. In the current research, no qualitative
analysis of the images was completed, but anecdotal evidence existed in multiple cases relative to edema around the nerve and visual signs of compression or swelling of portions of the nerve. Preliminary investigation of qualitative categorization of signs of compression in the longitudinal view of the median nerve show possible use in screening.\textsuperscript{9,10} However, the reliability and reproducibility of measures in longitudinal views of the median nerve require careful consideration for research and clinical methodologies.

Hypervascularization of the median nerve observed with power and spectral Doppler has been proposed as a method for predicting or identifying CTS.\textsuperscript{11,12} The lack of information provided in previous studies regarding vasodilatation status of the subjects, average systolic peaks, and other Doppler measurements presents challenges for understanding true utility of these measures. While more specific research is needed to standardize and understand blood flow data, spectral Doppler tracings are able to be obtained in subjects that may indicate changes in the median nerve sheath of symptomatic subjects (Figure 5.1). The use of contrast media is often used to enhance Doppler measures in various diagnoses and may improve the ability to obtain reliable data in median nerve vascularization.\textsuperscript{13} Further investigation of the utility of contrast materials and optimization of ultrasound equipment is needed to improve the reliability and validity of obtaining Doppler flow in the median nerve.\textsuperscript{14}
Figure 5.1 Spectral Doppler tracing of vascular flow within the median nerve

MRI has previously been utilized to observe the relative location and movement of the median nerve with various positions of the wrist,\textsuperscript{15,16} however, because dynamic scanning is possible with ultrasonography, multiple additional methods may be beneficial for screening protocols. Entrapment of the median nerve may occur with certain movements of the arm, wrist and fingers during various functional tasks. Similarly, with repetitive movements, continuous sliding of the nerve or surrounding structures may cause friction, leading to nerve pathology. Indirect measurement of anatomical movement in grey-scale images have been proposed to measure the longitudinal excursion of the median nerve with dynamic wrist\textsuperscript{17,18} and finger motions.\textsuperscript{19,20} Other research indicates that direct measurement of median nerve
movement with spectral Doppler ultrasound may be better than grey-scale for investigating tracking of the longitudinal movement of the nerve during wrist movement.\textsuperscript{21, 22} In addition to longitudinal excursion, dynamic ultrasonographic scanning increases the ability to observe entrapments, deformations, and lateral displacements of the median nerve with movements of the wrist and fingers and with certain functional activities.\textsuperscript{23}

The ability for ultrasonography to identify acute changes in pathology that may be present prior to secondary nerve damage is a primary consideration for continued research in the utility of musculoskeletal sonography. In addition to identification of diagnostic thresholds, it is imperative that the progression of pathology be well understood across the various measurement methods. Further investigation of qualitative methods, Doppler investigation of vascularization, and dynamic movements of the nerve, especially those that show changes in subjects with known CTS\textsuperscript{24} or following surgery,\textsuperscript{25} can provide valuable information for the use of ultrasonography as a screening tool. Comparison of asymptomatic subjects and diagnostic subjects to a group of symptomatic subjects that have negative EDX may provide the best opportunity to understand how sonography may be beneficial in identification of acute changes in the development of CTS and WRMSD. Few studies have evaluated sonographic measurements in this population.\textsuperscript{26, 27} Without understanding the full spectrum of changes in physiology, valuable screening techniques remain undeveloped.
5.3.2 Carpal Tunnel Syndrome Risk Factors

Gender differences and anthropometric measures have the most direct relationship to carpal tunnel in previous research and similar correlations are noted in this current research; however, additional personal factors may require further investigation. Previous medical histories, including past or current comorbidities (e.g. diabetes) and past history of wrist trauma,\(^28\) can double or triple the risk for developing carpal tunnel syndrome.\(^29\) Similarly, a concurrence of depressive symptoms has a high positive correlation with upper extremity symptoms and disorders.\(^30\) Additionally, it is important to realize that not only do personal factors interact together, but these factors also interact with psychosocial and environmental factors.\(^31\) In a study of the Italian population, the specific combination of factors that elevated population risk for developing carpal tunnel syndrome symptoms were females in their sixth decade who lived in rural-industrial populations.\(^32\)

This set of studies was not able to effectively identify the impact of the psychosocial work environment; however, without a better understanding of the psychosocial factors, ergonomic interventions and health promotions may fail.\(^33\) Continued investigation of the control-demand job strain model is warranted. Previous evidence ties both passive and high-strain jobs to WRMSD; therefore, it is possible that job control has a larger impact on health than demands in this model. If this is true, changes in administrative policies or working conditions that provide workers with more decisions or control in the work environment may result in decreased strain, followed by
decreased psychological stress and improved health.\textsuperscript{34} Further consideration is needed to understand the relationship of low decision latitude (control) to other personal factors, including gender, ethnicity, and income.\textsuperscript{35}

