DISSERTATION

REFERENCE VALUES OF THE DISTAL SENSORY MEDIAN AND ULNAR NERVES AMONG NEWLY HIRED WORKERS

Submitted by

Molly Hischke

Department of Environmental and Radiological Health Sciences

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2021

Doctoral Committee:

Advisor: John Rosecrance

Andreas Neophytou
Brooke Anderson
Fredric Gerr
Raoul F. Reiser II

ABSTRACT

REFERENCE VALUES OF THE DISTAL SENSORY MEDIAN AND ULNAR NERVES AMONG NEWLY HIRED WORKERS

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremity and more common among workers in industrial occupations than in the general population (Atroshi et al., 1999; Mattioli et al., 2009; Palmer, Harris, & Coggon, 2007). Because of the high prevalence of CTS in certain industries, some employers have implemented post-offer pre-placement screening programs using nerve conduction studies (NCS) to identify those at higher risk of developing CTS. NCS are commonly used to identify the median neuropathy characteristic of CTS by assessing the nerve conduction speed of the median nerve. There have been a number of retrospective and prospective cohort studies that have examined the relationship between NCS indicating median neuropathy among workers and the subsequent development of CTS (Werner et al., 2001; Franzblau et al., 2004; Gell et al., 2005; Silverstein et al., 2010; Dale et al., 2014). These studies have indicated that workers with NCS indicating median neuropathy across the carpal tunnel who were initially asymptomatic for CTS, eventually developed CTS at a statistically significant greater rate than workers with normal nerve studies. Some employers have used NCS to identify workers at higher risk of developing CTS and placing them into low hand-intensive work tasks to reduce the high prevalence of work-related CTS. To identify workers at higher risk, their NCS results are often compared to population-based reference values. However, many of these published reference values are limited by their small samples sizes and unsuitable statistical methodologies (Dillingham et al., 2016). Further,

some researchers have questioned whether population-based reference values are representative of working populations, especially those in industries with a high prevalence of abnormal NCS (Dale, Gardner, Buckner-petty, Strickland, & Evanoff, 2016; Salerno et al., 1998). The purpose of this dissertation research was to (1) establish reference values for NCS outcomes of the distal upper extremity from a large sample (N=17,630) of newly hired manufacturing workers using novel statistical methods more appropriate for nerve conduction data, (2) investigate comorbid conditions associated with nerve conduction outcomes, and (3) determine the sensitivity and specificity of CTS symptoms for identifying workers with median mononeuropathy.

ACKNOWLEDGEMENTS

There are so many people who have helped me through this process. I would like to take a moment to thank them.

I would first like to thank my advisor, Dr. John Rosecrance, for helping me navigate this process and for his expertise in the subject area for my research. I would also like to thank my dissertation committee, Dr. Fredric Gerr, Dr. Brooke Anderson, Dr. Andreas Neophytou, and Dr. Raoul Reiser. Your insightful feedback was invaluable and brought my work to a much higher level.

I would like to thank my funding source, the NIOSH Mountain and Plains Education Research Center. I would like to thank the CSU Writing Center and Aurora Finley for their support through the writing process. I would like to thank the Franklin A. Graybill Statistical Laboratory and Kirsten Eilertson for guidance and expertise with the statistical technique I used in my work. I would also like to extend a special thank you to Kayna Hobbs, Colleen Brents, Charlotte Kupsh, JoiLynn Drescher, Isabel Olmedo-Nockideneh, Emily Compton, Livia Bracker, and Luda Akyea.

In addition, I would like to thank my partner for his kindness and patience throughout this process. Finally, I could have not completed this dissertation without the support of my parents and family who were always there to listen when I needed to talk and provided me with much needed encouragement.

TABLE OF CONTENTS

1. Chapter 1: Overview

Carpal Tunnel Syndrome (CTS) is the most common entrapment neuropathy in the distal upper extremity (Atroshi et al., 1999; Mattioli et al., 2009; Palmer et al., 2007). Many employers, particularly those in industries with hand-intensive tasks and high incidence of CTS cases, have adopted the strategy of using NCS in a screening procedure to identify workers more susceptible to developing CTS. Researchers hypothesize that those with impaired nerve physiology prior to employment renders them more susceptible to clinical CTS when subject to high hand/wrist forceful and repetitive exposures (Dale et al., 2014; Werner, Gell, Franzblau, & Armstrong, 2001). Some companies use NCS during post-offer pre-placement job screenings to identify newly hired workers with an impaired median nerve; and thus, an increased likelihood of developing CTS in the hand-intensive working conditions (Dale et al., 2014; Werner et al., 2001).

As with most screening tools in health care, an individual's NCS results are compared to reference values to determine if an individual's results are within the range of expected values within the population. Typically, "normal" is defined within an explicitly defined upper (commonly the 95^{th}, 97.5^{th} or 99^{th} percentiles) and lower (5^{th}, 2.5^{th}, or 1^{st} percentiles) bounds of the distribution. Previous researchers developing reference values have used common parametric methodologies that require assumptions regarding the distribution of the neurophysiological outcomes. The assumption that data follows a normal or Gaussian distribution allows the researcher to extrapolate information about the upper and lower bounds of the distribution necessary for defining reference values. However, it is well known that neurophysiologic data from NCS do not meet these assumptions, which could potentially underestimate the effect of important covariates in the reference value models. More recently, quantile regression has gained traction in the development of nerve conduction reference values. Rather than extrapolating information about the upper and lower bounds of the distribution from the mean as completed in a linear regression model setting, quantile regression models one or more percentiles of the outcome while allowing for adjustment of multiple covariates (Benatar, Wuu, & Peng, 2009; Dillingham et al., 2016; Esteves et al., 2020; Koenker & Hallock, 2001; Peng, Wuu, & Benatar, 2009).

The quality of the published conduction reference values was recently under scrutiny by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) (Dillingham et al., 2016). Many of the available reference values are limited by (1) small sample sizes, (2) the use of statistical methods that are unsuitable for the non-Gaussian distribution of nerve conduction measures, and (3) not adjusting for characteristics known to influence NCS outcomes (Chen et al., 2016; Dillingham et al., 2016). In addition to the statistical limitations, currently available population-based reference values may not be representative of the normative nerve conduction values of newly hired workers (Dale et al., 2014; Salerno et al., 1998; Werner, 2006).

Using reference values not developed for the population of interest or NCS technique can result in mis-categorizing individuals' nerve function resulting in potentially withholding or administering unnecessary prevention methods or treatments. The purpose of Specific Aim 1 in this dissertation was to address the limitations of currently published reference values by using quantile regression to develop median and ulnar nerve conduction reference values that adjust for individual characteristics among a large sample of newly hired workers. When creating reference values, persons with health conditions that could affect NCS outcomes should be excluded. In

Specific Aim 1, the investigators developed reference values that excluded workers with pre-existing conditions that could influence the nerve conduction outcomes.

The purpose of Specific Aim 2 was to investigate the relationship between selected comorbid conditions and NCS outcomes while adjusting for individual characteristics. The investigators examined the association between the nerve conduction outcomes and comorbidities used as exclusion criteria in Specific Aim 1.

Individuals with CTS often experience numbness and tingling of the hands/fingers innervated by the median nerve (Weiss, 2004a). Other researchers have investigated the performance classification of symptoms characteristic of CTS as a rapid and cost efficient way for workplace surveillance of CTS (Franzblau et al., 1994). However, there are no published studies that have investigated the performance classification of symptoms with newly hired workers. Thus, the purpose of Specific Aim 3 was to determine the performance classification (via measures of sensitivity and specificity) of symptoms consistent with CTS during a post-offer pre-placement job screening for median mononeuropathy with newly hired workers.

1.1 Specific Aims

The purpose of this dissertation was to investigate NCS from newly hired workers. Over a 16-year period, NCS were collected as a part of a post-offer pre-placement job screening for newly hired workers seeking employment at food processing facilities. Two different NCS techniques were used for the post-offer pre-placement job screening – an 8 cm orthodromic technique and a 14 cm antidromic technique.

Specific Aim 1: To determine reference values for median and ulnar nerve conduction outcomes among a sample of newly hired workers.

Objectives:

1. Establish reference values for 8 cm palm-to-wrist median and ulnar sensory orthodromic NCS from a sample of 10,038 workers. The NCS variables of interest were the median sensory peak latency, amplitude, and conduction velocity. Quantile regression was used to estimate percentiles of the distribution of interest while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand (either dominant or nondominant)).
2. Establish reference values for 14 cm wrist-to-finger distal median and ulnar sensory antidromic NCS from a sample of 4,433 workers. The NCS variables of interest were median and ulnar sensory peak latency, amplitude, and velocity as well as the difference between the median-ulnar sensory peak latencies. Quantile regression was used to estimate percentiles of the distribution of interest while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand (either dominant or nondominant)).

Specific Aim 2: To examine the relationship between select comorbid conditions and NCS outcomes among a sample of newly hired workers.

Objectives:

1. Quantify the associations between 8 cm palm-to-wrist median sensory orthodromic NCS outcomes and select comorbidities (diabetes, thyroid disease, previous fracture of the hand/wrist, previous CTS diagnosis, previous hand surgery, previous CTS surgery, and symptoms characteristic of CTS) while adjusting for individual characteristics (age, sex,

height, BMI, hand temperature, and hand). The NCS outcomes of interest were the median sensory peak latency, amplitude, and conduction velocity.

2. Quantify the associations between 14 cm wrist-to-finger median sensory antidromic NCS outcomes and select comorbidities (previous CTS diagnosis, previous CTS surgery, and symptoms characteristic of CTS) while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand). The NCS outcomes of interest were the median sensory peak latency, amplitude, and conduction velocity as well as the difference between the median-ulnar sensory peak latencies.

Specific Aim 3: To determine the performance classification of hand-related symptoms to identify newly hired workers with abnormal NCS outcomes.

Objectives:

1. To determine the sensitivity and specificity of CTS symptoms relative to a median mononeuropathy as determined by 8 cm orthodromic NCS conducted during a post-offer pre-placement screening.

2. To determine the sensitivity and specificity of CTS symptoms relative to a median mononeuropathy as determined by 14 cm antidromic NCS conducted during a post-offer pre-placement screening.

2. Chapter 2: Literature Review

CTS is a uniquely challenging and prevalent work-related injury. Work-related CTS is multifaceted. It is an overlap of occupational illness and injury, disorder of the peripheral nerves, and clinical CTS. As such, the literature review is organized into four major categories: (1) the peripheral nervous system and related disorders (i.e., CTS), (2) methods for assessing CTS, (3) normative values used in the assessment of CTS, and (4) health conditions associated with abnormal nerve function.

2.1 Work-related Illnesses and Injuries

Work-related injuries and illnesses either result from or are exacerbated by the work environment and conditions (Division of Population Health National Center for Chronic Disease Prevention and Health Promotion, 2020). Musculoskeletal disorders (MSDs) have been recognized as a significant contributor to overall reported work-related injuries and illnesses (National Research Council and Institute of Medicine, 2001). MSDs "are injuries or disorders of the muscles, nerves, tendons, joints, cartilage, and spinal discs" (Division of Population Health National Center for Chronic Disease Prevention and Health Promotion, 2020). In 2019, the incidence rate of MSDs in industry was 26.1 per 10,000 workers, and the median days away from work for MSDs was 13 days (U.S. Bureau of Labor Statistics, 2019b). The prevalence of MSDs is typically higher in industries with job tasks involving high-force, repetitive movement, and awkward postures (Punnett & Wegman, 2004). MSDs can affect any part of the musculoskeletal system and range from back pain to neurological disorders. One of the most common work-related MSDs is CTS.

2.1.1 *Carpal Tunnel Syndrome Burden*

The prevalence of CTS among those in working populations in industries with hand-intensive job tasks (7.8% - 55%) is higher than that reported for the general population (2.7%) (Atroshi et al., 1999; Bonfiglioli, Mattioli, Spagnolo, & Violante, 2006; Burt et al., 2011; Cartwright et al., 2012; Dale et al., 2013; Mattioli et al., 2009; Musolin & Ramsey, 2017; Musolin, Ramsey, Wassell, & Hard, 2014; Palmer et al., 2007; Patil, Rosecrance, Douphrate, & Gilkey, 2012; Rosecrance, Cook, Anton, & Merlino, 2002; Rosecrance, Marras, Murgia, Tartaglia, & Baldasseroni, 2013; Werner, Franzblau, Albers, & Armstrong, 1997). Some industries with the highest prevalence of CTS include manufacturing (i.e., poultry processing, assembly, textiles), construction, and agriculture, forestry and fishing (Palmer et al., 2007). In 2018, the median number of days away from work due to CTS was 30, which was the fourth highest median number of days away from work just after multiple injuries with fracture (48), fractures (32) and amputations (31) (U.S. Bureau of Labor Statistics, 2019a). Work-related CTS diagnoses have continued to have immense costs for both employers and employees. In 2007, the direct and indirect costs of work-related CTS were estimated at $110 million and $130 million, respectively (Bhattacharya, 2014). Furthermore, over the course of six years, workers with CTS earned $197 million to $382 million less than workers with either upper extremity fracture or dermatitis (Foley, Silverstein, & Polissar, 2007). The high prevalence and cost of work-related CTS has resulted in employers and researchers prioritizing initiatives and research to be able to identify workers at higher risk of developing the peripheral nervous system disorder.

2.2 Anatomy and Physiology of the Peripheral Nervous System

The peripheral nervous system is one component of the nervous system that connects the central nervous system (i.e., brain and spinal cord) with the rest of the body (Romero-Ortega, 2015). Neurons are the cellular unit of the peripheral nervous system, and are composed of a cell body and axons which extend to and innervate with the skin, muscles, joints, and organs (Romero-Ortega, 2015). The peripheral nerves transport electrical signals, also known as action potentials, by the exchange of ions between the inside and outside of the cell body (J. Kimura, 1989). An important component of a neuron are the Schwann cells that surround the axon which influence speed at which an action potential propagates (Rempel, Dahlin, & Lundborg, 1999). Myelinated nerves are those that have individual Schwann cells surrounding the length of the axon whereas unmyelinated nerve fibers share a single Schwann cell (J. Kimura, 1989). The myelin sheath increases the speed at which information propagates along the length of the nerve (Rempel et al., 1999). Each bundle of nerves, or a nerve trunk, is composed of myelinated and unmyelinated nerve fibers enclosed within multiple layers of connective tissue (Romero-Ortega, 2015).

Nerves that transport the electrical signal to the spinal column with information about the surrounding environment are called sensory nerves (Weiss, Weiss, Pobre, & Kalman, 2004). Sensory nerves transport thermal, chemical, or mechanical stimuli to the brain and spinal cord for interpretation and response (Romero-Ortega, 2015). In contrast, motor nerves transport signals from the spinal cord with information to allow for purposeful movement (Weiss et al., 2004). Impairment of the peripheral nervous system is called a neuropathy.

2.2.1 Peripheral Neuropathy

Peripheral neuropathy is defined as a range of disorders arising from a dysfunction of the peripheral nervous system (J. Kimura, 1989). Peripheral neuropathy can be diffuse (occurring equally across all nerves in the peripheral nervous system) as a result of certain drugs (e.g., amiodarone, disulfiram, or cisplatin), chemical exposures (e.g., acrylamide, carbon disulfide, or mercury), or chronic illnesses (e.g., diabetes, hypothyroidism, alcoholism) (Aroori & Spence, 2008; J. Kimura, 1989). More relevant to CTS, peripheral neuropathy can also occur at a specific location on a single nerve, also known as a focal nerve entrapment. Focal nerve entrapment can result from acute or chronic injuries (J. Kimura, 1989). One of the most common entrapped nerves is the median nerve which is also known as CTS.

2.2.1.1 Carpal Tunnel Syndrome

CTS is one of the most common focal entrapment mononeuropathies of the distal upper extremity (Weiss, 2004a). The symptoms of CTS are numbness, tingling, or pain in the distribution of the hand supplied by the median nerve (thumb, index, long, and radial half of the ring finger) (Weiss, 2004a). CTS is thought to result from an increase in pressure within the carpal canal which causes compression of the median nerve that lies within it (J. Kimura, 1989). The neurophysiological effects resulting from compression of the median nerve may be temporary; however, prolonged compression of the nerve can result in greater damage to the nerve including demyelination or axonal loss (Keir & Rempel, 2005; J. Kimura, 1989; Rempel et al., 1999). Demyelination and axonal loss results in reductions in the speed at the site of compression and magnitude distal to the site of compression of the action potentials (Keir & Rempel, 2005). Highly repetitive activity, high force tasks, and nonneutral postures of the hand/wrist have been shown to increase the pressure within the carpal canal causing compression on the median nerve (Keir & Rempel, 2005). Some researchers suggest nerve compression within the carpal canal due to high-intensive hand tasks could explain why certain industries have reported higher rates of CTS (Keir & Rempel, 2005). Some other potential causes of CTS are from acute injuries (e.g., distal radial fracture), rheumatoid arthritis, diabetes, hypothyroidism, menopause, and alcoholism (Aroori & Spence, 2008; Herbert, Gerr, & Dropkin, 2000; J. Kimura, 1989; Pourmemari & Shiri, 2016; Solomon, Katz, Bohn, Mogun, & Avorn, 1999).

2.3 Methods for Assessing Carpal Tunnel Syndrome

Assessment tools used to evaluate the health of the median nerve include self-reported symptoms, physical examinations, and NCS (Aroori & Spence, 2008). Technicians, clinicians, and researchers usually use a combination of assessment methods to assess or screen potential CTS cases (Aroori & Spence, 2008).

2.3.1 *Symptomology*

Persons with CTS experience uncomfortable symptoms such as numbness, tingling, and pain in the distribution of the hand supplied by the median nerve (Weiss, 2004a). A number of symptom surveys have been developed and evaluated to standardize the collection of symptoms for use in epidemiological and clinical research. Researchers have evaluated many methods to collect hand-related symptoms to improve the sensitivity and specificity of these tools for applications within clinical, research, and workplace settings. The evidence provided by other researchers suggests that the sensitivity and specificity of a symptom-only case definition is weak (Atroshi et al., 1999; Franzblau, Blitz, et al., 1993; Werner et al., 2005). As a result, a large number of persons will meet a symptom-based case definition of CTS even though they do not actually have CTS and, conversely, a large number of persons will not meet a symptom-based case definition even though they do actually have CTS.

2.3.2 *Physical Examinations*

Physical examinations used in evaluating persons for CTS typically involve placing the patient's hand in a position for a period of time or tapping the median nerve and monitoring them for whether or not they develop numbness and tingling. The most referenced and performed physical examinations to assess the median nerve are Tinel's and Phalen's sign (Aroori & Spence, 2008). Researchers have concluded that physical examinations hold little diagnostic utility when assessing patients or workers for CTS (Dale, Descatha, Coomes, Franzblau, & Evanoff, 2011; Gerr & Letz, 1998).

2.3.3 Nerve conduction studies

A single nerve signal is difficult to measure; however, the sum of multiple action potentials is measurable with specialized equipment, also known as electrodiagnostic testing (J. Kimura, 1989). NCS are a specific type of electrodiagnostic testing. NCS have been used for decades to assess the neurophysiologic status of nerves and muscles in the diagnosis of neuromuscular disorders (J. Kimura, 1989; Silver, 2004). NCS are conducted by placing electrodes on the skin and stimulating a nerve to evoke an electrical response (Silver, 2004). The electrical response, also known as an action potential, is recorded and assessed based on the nerve conduction speed and magnitude.