A third dimension of psychosocial stress in the workplace that may also require investigation is social support.\textsuperscript{36} Low social support received from supervisors and co-workers contributes to stress due to isolation (iso-strain) and decreases the overall health of working individuals.\textsuperscript{37} When iso-strain conditions occur (high demands, low control, and low support), workers tend to experience the lowest level of psychological well-being.\textsuperscript{38} Job demands have been shown to have an inverse relationship to environmental conditions and job control has been related to social relationships, but research on the aspects of social support has shown a direct relationship to multiple domains of quality of life.\textsuperscript{31,37} Therefore, social support may be more relevant than either demand or control.\textsuperscript{30}

While the job strain model may effectively measure the view of individuals within their jobs, this model may not fully evaluate the culture of the occupation or work environment, especially in occupations outside of the industrial model. First person narrative may provide a deeper understanding of the work environment and identify other stressors. Occupational and physical therapists have indicated that the professional culture is to put patients first. As a result, more than 95\% of occupational and physical therapists who reported sustaining a work related injury continued to work despite their injury.\textsuperscript{39} This phenomenon of presenteeism in many health care
occupations may lead to an exponential decline in performance and result in disability leading to a change in jobs. Similarly, 90% of sonographers and vascular technologists note working with some sort of work-related pain or discomfort. Despite evidence to the contrary, these same professionals are often not willing to change their postures or work environment for fear of reduced quality in their work, leading to misdiagnosis.

Finally, improved measurement of physical and environmental risk factors is needed to further understand the interrelationship of factors related to the development of CTS. Assessment of physical exposures is best measured through observational studies within the work context. While many ergonomic tools investigate postures and positions used or chosen by the individual worker, neither these tools, nor any other commonly used ergonomic assessment tools, assess the comprehensive listing of physical, psychosocial and personal factors that may increase the risk of WRMSDs. A questionnaire that attempts to combine these factors has been developed; however, as was the limitation in the current research, this questionnaire relies only on input from the individual and does not account for any objective, quantitative measures of the chosen work style of the individual.

5.3.3 Work Injury Model

Workers may be up to 5.5 times more likely to report decreased work productivity when certain combinations of psychosocial, physical and personal risk factors exist. Because WRMSDs lead to reduced productivity, work disability and decreased quality of life, a validated injury model is need in order to develop effective
prevention and treatment interventions. Creating and testing of a model that takes into account the multi-factorial origin of risk and the numerous pathways that exists among psychosocial, physical, and personal stressors is imperative. In keeping with the categories described by Bongers et al., and combining the knowledge of the various specific risk factors and interactive pathways based on WRMSD research, a modified version of the work style model might be further explored (Figure 5.2).

![Modified workstyle model]

**Figure 5.2 Modified workstyle model**

This work style stress model allows for closer investigation of specific stressors in each category, such as job demands and control, and includes individual/personal factors omitted in the original model. Additionally, it is possible that various pathways
exist within work style factors that may mediate pain and disorders. For example, regardless of physiological changes, pain can be modified strictly through cognitive processes. Therefore, the behavioral, cognitive, and physiological work style components may have differing and interrelated effects. This relationship, originally presented in a linear manner, has been modified to a triangular arrangement.

While merely theoretical, this model provides a framework for investigating the salient risk factors for development of upper extremity work-related musculoskeletal disorders. Further exploration of additional factors that have not been well measured is required to help validate this model. Specific environmental stressors due to the occupational environment require exploration in this new model, such as pressure for high productivity with exceptional quality in the sonography profession and the culture of presenteeism in health providers. Results of the exploratory regression analysis in this report have suggested that sonographic measures may be an appropriate primary dependent measure for the investigation of factors in this model. However, these physiologic measures must further be tied to work disability, measured by individual report of quality of life, through a measure of work productivity, or by another means.

There is a grave need for prospective, longitudinal studies to understand the impact of the constellation of stressors to the pathophysiology of WRMSD and to the individual quality of life in this work injury model. These future studies will require large sample sizes and identification of measurement techniques and tools that provide a valid evaluation of the specific factors of interest. Following cohorts of students
transitioning from school to careers, or new employees, within specific occupations, such as allied health professions, may provide valuable data for investigation of this work injury model. Validation of interrelationships among risk factors through statistical factor analysis techniques will provide guidance for the development of prevention or rehabilitation programs that address multiple areas instead of generalized interventions for individual factors.