NCS outcomes provide valuable information to assess health status of a nerve and diagnose neuropathic disorders (Dillingham et al., 2016; J. Kimura, 1989; Silver, 2004). One of the most common entrapment neuropathies is CTS (Weiss, 2004a). NCS are commonly used to identify the median neuropathy characteristic of CTS. A slowed conduction response of the median nerve indicates damage to the nerve, and if accompanied with specific neurologic symptoms in the hand, a diagnosis of CTS. Although CTS is common, there are other health conditions that present similar symptomology and reductions in the conduction speed of the median nerve (Duncan & Kakinoki, 2017). Therefore, in addition to evaluating the median nerve, often a NCS will be performed on another nerve of the distal upper extremity (i.e., ulnar or radial) to determine if the physiologic changes are isolated to the median nerve (which is characteristic of CTS) or span across multiple nerves of the distal upper extremity indicative of another peripheral neuropathy (Duncan & Kakinoki, 2017).

2.3.3.1 Usage Scenarios of Nerve Conduction Studies

NCS are used both in clinical settings and occupational health research to identify physiologic changes in the action potential characteristics of the median nerve. In a clinical setting, clinicians and technicians use a combination of patient health history, location of symptoms, and NCS to establish a diagnosis of CTS (Duncan & Kakinoki, 2017; Padua et al., 2016). In research, typically symptomology and NCS outcomes are used to define a CTS case (Rempel et al., 1998). One epidemiologic case definition for CTS recommended by Rempel et al. (1998) for use in occupational health studies is: (1) numbness, tingling, or pain reported in two out of the four first digits and (2) an abnormal NCS.

In addition to clinics and epidemiologic research, many employers, particularly those in industries with hand-intensive tasks and high incidence of CTS cases, have adopted the strategy of using NCS in a screening procedure with newly hired workers to identify those more susceptible to developing CTS. Researchers hypothesize that those with impaired nerve physiology prior to employment renders them more susceptible to clinical CTS when subject to high hand/wrist forceful and repetitive exposures (Dale et al., 2014; Werner et al., 2001). Workers who were asymptomatic with an abnormal NCS at the time of hire were more likely to develop CTS than asymptomatic workers with a normal NCS (Dale et al., 2014; Werner et al., 2001). Given these findings, companies use NCS during post-offer pre-placement job screenings to identify newly hired workers that exhibit impaired physiologic function of the median nerve; thus, an increased susceptibility of developing CTS in hand-intensive working conditions. One prevention strategy involves placing workers with an abnormal median nerve response into low rather than high hand intensive jobs, which may decrease the likelihood of the worker developing CTS (Werner, 2006). Although some have questioned the cost effectiveness of NCS screening in the workplace (Dale et al., 2016, 2014; Franzblau, Werner, & Yihan, 2004) as well as the legal implications related to employment decisions based on NCS findings (U.S. Equal Employment Opportunity Commission, 2013), NCS are still being used to identify workers with abnormal median nerve responses to reduce the prevalence of CTS in the workplace and the subsequent workers' compensation costs.

2.3.3.2 Nerve Conduction Outcomes

Typical nerve conduction outcomes of interest in CTS research include the latency and amplitude of the nerve conduction signal (Silver, 2004) (Figure A1 in Appendix A). Onset latency is the time interval between the nerve stimulation and the onset of the electrical response. Peak latency is the time interval between the stimulation and the peak of the electrical response. Onset latency represents the fastest nerve fibers whereas peak latency represents the mode of the conduction velocity of the nerve fibers involved in the action potential (Valls-Sole, Leote, & Pereira, 2016). The amplitude represents the sum of the individual action potential amplitudes generated by the muscle or nerve (Weiss et al., 2004). Sensory and motor nerve amplitudes are measured in microvolts (μV) and millivolts (mV), respectively (J. Kimura, 1989). Conduction velocity is the speed of the action potential in units $distance/time$ (Weiss et al., 2004). The median nerve absolute latency, amplitude, and conduction velocity have been used to identify nerve conduction abnormalities related to CTS; however, more often the median sensory latency and ulnar sensory latency are compared on the ipsilateral side (Atroshi, Gummesson, Johnsson, & Ornstein, 2003; Werner, 2006; Werner & Andary, 2011). Using a nerve that does not run through the carpal canal, like the ulnar or radial, serves as a within person control to differentiate if the nerve impairment is isolated to the median nerve (indicative of CTS) or spans across other nerves within the distal upper extremity. In addition, comparing latencies between different nerves at the wrist within person controls for age, height, weight, sex, and other individual characteristics that could influence nerve conduction outcomes (Werner, 2006; Werner & Andary, 2011). Abnormal action potential characteristics may indicate a nerve-related injury or disorder. An increase in the latency and decrease in conduction velocity could be indicative of demyelination (i.e., damage to the myelin sheath) (Weiss, 2004b). Whereas, reductions in the amplitude is caused by axonal loss (Weiss, 2004b). Both demyelination and axonal loss are typically involved in the nerve-related injury or disorder (Weiss, 2004b).

2.3.3.3 Nerve Conduction Study Techniques

Two techniques used in sensory NCS are orthodromic and antidromic testing. Orthodromic testing measures a sensory action potential that travels in the same direction as normal nerve function (for example, if a sensory nerve signal were to travel towards the spinal column) (Silver, 2004). Antidromic testing measures a sensory action potential that travels the opposite direction of normal nerve function (for example, if a sensory nerve signal were to travel away from the spinal column) (Silver, 2004). Both orthodromic and antidromic techniques are widely used by clinicians and researchers (Dillingham et al., 2016; Valls-Sole et al., 2016). Regardless of NCS technique, the same features of the nerve impulses are evaluated when assessing the quality of nerve responses.

2.4 Normative Values

Access to high-quality normative nerve conduction data is important for clinicians, technicians, occupational health researchers, and employers to accurately assess or screen for neurological disorders, like CTS (Campbell & Robinson, 1993; Dale et al., 2014; Werner et al., 2001). The term “normative” data or values is defined as test results from a disease-free population (Dorfman & Robinson, 1997). “Normative” and “reference” values will be used interchangeably throughout this dissertation. Normative data are created from a sample of individuals (without diseases of interest), and results drawn from that sample are extrapolated to infer information about the larger population (Campbell & Robinson, 1993; Elveback, 1973). There is a wide range of inclusion criteria for developing normative values. The least stringent criteria is an individual that appears to be healthy or has no signs of the disease (Dorfman & Robinson, 1997). A more rigorous classification would require interviews or questionnaires to understand the history or symptoms of the disease(s) of interest (Dorfman & Robinson, 1997). Normative data can provide the expected distribution of values from a particular population. Normative data not truly representative of the population of interest may result in many false positives or false negatives.

Typically, “normal” is defined by within the upper (95^{th}, 97.5^{th} or 99^{th} percentiles) and lower (5^{th}, 2.5^{th}, or 1^{st} percentiles) bounds of the distribution. Many statistical methods have been used when defining reference value ranges like the mean +/- 2 standard deviations and ordinary linear regression; however, these statistical methods have several limitations that make them unsuitable for use to develop reference values. For example, using the mean +/- 2 standard deviations to describe a distribution becomes increasingly more challenging when stratifying the outcome by multiple factors (e.g., age, sex height, and BMI). Alternatively, linear regression is used to quantify the change in the dependent variable per unit of change in the independent variable while being able to adjust for covariates in the model (Ott & Longnecker, 2010). However, linear regression requires the user to make assumptions about the distribution in order to extrapolate information about the upper and lower bounds from the mean response (Ott & Longnecker, 2010).

More recently, quantile regression has gained traction for use to model percentiles of the distribution for nerve conduction reference values (Benatar et al., 2009; Dillingham et al., 2016; Esteves et al., 2020; Koenker & Hallock, 2001; Peng et al., 2009). Quantile regression directly models one or multiple quantiles as specific percentiles of interest of the dependent variable while allowing for adjustment of multiple covariates. Although quantile regression was first introduced in 1978, the statistical technique has not been widely used until the past two decades due to the required computing power and the fact that aspects of quantile regression are still in development for use in mainstream statistical software (e.g., R, SAS, SPSS) (Koenker & Hallock, 2001). Despite its advantages and use in other fields, quantile regression has been relatively underused in occupational epidemiologic research (Abrevaya, 2001; Beyerlein, 2014). Quantile regression is particularly advantageous in research where the tail ends of the distribution rather than the mean response is of interest (Beyerlein, 2014; Dillingham et al., 2016; Geraci, 2014; Koenker & Hallock, 2001; Waldmann, 2018). When establishing reference values, estimating the tail ends of the distribution is more practically relevant than an estimation based on the mean as researchers and clinicians are often most interested in determining if a value is outside the range of values expected within a population (Dillingham et al., 2016; Dorfman & Robinson, 1997; Peng et al., 2009). An infinite amount of percentiles can be modeled with quantile regression which results in a set of coefficients for each percentile modeled that help describe the variability in the response across different covariates and percentiles of the distribution (Geraci, 2014; Geraci & Bottai, 2014; Koenker & Hallock, 2001)

(Figure 1). Quantile regression addresses many of the limitations of other statistical methods used when developing reference values.

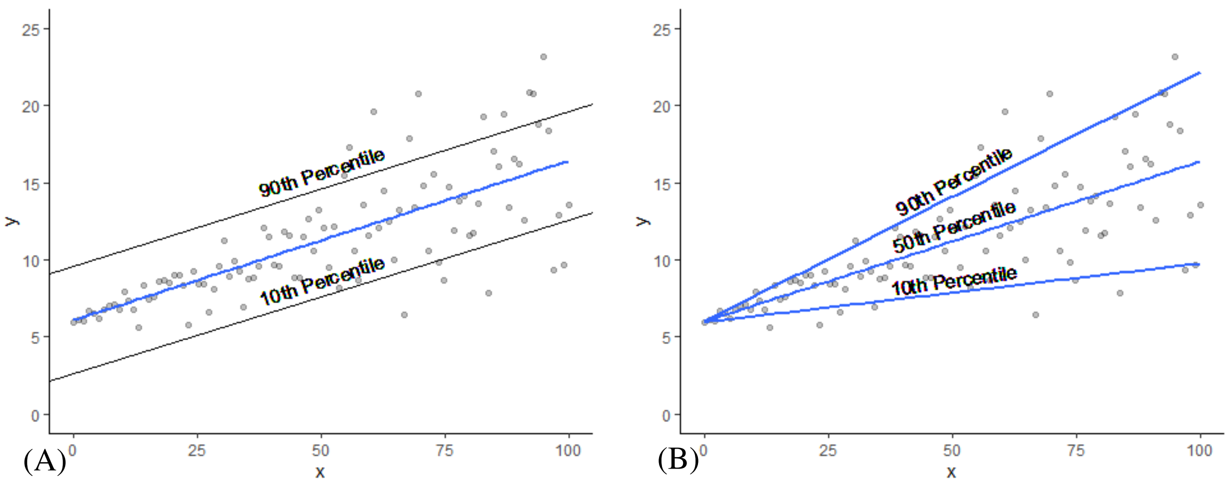


Figure 1. The data used for this example are simulated to show the difference between linear and quantile regression with unequal variance (Ford, 2015). (A) Linear regression model representing the relationship between x and y. Linear regression models on the mean of the response variable and will have a constant slope regardless of percentile of the distribution. The linear regression model does not include parameter estimates for the response at the 10^{th} and 90^{th} percentiles. Instead, the 10^{th} and 90^{th} percentiles are estimated based on the mean response and distributional assumptions. (B) Quantile regression model representing the relationship between x and y specifying the 10th, 50th and 90th percentiles. The graph demonstrates that for a specific covariate (in this case x) there could be differences in the response across percentiles of the distribution. The differences in the response (y) between the 90th percentile and 10th percentile is captured using quantile regression.

Often, laboratory technicians, and researchers rely on nerve conduction normative values from research reported in peer reviewed journals. However, many published studies lack the rigorous methodologies and statistical methods required to establish high-quality population-based normative values (Dillingham et al., 2016). The AANEM created The Normative Data Task Force to review currently published nerve conduction methodologies and reference values to develop criteria for high-quality normative values. These criteria were created to review already published nerve conduction reference values as well as evaluate the quality of future published reference values (Dillingham et al., 2016). Dillingham et al. (2016) reviewed the nerve conduction reference value literature and identified common methodological shortcomings. From the identified shortcomings, the AANEM task force developed criteria to define high-quality normative nerve conduction values that would be suitable for widespread use (Dillingham et al., 2016) (Table 1).

Table 1. Criteria for evaluating normative values for nerve conduction studies (Recreated table from Dillingham et al. (2016)).

1. Year published	Published during or after 1990 Written or translated from other languages to English
2. Sample size	>100 subjects
3. Subjects	Inclusion and exclusion criteria must be methodologically sound and reflect a true "normal" group of asymptomatic individuals
4. Testing factors	Use of digital electromyographic equipment Methods of temperature control stated Testing techniques with electrode placement and distances between stimulating and recording electrodes specified Filter setting specified Screen display parameters (milliseconds per division, microvolts/millivolts per division) specified
5. Age	Wide distribution of subject ages >18 years with adequate sampling of the elderly
6. Statistical analyses	Account for effects of age using sample subsets or multivariate statistics The data distribution should be described, and appropriate statistical methods use to account for non-Gaussian distributions Cut-off values can be expressed and derived as percentiles of the distribution (the preferred method) The percentage of subjects who have an absent response should be reported
7. Data presentation	Reference values and cut-off points for NCS parameters are clearly presented in a useful format

The majority of the published nerve conduction reference values (>7,500 studies) are limited by small sample sizes and using statistical methods that are questionable for the non-Gaussian distribution of nerve conduction outcomes (Table 2, Table 3, and Table 4) (Chen et al., 2016). Only three studies meet the AANEM task force criteria in establishing current reference values for the median and ulnar nerves (Buschbacher, 1999a, 1999b; Esteves et al., 2020). Unfortunately, none of the published studies following the AANEM task force criteria include NCS reference values developed from orthodromic techniques or adjust for the multitude of individual characteristics that are associated with nerve conduction outcomes (i.e., age, sex, height, BMI, hand temperature, hand dominance) (Becker et al., 2002; Boz, Ozmenoglu, Altunayoglu, Velioglu, & Alioglu, 2004; Kouyoumdjian, Zanetta, & Morita, 2002; Shiri, Pourmemari, Falah-Hassani, & Viikari-Juntura, 2015; Silverstein et al., 2010; Valls-Sole et al., 2016; Violante, Bonfiglioli, Isolani, & Raffi, 2004; Zambelis, Tsivgoulis, & Karandreas, 2010). Further, these studies may not be representative of the normative nerve conduction values in a working population (Dale et al., 2014; Salerno et al., 1998), are limited by small sample sizes of older adults (Buschbacher, 1999a, 1999b; Esteves et al., 2020), and represent only a few geographic regions which limits their generalizability to other locations (Buschbacher, 1999a, 1999b; Chen et al., 2016; Esteves et al., 2020). Specific Aim 1 of the proposed study will address these gaps in the literature by developing normative values of the median and ulnar sensory nerve among members from a population of newly hired workers in the United States.

Table 2. Abnormal thresholds reported in the literature for the difference between the median and ulnar peak latency.

NCS Technique	Investigators	Statistical Method	Sample Size	Mean ± SD	Upper Bound	Median-Ulnar Difference (ms) Bound
Mid-palmar, 8 cm, orthodromic	Stevens (1987)	Range	505	-	Upper Range Value	0.2
	Jackson & Clifford (1989)	Mean ± SD	53	0.10 ± 0.11 [-0.08-0.34]	97.5th Percentile	0.31
	Bingham et al. (1996)	Mean ± SD *(with newly hired industrial workers)*	1021	0.19 ± 0.26	-	-
	Patil et al. (2012)	Mean ± SD *(with non- parlor dairy workers)*	55	0.23 ± 0.27	-	-
	Anton, Gerr, Merlino, & Rosecrance (2014)	Mean ± SD, Percentile *(with rural aged population)*	248	0.32 ± 0.30	95th Percentile	0.93
Digit 4, 14 cm, antidromic	Johnson, Kukla, Wongsam, & Piedmonth (1981)	Percentile	37	-	93rd Percentile	0.4
Digit 2 & digit 5, 14 cm, antidromic, dominant	Salerno et al. (1998)	Mean ± SD, Range, Percentile *(with active workers)*	324	0.2 ± 0.4 [-0.8-2.6]	95th Percentile	0.8
Digit 2 & digit 5, 14 cm, antidromic, nondominant	Salerno et al. (1998)	Mean ± SD, Range Percentile *(with active workers)*	324	0.1 ± 0.3 [-0.7-2.8]	95th Percentile	0.7

Table 3. Nerve conduction normative values and Mean ± Standard Deviation (SD) using an 8 cm orthodromic technique.

					Peak Latency (ms)		Amplitude (µV)		Conduction Velocity (m/s)	
Investigators	Statistical Method	Upper/ Lower Bounds[1]	Nerve	Sample Size	Mean ± SD [Range]	Upper/ Lower Bound	Mean ± SD [Range]	Upper/ Lower Bound	Mean ± SD	Upper/ Lower Bound
Stevens (1987)[2]	Mean ± SD	2.5th/97.5th Percentile	Median (Palmer)	505	1.8 ± 0.02	1.84	100 ± 5.1	89.8	66 ± 1.4	63.2
Jackson & Clifford (1989)	Mean ± SD, Range	2.5th/97.5th Percentile	Median (Palmer)	38	2.03 ± 0.12 [1.80-2.40]	2.27	32.9 ± 10.4 [10-54]	12.1	-	-
Redmond & Rivner (1988)	Mean, Range	-	Median (Palmer)	53	1.8 [1.5-2.2]	-	131 [46-285]	-	-	-
Anton, Gerr, Merlino, & Rosecrance (2014)	Mean ± SD, Percentiles *(with rural aged population)*	95th Percentile	Median (Palmer, Dominant)	252	2.22 ± 0.32	2.85	-	-	-	-
Patil et al. (2012)	Mean ± SD *(with non-parlor dairy workers)*	-	Median (Palmer, Right hand)	55	2.07 ± 0.28	-	-	-	-	-

[1] The upper bound is for the peak latency and the lower bound is for the amplitude and conduction velocity.
[2] The investigators in the present study suspect Stevens (1987) reported the standard error rather than the standard deviation values.

Table 4. Nerve conduction normative values and Mean ± Standard Deviation (SD) using a 14 cm antidromic technique.