5.3.4 Interventional Research

The ultimate goal of WRMSD research is to inform interventions that will prevent, reduce or remediate disorders. Workplace ergonomic interventions are traditionally directed at the work organization or to the individual to reduce risk\(^\text{30}\). Primary interventions include engineering controls, administrative controls, and protective equipment.\(^\text{53}\) The effectiveness of using engineering controls to redesign entire workplaces and reduce physical loads remains inconclusive,\(^\text{54}\) but there is moderate evidence that individual workstation adjustments can reduce symptoms.\(^\text{55}\) Some encouraging evidence exists with administrative interventions, but an interaction effect was noted as positive workers tended to profit more than users who did not have a positive outlook.\(^\text{54}\) Similarly, little evidence exists for the effectiveness of education, lectures and training interventions alone,\(^\text{55}\) and conflicting evidence is noted when education is combined with other interventions.\(^\text{56}\) CTS is often managed with splinting, to reduce pressure on the median nerve due to awkward hand positions;\(^\text{57}\) however, by
the time symptoms are reported, nerve pathology has typically progressed enough that protective equipment alone will not remediate the problem completely.

These primary interventions tend to be reactive rather than proactive; therefore, secondary interventions that indirectly mediate psychosocial, physical and personal work stressors may be more successful. These interventions may be aimed at changing the attitude of management and the general atmosphere in the workplace, or aimed at individual training for coping with daily stressors. Cognitive-behavioral intervention strategies are the most widely used technique for individual coping. This training includes instruction in motivational self-talk, relaxation techniques, coping mechanisms, assertiveness, reframing of negative thoughts, and other techniques to more positively manage and confront situations. Using these techniques to train individuals to modify their work style based on daily or regular occurring situations, such as increased work demands, may help reduce symptoms.

With very little evidence backing any one of these primary or secondary interventions alone, it may be necessary to begin creating interventions that cross all the different constructs. There is limited research on interventions that have a combined focus on a variety of different risk factors. Comprehensive rehabilitation programs that focus on various domains have been shown to have a greater effect on improved functional abilities versus traditional rehabilitation programs with a narrow treatment focus, therefore, it is logical to think that a comprehensive intervention for preventing disorders would be more effective than limited focus interventions.
Combined methodologies with synchronized data collection from multiple disciplines with questionnaires, interviews, and observations are an appropriate framework for studying WRMSD pathology. Low back pain research indicates that both the worker and the organization must be targeted in order for an intervention to be successful, but very little research on comprehensive treatments for the upper extremities exists.\textsuperscript{30} One group of researchers used a multidisciplinary approach with a goal of improving work style through body posture and worksite modifications, administrative work demand changes (i.e. break schedules), and individual training in coping with high work demands.\textsuperscript{63} This holistic approach has been shown to reduce pain and symptoms\textsuperscript{64} and has had a positive effect on work style behaviors in individuals.\textsuperscript{65}

Validating the positive effects of a comprehensive intervention through identification of changes in physiology is a logical next step. The portability and advancing quality of sonographic equipment situates this technology perfectly for the investigation of acute physiologic changes.\textsuperscript{66} Ultrasonography has been successfully used in the work place to collect images of subjects without being obtrusive.\textsuperscript{11} With the development of longitudinal, prospective studies, sonography could be a highly useful tool for monitoring the changes of the median nerve due to various exposures.\textsuperscript{67} There is an urgent need for bio-behavioral or biopsychosocial intervention techniques and ultrasonography may be the ideal tool for monitoring changes in physiology due to these intervention techniques.
5.4 Conclusion

The incidence of upper extremity work-related musculoskeletal disorders continues to be a significant concern in the working population. In all research investigating the effects of these factors on the development of upper extremity disorders, two limitations continuously surface: 1) no comparison of risk factors to physiological changes and 2) lack of prospective, longitudinal designs with adequate follow-up.

The lack of measurement for acute physiological changes results mainly from the lack of an efficient measurement tool that can identify these changes. The studies completed in this research support the hypothesis that given a standard protocol, ultrasonography can be a valid, non-invasive screening tool for investigating these physiologic changes as they relate to the development and diagnosis of carpal tunnel syndrome. Continued research is required to refine ultrasonographic measurement techniques and investigate the relationship of these measurements to various risk factors.

Ultrasonography is well positioned to become a useful research tool to identify acute changes in physiology over time to better understand the milieu of risk factors for WRMSD. Prospective designs are needed to determine the relationship of these risk factors to physiological changes and randomized control trials are needed to determine the impact of comprehensive, multidisciplinary interventions on work and health outcomes.
5. References


References

Akcar, N., Ozkan, S., Mehmetoglu, O., Calisir, C., & Adapinar, B. Value of power Doppler and gray-scale US in the diagnosis of carpal tunnel syndrome: contribution of cross-sectional area just before the tunnel inlet as compared with the cross-sectional area at the tunnel. Korean J Radiol, 11(6), 632-639.


Appendix A: Subject Questionnaire
Each subject completed the subject questionnaire during the research visit. The form was composed of questions from available questionnaires to capture various psychosocial and personal factors.