						Peak Latency (ms)		Amplitude (µV)		Conduction Velocity (m/s)	
Investigators	**Statistical Method**	**Lower/ Upper Bounds[1]**	**Nerve**	**Sample Size**	**Age (Years)**	**Mean ± SD [Range]**	**Upper Bound**	**Mean ± SD [Range]**	**Lower Bound**	**Mean ± SD**	**Lower Bound**
Stevens (1987)	Mean ± SD	2.5th/97.5th Percentile	Median	505	-	2.90 ± 0.10	3.1	40.4 ± 2.6	35.2	65.1 ± 1.6	61.9
Johnson et al. (1981)	Mean ± SD	2.5th/97.5th Percentile	Median (4th digit, Dominant)	10 10 7 10	20-29 30-39 40-49 50-59	3.12 ± 0.18 2.96 ± 0.15 3.19 ± 0.27 3.30 ± 0.23	3.5 3.3 3.7 3.8	-	-	-	-
			Median (4th digit, Non-dominant)	10 10 7 10	20-29 30-39 40-49 50-59	3.15 ± 0.18 2.96 ± 0.22 3.19 ± 0.30 3.28 ± 0.24	3.5 3.4 3.8 3.8				
Letz & Gerr (1994)	Mean ± SD	-	Median (1st digit)	~4000	-	-	-	23.67 ± 8.64	-	53.86 ± 6.19	-
Buschbacher (1999a)	Percentiles[2]	3rd/97th Percentile	Median (2nd digit)	258	-	3.40 ± 0.40	4.0	56 ± 31	13.0	-	-
Buschbacher (1999a)	Percentiles[2]	3rd/97th Percentile	Median (3rd digit)	258	-	3.40 ± 0.30	4.0	63 ± 33	17.0	-	-
Salerno et al. (1998)	Mean ± SD Range Percentiles *(with active workers)*	5th/95th Percentile	Median (2nd digit, Dominant)	324	-	3.2 ± 0.4 [2.6-6.0]	4.0	35.6 ± 14.8 [5.5-83.3]	14.0	-	-
			Median (2nd digit, Non-dominant)			3.2 ± 0.4 [2.4-5.7]	3.9	39.6 ± 17.2 [3.9-103.7]	13.7		
Benatar, Wuu, & Peng (2009)[3]	Quantile Regression	4th Percentile	Median (2nd digit)	100	30 50 70	-	-	-	24.0 12.0 6.0	-	40.0

Esteves et al. (2020)	Quantile Regression	3rd/97th Percentile	Median (4th digit, Right hand)	64 39 49 47 18	20-29 30-39 40-49 50-59 ≥ 60	-	3.1 3.2 3.3 3.4 3.5	-	23.5 22.6 20.1 15.6 10.5	-	40.0
Johnson et al. (1981)	Mean ± SD	2.5th/97.5th Percentile	Ulnar (5th digit, Dominant)	10 10 7 10	20-29 30-39 40-49 50-59	3.11 ± 0.15 2.89 ± 0.20 3.04 ± 0.20 3.08 ± 0.23	3.4 3.3 3.4 3.5	-	-	-	-
			Ulnar (5th digit, Non-dominant)	10 10 7 10	20-29 30-39 40-49 50-59	3.06 ± 0.16 2.91 ± 0.20 3.19 ± 0.29 3.12 ± 0.24	3.4 3.3 3.8 3.6				
Letz & Gerr (1994)	Mean ± SD	-	Ulnar (5th digit)	~4000	-	-	-	21.79 ± 9.24	-	55.24 ± 5.90	-
Buschbacher (1999a)	Percentiles[2]	3rd/97th Percentile	Ulnar (5th digit)	258	-	3.4 ± 0.30	4.0	50 ± 32	9.0	-	-
Salerno et al. (1998)	Mean ± SD Range Percentiles *(with active workers)*	5th/95th Percentile	Ulnar (5th digit, Dominant)	324	-	3.1 ± 0.3 [2.6-4.1]	3.6	33.6 ± 16.2 [4.0-102.7]	12.5	-	-
			Ulnar (5th digit, Non-dominant)			3.1 ± 0.2 [2.4 - 4.1]	3.6	35.7 ± 17.2 [4.9-101.5]	11.3		
Benatar et al. (2009)[4]	Quantile Regression	4th Percentile	Ulnar (5th digit)	100	30 50 70	-	-	-	18.0 11.0 7.0	-	44.0
Esteves et al. (2020)	Quantile Regression	3rd/97th Percentile	Ulnar (5th digit, Right hand)	64 39 49 47 18	20-29 30-39 40-49 50-59 ≥ 60	-	2.5 2.6 2.7 2.8 2.9	-	13.2 12.1 12.1 11.1 8.9	-	44.0 44.0 41.0 41.0 41.0

[1] The upper bound of the distribution is for the peak latency and the lower bound is for the amplitude and conduction velocity.
[2] Analysis included data transformation technique.
[3] 13 cm Antidromic technique.
[4] 11 cm Antidromic technique.

2.5 Factors Associated with Nerve Conduction Studies

Working populations, particularly those in industries with hand-intensive tasks, have an increased risk of developing physiological evidence of mononeuropathy of the median nerve and CTS (Barcenilla, March, Chen, & Sambrook, 2012; Burt et al., 2011; Garg et al., 2012; Gell, Werner, Franzblau, Ulin, & Armstrong, 2005; Gerr et al., 2014; Harris-Adamson et al., 2015; Kapellusch et al., 2014; Violante et al., 2016). As discussed previously, employers in industries with hand-intensive job tasks with high rates of CTS initiated efforts to be able to identify those more susceptible to developing CTS by using NCS in post-offer pre-placement screenings. NCS are an important tool to help assess nerve function; however, an abnormal result is a non-specific indicator of a neurological disorder. Understanding individual characteristics, existing health conditions, occupational exposures, and NCS testing conditions are important in accurately characterizing nerve conduction abnormalities for optimal prevention and treatment.

Researchers have identified many factors associated with nerve conduction outcomes including: individual characteristics such as age, sex, height, body mass index (BMI) and handedness (Becker et al., 2002; Boz et al., 2004; Kouyoumdjian et al., 2002; Shiri et al., 2015; Werner et al., 1997; Zambelis et al., 2010), acute trauma (e.g., facture and surgery), and systemic health conditions (e.g., diabetes, hypothyroidism, and pregnancy) (Ahmad, Moinuddin, Ahsan, & Goel, 2016; Aroori & Spence, 2008; Herbert et al., 2000; Pope & Tang, 2018; Pourmemari & Shiri, 2016; Solomon et al., 1999; Werner et al., 2005). In addition, hand temperature and technician-specific variations in NCS technique are established covariates of nerve conduction measures. (Chaudhry et al., 1991; Jablecki, Andary, So, Wilkins, & Williams, 1993; Letz & Gerr, 1994). Individual characteristics and methodological differences are important to consider when assessing nerve conduction outcomes and establishing nerve conduction reference values

(Dillingham et al., 2016). Specific Aim 1 primarily focuses on establishing reference values for a working population which will be completed by excluding those with co-morbid conditions that could influence the nerve conduction outcomes (an example being previous diagnosis of CTS). The purpose of Specific Aim 2 will be to create normative values including individuals with select comorbid conditions as predictors to provide estimations of nerve conduction outcomes for those with comorbidities. In particular, the investigators wanted to explore the association between those comorbid conditions that were not a part of the 14 cm antidromic NCS questionnaire to gain insights about the impact of including those with diabetes, thyroid disease, previous hand/wrist fracture, and previous hand/wrist surgery in the reference values developed in Specific Aim 1.

2.6 Symptoms and Nerve Conduction Studies in a Working Population

NCS have been used in post-offer pre-placement screenings to identify those workers at higher risk for developing CTS (Dale et al., 2014; Werner et al., 2001). In addition to NCS, post-offer pre-placement screenings may have questions about demographics and health history as these are important to consider along with the NCS results as understanding previous diagnoses (e.g., diabetes, or thyroid disease) may assist in determining if an individual has CTS (Aroori & Spence, 2008; Becker et al., 2002; Boz et al., 2004; Herbert et al., 2000; Kouyoumdjian et al., 2002; Pourmemari & Shiri, 2016; Shiri et al., 2015; Solomon et al., 1999; Zambelis et al., 2010). Although symptoms and NCS results are associated (Katz et al., 1990), some researchers have observed workers in hand-intensive jobs are not forthcoming with symptoms (Taylor Moore, Cigularov, Sampson, Rosecrance, & Chen, 2013). Researchers have also reported that workers underreport symptoms during a post-offer pre-placement screening (Dale et al., 2016). However, little empirical evidence exists on the classification performance for symptoms collected during post-offer pre-placement job screening. Specific Aim 3 will address the gaps in the literature by determining the sensitivity and specificity of symptoms for detection of NCS consistent with CTS among workers undergoing post-offer pre-placement screening.

2.7 Significance

Currently published reference values are limited by small sample sizes and unsuitable statistical techniques. Further, these reference values may not be suitable for use with a working population. The purpose of this research was to establish reference values for the median and ulnar nerves for newly hired workers using the AANEM criteria as a guide. This study was the first to produce nerve conduction reference values for dominant and non-dominant hands using quantile regression, to publish median and ulnar NCS reference values for a sample of newly hired workers, and to report orthodromic median sensory NCS reference values. In addition, the investigators determined comorbidities that affect nerve conduction outcomes and determined the sensitivity and specificity of symptoms consistent with CTS.

3. Chapter 3: Reference Values for the median and ulnar nerve among newly hired workers

Specific Aim 1: To determine reference values for median and ulnar nerve conduction outcomes among a sample of newly hired workers.

Objectives:

1. Establish reference values for 8 cm palm-to-wrist median and ulnar sensory orthodromic NCS from a sample of 10,038 workers. The NCS variables of interest were the median sensory peak latency, amplitude, and conduction velocity. Quantile regression was used to estimate percentiles of the distribution of interest while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand (either dominant or nondominant)).
2. Establish reference values for 14 cm wrist-to-finger distal median and ulnar sensory antidromic NCS from a sample of 4,433 workers. The NCS variables of interest were median and ulnar sensory peak latency, amplitude, and velocity as well as the difference between the median-ulnar sensory peak latencies. Quantile regression was used to estimate percentiles of the distribution of interest while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand (either dominant or nondominant)).

2.1 Summary

Objective: To establish reference values of median and ulnar sensory nerve conduction studies using an 8 cm orthodromic and 14 cm antidromic technique for newly hired workers.

Methods: Seventeen thousand six-hundred and eighty-two (N = 17,682) newly hired workers were administered post-offer pre-placement testing for the median mononeuropathy associated with CTS between 2005 and 2020. Ten thousand and thirty-eight workers (N = 10,038) were included in the analyses of NCS performed with orthodromic technique, and 4,433 workers were included in the analyses of NCS performed with 14 cm antidromic technique. Linear quantile mixed regression models were fit where the nerve conduction outcomes, which included median and ulnar sensory peak latencies, amplitudes, and velocities as well as the difference between the median and ulnar peak latencies, were the dependent variables. The fixed effects were individual characteristics (age, height, BMI, sex, hand temperature, and hand), and workers were the random effect. The 50th percentile and either 5th or 95th percentile were presented.

Results: Most of the individual characteristics (age, sex, height, BMI, hand temperature, and hand) were statistically significantly associated with the nerve conduction outcomes ($p < 0.05$). The effects of age and BMI were consistently greater at the upper and lower bounds of the distribution.

Conclusions: The reference values in the present study for the median and ulnar NCS outcomes provide individualized thresholds to categorize NCS results. The findings in present study emphasize the importance of quantitative adjustment for age, BMI, height, sex, hand temperature, and hand (dominant versus nondominant). The effects of age and BMI were consistently greater at the upper and lower bounds of the distribution when compared to the effect sizes estimated at the 50th percentile. This observation provides further evidence that quantile regression is well suited for reference values as it captures the differences in the effect of independent variables across the distribution of the response variable.

2.2 Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the median nerve in the distal upper extremity (Atroshi et al., 1999; Mattioli et al., 2009; Palmer et al., 2007). The disorder is more common among workers in occupations requiring hand-intensive work than in the general population (Atroshi et al., 1999; Mattioli et al., 2009; Palmer et al., 2007). Because of the cost of treatment and impact on productivity of CTS among workers who perform hand-intensive work, some employers have attempted to detect the condition both among newly hired workers (post-offer, pre-placement screening) and among current workers (surveillance testing). Nerve conduction studies (NCS) are considered the gold standard to assess the neurophysiologic status of nerves and muscles and are used by clinicians and researchers to identify the median neuropathy characteristic of CTS. Some employers have adopted a strategy of using NCS to screen newly hired workers for median neuropathy across the carpal tunnel. Researchers have reported that workers with median neuropathy at the time of hire are more likely to eventually develop CTS than those without the neuropathy at time of hire (Dale et al., 2014; Werner et al., 2001). Given these findings, companies have used NCS during post-offer pre-placement screenings to identify newly hired workers with median neuropathy and place them in jobs that are less hand intensive. In order to correctly categorize NCS results among workers as consistent with CTS (or not), covariate adjusted NCS reference values appropriate for the population being screened are needed. Reference values in the literature are currently limited by modest sample sizes, sampling from populations that may not be fully representative of working populations, and limited information about the effect of relevant covariates.

When using continuous measure (e.g., NCS) to characterize individuals as disease positive or disease negative, an important step is to determine whether the results of that measure are within the range of values expected within the population of interest. Many statistical methods have been used to characterize population data and to define reference value ranges. Typically, a “normal” range is defined by values within the upper (95th, 97.5th or 99th percentiles) and lower (5th, 2.5th, or 1st percentiles) bounds of the distribution. Most commonly, linear regression or other parametric methods have been used. Under such an approach, the required assumption of normally distributed residuals and equal variance of the residuals across the entire distribution would be violated given the nature of the data. A statistical method gaining acceptance for characterizing non-normal distributions is quantile regression (Benatar et al., 2009; Dillingham et al., 2016; Esteves et al., 2020). Quantile regression has only recently been used to characterize nerve conduction data (Benatar et al., 2009; Dillingham et al., 2016; Esteves et al., 2020).

Review of the literature shows that the most commonly used statistical method to estimate a range of normal nerve conduction values within a population has been to calculate the mean +/- 2 standard deviations. However, because NCS results are not normally distributed, using the mean +/- two standard deviations for nerve conduction values often requires data transformation techniques (Chen et al., 2016; Dillingham et al., 2016; Dorfman & Robinson, 1997; Esteves et al., 2020; Peng et al., 2009). Even with data transformation techniques, describing the distribution in terms of the mean +/- 2 standard deviations becomes increasingly more challenging when there is a need to stratify across numerous demographic variables that are associated with the nerve conduction outcomes of interest (Aroori & Spence, 2008; Becker et al., 2002; Boz et al., 2004; Herbert et al., 2000; Kouyoumdjian et al., 2002; Letz & Gerr, 1994; Peng et al., 2009; Pourmemari & Shiri, 2016; Shiri et al., 2015; Solomon et al., 1999; Zambelis et al., 2010). Stratifying the nerve conduction outcomes by demographic variables such as age, BMI, height, sex, hand temperature, and handedness reduces the data into small sample sizes affecting the precision of the estimates.

Alternatively, linear regression has been used to develop reference values by estimating the mean response while adjusting for covariates in the model (Anton et al., 2014; Ott & Longnecker, 2010; Salerno et al., 1998). However, linear regression requires the user to make assumptions about the distribution (e.g. normally distributed residuals and equal variance of the residuals across the entire distribution) in order to extrapolate information about the upper or lower bounds from the mean response (Ott & Longnecker, 2010).

A more appropriate statistical method for developing referent values from non-normal distributions is quantile regression (Koenker & Hallock, 2001; Peng et al., 2009). Quantile regression can be used to model one or multiple quantiles (also termed percentiles) of the dependent variable while allowing the analyst to adjust for multiple covariates (Koenker & Hallock, 2001). Quantile regression is particularly advantageous for defining reference values of nerve conduction variables at the upper and lower ends of distribution (Figure 2). Quantile regression is not confined by the assumptions of a normal distribution or equal variance of residuals. Thus, the use of quantile regression provides an improved method to model nonparametric nerve conduction data for more accurate estimates of reference values at both ends of the distribution (Beyerlein, 2014; Dillingham et al., 2016; Dorfman & Robinson, 1997; Geraci, 2014; Geraci & Bottai, 2014; Koenker & Hallock, 2001; Waldmann, 2018).

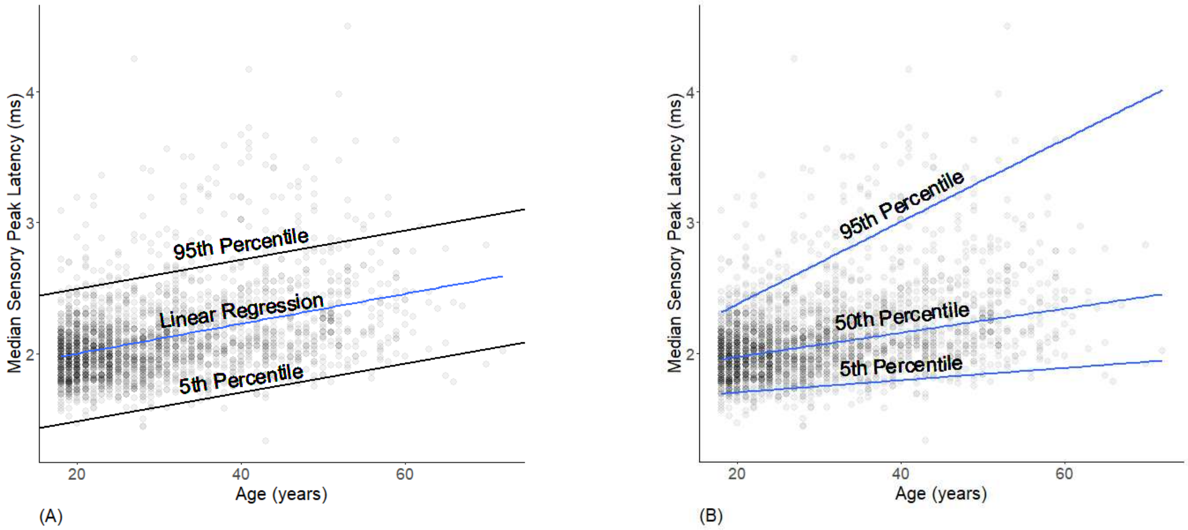


Figure 2. The graphs illustrate the relationship between age and the median sensory peak latency (using an 8 cm orthodromic technique) from a random sample of 2,500 workers in the present study to show the difference between linear and quantile regression. (A) Linear regression model representing the relationship between age and median sensory peak latency. Linear regression models the mean of the median sensory peak latency and has a constant slope regardless of percentile of the distribution. (B) Quantile regression model representing the relationship between age and median sensory peak latency specifying the 5th, 50th and 95th percentiles. The slopes between the 5^{th}, 50^{th}, and 95^{th} percentiles are different. An increase in age at the 95^{th} percentile results in a larger increase in median sensory peak latency when compared to the 5^{th} and 50^{th} percentiles.

Several methodologic shortcomings are noted in the current literature in which reference values for NCS are estimated. Specifically, the majority of published studies related to nerve conduction reference values are limited by small sample sizes, the use of statistical methods that are unsuitable for the non-Gaussian distribution, and by the inability to adequately adjust for individual characteristics associated with nerve conduction outcomes (Buschbacher, 1999a, 1999b; Chen et al., 2016; Dillingham et al., 2016; Esteves et al., 2020). Many of these issues have been recognized as limitations in electrophysiological research design and methodology of NCS by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) (Dillingham et al., 2016). Additionally, there are no occupation-related population-based reference values available to use during post-offer pre-placement job screenings aimed at identifying the median mononeuropathy characteristic of CTS (Dale et al., 2014; Salerno et al., 1998). The limitations of the currently available, general population-based, and frequently used reference values results in clinicians, practitioners, researchers, and employers relying on reference values with questionable statistical, clinical, or epidemiological relevance to workers, which may result in mis-categorizing workers as having abnormal nerve function. The present study addresses some of the limitations of currently published reference values by using quantile regression to develop reference values for the median and ulnar sensory nerve outcomes among members of a large sample of newly hired workers.