The composition of questions on the attached form includes:

- Short-Form 12 Physical and Mental Health Status (#1-#12)
- Boston Carpal Tunnel Questionnaire Symptom Severity (#13-#23) and Functional Status (#24)
- Visual Analogue Pain Scale (#25)
- Demographic Questions (#26-#29)
- Job Content Questionnaire Decision Latitude (#30-#32) and Psychological Demands (#33-#37)
The following survey asks for your views about your health and current symptoms. This information will help us understand how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box as indicated. If you are unsure about how to answer, please give the best answer you can.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2. Moderate activities, such as moving a Table, pushing a vacuum cleaner, bowling, or playing golf

   | Yes, Limited | Yes, Limited | No, Not |
   | A Lot        | A Little     | Limited | All   |
   | □            | □            | □       | □     |

3. Climbing several flights of stairs

   | □ | □ | □ |

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>
   4.  | □   | □  |
   5.  | □   | □  |

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>
   6.  | □   | □  |
   7.  | □   | □  |
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Did pain interfere with your normal work (both outside the home and housework)?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. Have you felt calm and peaceful?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>10. Did you have a lot of energy?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>11. Have you felt downhearted and blue?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>12. How much of the time has your physical health or emotional problems interfered with social activities (visiting with friends, etc.)?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Once</th>
<th>2 or 3 Times</th>
<th>4 or 5 Times</th>
<th>&gt; 5 Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. How often did hand or wrist pain wake you up during a typical night in the past 2 weeks?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>14. How often did hand numbness or tingling wake you up during a typical night in the past 2 weeks?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>15. How often do you have hand or wrist pain during the daytime in the past 2 weeks?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>16. How long, on average, does an episode of pain last during the daytime in the past 2 weeks?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
The following questions refer to your symptoms for a typical 24-hour period **during the past 2 weeks**.

<table>
<thead>
<tr>
<th>Question</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. How severe is the hand or wrist pain at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Do you typically have pain in your hand or wrist during the daytime?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Do you have numbness (loss of sensation) in your hand?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Do you have weakness in your hand or wrist?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Do you have tingling sensations in your hand?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. How severe is numbness (loss of sensation) or tingling at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. How much difficulty do you have grasping and using small objects such as keys or pens?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
<th>No Difficulty</th>
<th>Mild Difficulty</th>
<th>Moderate Difficulty</th>
<th>Severe Difficulty</th>
<th>Cannot Do At All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Writing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buttoning of Clothes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holding a Book While Reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gripping A Telephone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening of Jars</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household chores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrying of Grocery Bags</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathing and Dressing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
25. Place a mark (-) across each of the three lines to indicate your current level of pain or discomfort in your hand/wrist today and the best and worst pain or discomfort experienced in the past 4 weeks. Indicate how bad your symptoms are between the extremes of “No Pain At All” on the bottom of the line and “Pain As Bad As It Could Be” on the top of the line.

<table>
<thead>
<tr>
<th>Today</th>
<th>Past Month Worst</th>
<th>Past Month Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain As Bad</td>
<td>Pain As Bad</td>
<td>Pain As Bad</td>
</tr>
<tr>
<td>As it Could Be</td>
<td>As it Could Be</td>
<td>As it Could Be</td>
</tr>
</tbody>
</table>

No Pain At All  | No Pain At All  | No Pain At All  |

26. What is your highest level of education completed?

- [ ] Some High School
- [ ] High School /GED
- [ ] Associate Degree
- [ ] Bachelor Degree
- [ ] Master Degree
- [ ] Doctoral Degree

27. What is your current employment status?

- [ ] Not Working /Unemployed
- [ ] Volunteer /Student
- [ ] Part-Time
- [ ] Full-Time
- [ ] Retired
- [ ] Other (please describe)
May we contact you in the future for additional follow-up related to this study?

Yes ☐  No ☐

Please complete the following section only if you are currently employed in part-time or full-time work.

28. How many hours do you work in an average week?

_______ Hours/Week

29. Please provide your occupation:

______________________________________________________________________________

These questions ask you about various aspects of your job. Please mark your agreement with each statement.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. My job allows me to make a lot of decisions on my own</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>31. On my job, I have very little freedom to decide how I do my work</td>
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<tr>
<td>32. I have a lot of say about what happens on my job</td>
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<tr>
<td>33. My job requires working very fast</td>
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<tr>
<td>34. My job requires working very hard</td>
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<tr>
<td>35. I am not asked to do an excessive amount of work</td>
<td>☐</td>
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<tr>
<td>36. I have enough time to get the job done</td>
<td>☐</td>
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<tr>
<td>37. I am free from conflicting demands that others make</td>
<td>☐</td>
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