2.3 Methods

2.3.1 Subject Selection

The present study analyzed two datasets of NCS conducted specifically for assessment of the median and ulnar nerves across the carpal tunnel. One dataset used an 8 cm orthodromic NCS technique and the other used a 14 cm antidromic NCS technique. All data were collected as part of a post-offer pre-placement screening procedure for the electrophysiological signature of CTS (i.e., median mononeuropathy at the wrist) among new employees at three food processing facilities. All newly hired employees were screened with NCS regardless of job classification.

2.3.2 Post-offer Pre-placement Screening Protocol

The screenings included a questionnaire and NCS that were conducted between 2005 and 2020 (16 years) by occupational health nurses employed at three processing facilities. The nurses completed the questionnaire with the worker in a structured interview format. The questionnaire included demographic information, a brief health history, and the presence of hand symptoms. There were more questionnaire items as part of the 8 cm orthodromic screenings than during the

14 cm antidromic screenings (Table 5, see Appendix B and Appendix C for example of screening records).

Table 5. The questionnaire items and corresponding variable type for the 8 cm orthodromic and 14 cm antidromic NCS screening.

Questionnaire Items	**Variable Type**	**8 cm Orthodromic Screening (N = 12,787)**	**14 cm Antidromic Screening (N = 4,844)**
Individual Characteristics			
Age	Continuous (Years)	X	X
Sex	Dichotomous (Male or Female)	X	X
Height	Continuous (Inches)	X	X
Weight	Continuous (Pounds)	X	X
Handedness	Categorical (Right, Left or Both)	X	X
Health History			
Diabetes	Dichotomous (Yes or No)	X	
Thyroid	Dichotomous (Yes or No)	X	
Fracture of the Hand/Wrist	Dichotomous (Yes or No)	X	
Hand/Wrist Surgery	Dichotomous (Yes or No)	X	
Previous CTS diagnosis	Dichotomous (Yes or No)	X	X
Previous CTS surgery	Dichotomous (Yes or No)	X	X
Numbness/tingling in hands or fingers (thumb, index, long, ring, or pinky)	Dichotomous (Yes or No)	X	X
Last time they had numbness/tingling in hands/fingers	Date (M/D/Y or Y)	X	X
Duration of Numbness/tingling	Continuous (Months)	X	X

The occupational health nurses who administered the NCS first completed a two-day nerve conduction procedures training session. Following the two-day training, each nurse was required to pass a written and practical examination to ensure competency prior to employee testing. Competency was defined as at least 90% correct on the written examination and 100% on the practical examination. Additionally, newly trained nurses were required to complete a minimum of 50 NCS under the supervision of nurses experienced in the testing procedures. Every NCS conducted on workers was then reviewed for completeness and validity by a registered physical therapist with more than 10 years of experience in electrophysiological assessments of distal upper limb neuropathy.

There were two techniques used for administering the sensory NCS, an 8 cm palm-to-wrist orthodromic and a 14 cm wrist-to-fingers antidromic method. Both techniques were based on recommendations from the AANEM (American Association of Electrodiagnostic Medicine, 2002). From December 2005 through April 2013, a commercially available electromyograph (Cadwell Sierra II Wedge, Cadwell Labs, Kennewick, Washington) with surface electrodes was used to collect 8 cm palm-to-wrist NCS. The median sensory peak latency and amplitude were obtained for the dominant and nondominant hands of each worker. If the median sensory peak latency exceeded 2.4 ms, then ulnar sensory NCS were also performed. The nerves were stimulated over the palm superficial to the respective nerve with the active recording electrode located 8 cm proximal to the cathode of the stimulating electrode. All tests were performed using supramaximal stimulation. Prior to the test, skin temperature of the palmar surface of both hands was measured with an infrared thermistor positioned 1-3 cm from the skin (Electro-Therm, Model #TM99A, Cooper Instrument Corporation). If the hand temperature was below 30° C, then the worker warmed both hands with warm water for one to three minutes.

From April 2013 to December 2020, a 14 cm wrist-to-finger antidromic sensory technique was used. Both median and ulnar sensory peak latencies and amplitudes were obtained from both hands of all workers. The nerves were stimulated at or just proximal to the distal wrist crease with the active recording electrode located 14 cm distal to the stimulating cathode. The tests were performed using supramaximal stimulation. Skin temperature was measured and recorded as described previously for both hands.

2.3.3 Data Reliability

There were a total of 17,682 NCS conducted on newly hired workers during the 16-year testing period. All individual records were stored as PDF formatted files and entered into an electronic database by five data coders. Each PDF file was read and manually coded into a Microsoft Excel spreadsheet. All personal identifiers (names) were removed from the data by the principal investigators.

The inter-rater reliability of the five data coders was assessed by having each of the coders enter a sample of records from the 8 cm orthodromic and 14 cm antidromic NCS databases. The principal investigator randomly selected a sample of 100 files to re-code, and each coder (n = 5) entered the same random sample. The intra-class correlation coefficient (ICC) was used to analyze the agreement of the coded entries between coders. The investigator selected ICC characteristics (model, type, and definition) for the present study. The ICCs were assessed with a 2-way mixed effects model. The five coders were the only coders of interest (as these results did not need to be generalizable to an entire population of coders) (Hallgren, 2012; Zou, 2012). The ICC type was the "mean of k raters" as there were a total of 5 coders entering worker data into the database (Hallgren, 2012; Zou, 2012). The investigators used an absolute agreement for the definition of the ICC model as they were interested in the agreement between entries (not necessarily the consistency of the entries per coder) (Hallgren, 2012; Zou, 2012). ICC values > 0.75 were considered to be in excellent agreement (Hallgren, 2012). One hundred data files were compared across the 5 coders. A power analysis was based on a conservative estimate that the ICC would be at least 0.80, with 5 coders, at an alpha of 0.05, and power of 0.80 indicated 100 observations was sufficient. ICC were computed for all variables (n = 38 for the orthodromic sample and n = 37 for the antidromic sample).

2.3.4 Data Cleaning

The initial review of the NCS results was performed within 24 hours of the occupational health nurse completing the nerve conduction test. The validity of the NCS was determined by visually reviewing the recorded waveform. If the recorded waveform was unacceptable, the NCS was repeated until it was deemed acceptable.

Range and validity checks were conducted on the data to identify nerve conduction values not physiologically plausible. The upper and lower thresholds selected to flag improbable results for subsequent review were based on previously reported reference values ranges (Esteves et al., 2020; Salerno et al., 1998; Stevens, 1987). For the NCS performed with orthodromic methods, values were flagged if the median sensory peak latency was < 1.00 ms, or > 4.95 ms or if the median sensory amplitude was < 10 μV or > 330 μV. For the NCS performed with antidromic methods, values were flagged if the median or ulnar sensory peak latency was < 2.5 ms or > 6.00 ms, or if the median or ulnar sensory amplitude < 7.00 μV or > 130 μV. Nerve conduction results exceeding the defined lower and upper thresholds were reviewed twice. The first review was to compare the original nerve conduction values generated from the electrophysiologic equipment with the database entries to ensure the entries were not subject to keystroke errors. Of the 748 original nerve conduction values within the orthodromic database that met criteria for review, a total of 67 nerve conduction values were identified as keystroke errors. Of the 4,196 original nerve conduction values within the antidromic database that met criteria for review, a total of 116 nerve conduction values were identified as keystroke errors. Those data that were not identified as keystroke errors were subsequently reviewed by comparing the original nerve conduction waveforms captured at the time of the NCS to the recorded value. If a nerve conduction value was verified through observation of the original waveform, the original result was kept. If a valid nerve conduction value was identified from the waveform, the new value was entered in place of the implausible value. If a valid nerve conduction value was not identified from the waveform, the implausible value was voided from the database (example found in Appendix G: Data voiding example). The investigators completing this data reconciliation procedure were blinded to other variables within the data file. For the orthodromic database, a total of 4 nerve conduction values were reconciled through reviewing the waveform recorded at the time of the NCS and 100 nerve conduction values were voided and treated as missing. For the antidromic database, a total of 12 nerve conduction values were reconciled through inspection of the waveform recorded at the time of the NCS and 259 nerve conduction values were voided and treated as missing.

Body Mass Index (BMI) was computed by dividing worker mass (kg) by the square of height (m^2). Conduction velocity was computed by dividing the distance between stimulating and recording electrodes (8 cm for orthodromic and 14 cm for antidromic NCS) by peak latency (ms) and was expressed in units of meters/second (m/s). Because of the small proportion of workers who reported "both" for handedness (0.09% of the orthodromic dataset and 0.12% of the antidromic dataset), "both" was re-classified as right hand dominant. For the 14 cm antidromic dataset, previous CTS diagnosis and previous CTS surgery were coded from the open-ended "comments" field. The median-ulnar difference was calculated by subtracting the ulnar sensory peak latency from the median sensory peak latency and was expressed in ms. Self-reported hand symptoms was used to exclude workers with possible focal or diffuse in the distal upper extremity (e.g., pronator syndrome, ulnar tunnel syndrome, or diffuse neuropathies) (Shrivastava & Szabo, 2008) from the symptom-free data set used to establish referent values. Self-reported hand symptoms were defined as reported numbness, tingling, or pain of the thumb, index, middle, ring, or little finger of at least two weeks duration within the past year (Armstrong, Dale, Franzblau, & Evanoff, 2008; Franzblau, Werner, Valle, & Johnston, 1993; Patil et al., 2012; Shrivastava & Szabo, 2008; Werner et al., 2005). All data cleaning steps were completed using RStudio Version 3.6.1.

2.3.5 Data Analysis

2.3.5.1 Exclusions

Exclusion criteria for the present study were based on (1) cutoff values selected for worker demographics (age, height, weight, BMI, and hand temperature) and (2) reported (or missing) comorbid conditions that have been shown to influence nerve conduction outcomes. Workers with specific comorbid conditions (and those with missing comorbid conditions data) were excluded to yield normative values that were free from the disease of interest (i.e., CTS) and from conditions that could affect the nerve conduction values (Dillingham et al., 2016; Dorfman & Robinson, 1997). All comorbid conditions included in the post-offer pre-placement CTS screening questionnaire were used as exclusion criteria. The post-offer pre-placement CTS screening questionnaire items used to ascertain comorbid conditions were slightly different between the 8 cm orthodromic and 14 cm antidromic screening periods. Fewer comorbid items were included in the 14 cm antidromic screenings. For the 8 cm orthodromic NCS dataset, workers were excluded from the analyses used to establish reference values if they self-reported co-morbid conditions of diabetes, thyroid disease, wrist/hand fracture, wrist/hand surgery, previous CTS diagnosis, previous CTS surgery, or symptoms consistent with neuropathic conditions of the distal upper extremity. For the 14 cm antidromic dataset, workers were excluded from the analyses used to establish reference values if they reported a previous CTS diagnosis, a previous CTS surgery, or symptoms related to possible neuropathic conditions of the distal upper extremity.

Of the 12,821 newly hired workers in the orthodromic dataset, 2,783 (21.7%) were excluded from the dataset used to develop the reference values (Table 6). Of the 4,861 newly hired workers in the antidromic dataset, 428 (8.80%) were excluded from the analyses (Table 6). The orthodromic dataset likely had a greater proportion of workers excluded from the analysis when compared to the antidromic dataset because there were more comorbid conditions included in the orthodromic screening questionnaire.

Table 6. Exclusion criterion for developing nerve conduction reference values.

Exclusion Criterion*	**Orthodromic N (%)**	**Antidromic N (%)**
Demographics		
Age < 18 or > 75 years	9 (0.07)	6 (0.12)
Height < 132.1 cm or > 203.2 cm	12 (0.09)	1 (0.02)
Weight < 40.8 kg or > 192.7 kg	6 (0.05)	6 (0.12)
BMI < 16 kg/m^2 or > 65 kg/m^2	7 (0.05)	4 (0.08)
Hand temperature < 30 °C or > 38°C	5 (0.04)	0 (0)
Comorbidities		
Diabetes	319 (2.5)	-
Thyroid	163 (1.27)	-
Fracture of Hand/Wrist	1,588 (12.4)	-
Hand/Wrist Surgery	641 (5.00)	-
Previous CTS Diagnosis	252 (1.97)	44 (0.91)
Previous CTS Surgery	140 (1.09)	27 (0.56)
Symptoms related to possible neuropathic conditions	612 (4.77)	393 (8.08)

For the orthodromic dataset, a total of 2,784 (21.7%) out of 12,821 workers were excluded, and 10,038 (78.3%) were included in the analysis.
For the antidromic dataset, a total of 428 (8.8%) out of 4,861 were excluded, and 4,433 (91.2%) were included in the analysis.

*Some workers met more than one criterion.

2.3.5.2 Statistical Methods

The analyses was conducted using R and the lqmm package (Geraci, 2014; Geraci & Bottai, 2014). Linear quantile mixed models were used to fit separate models with each of the four nerve conduction outcome (peak latency, amplitude, conduction velocity, and median-ulnar sensory peak latency difference) as the response variable. The lqmm package is relatively new in R, and allows a user to fit mixed models with quantile regression (Geraci, 2014; Geraci & Bottai, 2014). Although quantile regression has been used in the past to estimate nerve conduction reference values (Benatar et al., 2009; Esteves et al., 2020), there are no published studies that use a mixed model quantile regression for developing nerve conduction reference values. Because each newly hired worker had an NCS performed on their dominant and non-dominant hand, the worker was included as a random effect. Fixed effect variables were selected based on the data collected at the time of the post-offer pre-placement screening and previous research (Becker et al., 2002; Boz et al., 2004; Kouyoumdjian et al., 2002; Letz & Gerr, 1994; Shiri et al., 2015; Zambelis et al., 2010). The fixed effects were age, sex, height, BMI, hand temperature, and hand dominance.

For the 8 cm orthodromic dataset, reference values were established only for the distal median sensory nerve because of the conditionality of the ulnar NCS on the median sensory NCS result. Specifically, the ulnar NCS was only performed if the distal median sensory peak latency was > 2.4 ms (considered abnormal in the screening). Three separate models were developed corresponding to the three nerve conduction outcomes of interest as the dependent variables (peak latency, amplitude, and velocity). For the 14 cm antidromic dataset, reference values were developed for the median and ulnar sensory nerves as both nerves were assessed regardless of median sensory latency for all workers. For the antidromic dataset, a total of seven separate models were fit corresponding to the three nerve conduction outcomes of interest as the dependent variables (peak latency, amplitude, and velocity) for the median and ulnar nerve and the difference between the median and ulnar nerve peak latency.

The 95th or 5th percentile of the nerve conduction outcome's distributions and confidence intervals were presented in the results because the tail ends of the distribution were primarily of interest for determining reference values (Dorfman & Robinson, 1997). The 50th percentile of the distribution was also included to compare to the upper/lower bounds of the distribution. The upper bound (95^{th} percentile) of the distribution was selected for the peak latency and median-ulnar sensory peak latency difference as increases in these values are indicative of nerve impairment. In contrast, the lower bound of the distribution (5^{th} percentile) was presented for the amplitude and conduction velocity as decreases in these values are typically indicative of nerve impairment. A range of quantiles (2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5^{th}) for all NCS outcomes are presented in Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.

2.4 Results

2.4.1 Data Reliability

Four coders entered the original data files into the orthodromic database whereas five coders entered data for the antidromic database. Acceptable ICCs (> 0.75) were observed for all variables. Specifically, for both the orthodromic and antidromic sample, 89% of the variables had an ICC greater than or equal to 0.98. ICC and 95% confidence intervals are presented in Table H1 in Appendix H: Intraclass correlation coefficient table.

2.4.2 Description of Worker Demographics

Demographic characteristics of the 10,038 workers included in the orthodromic analyses and 4,433 workers included in the antidromic analyses are presented in Table 7. The sample was predominately male, relatively young, and somewhat overweight (Table 7). For the orthodromic dataset, 6.75% of the sample were ≥ 50 years old (see Table D1 in Appendix D: Sample sizes across age distribution categories). For the antidromic dataset, 8.20% of the sample were ≥ 50 years old (see Table D1 in Appendix D: Sample sizes across age distribution categories). The majority (90%) of the sample were right-hand dominant.

Table 7. Summary statistics of worker demographics for the 8 cm orthodromic and 14 cm antidromic dataset.

Characteristics	Value (units)	Orthodromic Dataset (N = 10,038)	Antidromic Dataset (N = 4,433)
Sex:	Male n[b] (%)[c]	6,160 (61.4)	2,717 (61.2)
	Female n (%)	3,877 (38.6)	1,715 (38.8)
	Unknown n (%)	1 (0)	1 (0)
Age:	Mean ± SD[d] (years)	30.1 ± 10.8	31.4 ± 11.1
	Range (min-max)[e] (years)	18-74	18-75
Height:	Mean ± SD (cm)	169.8 ± 10.2	169.8 ± 10.2
	Range (min-max) (cm)	132.1-203.2	132.1-203.2
Mass:	Mean ± SD (kg)	82.6 ± 21.8	83.7 ± 24.1
	Range (min-max) (kg)	40.8-190.5	40.8-192.8
BMI:	Mean ± SD (kg/m^2)	28.6 ± 6.8	28.9 ± 7.3
	Range (min-max) (kg/m^2)	16-64.6	16.1-63.6
Handedness:	Right n (%)	8,950 (89.2)	4,036 (91.0)
	Left n (%)	960 (9.6)	364 (8.2)
	Unknown n (%)	116 (1.1)	4 (0.1)
Hand Temperature	Mean ± SD (°C)	32.3 ± 1.09	31.9 ± 1.31
	Range (min-max) (°C)	30-38	30-35

[a] N = Total number of subjects per group.
[b] n = Total number
[c] % = Percentage.
[d] SD = Standard deviation.
[e] (min-max) = Minimum value of the range and maximum value of the range.

2.4.3 Description of Nerve Conduction Outcomes

The number of hands included in the analysis, means, standard deviations (SD), and number of absent responses for the nerve conduction outcomes for the orthodromic and antidromic results are found in Table 8 and Table 9, respectively. The peak latency, amplitude, and velocity were similar between the dominant and nondominant hands. The mean median and ulnar peak latency difference for the dominant hand was slightly greater than the nondominant hand (Table 9).

The reason the number of hands in the sample varied across the nerve conduction outcomes was in part due to the data cleaning procedure previously described in the Methods Section. The amplitudes had the smallest sample sizes as these values were most frequently voided due to the poor signal-to-noise ratios observed on the original waveform (see Appendix G: Data voiding example). In addition, a portion of the missing observations for the peak latency, amplitude, and conduction velocity were due to nerves for which the technicians could not elicit a response. An absent nerve response could be due to a variety of reasons including significant nerve impairment or errors in setting up electrodiagnostic equipment.

Table 8. Summary statistics of the 8 cm Orthodromic median sensory nerve conduction outcomes stratified by hand.

		All Workers		**Dominant Hand**		**Nondominant Hand**		**Unknown Hand**	
Nerve	**Nerve Conduction Outcome (units)**	**Hands[a]**	**Mean ± SD[b]**	**Hands**	**Mean ± SD**	**Hands**	**Mean ± SD**	**Hands**	**Mean ± SD**
Median	Peak Latency (ms)[c]	19,927	2.11 ± 0.33	9,837	2.12 ± 0.34	9,858	2.10 ± 0.32	232	2.07 ± 0.32
	Amplitude (µV)[d]	19,865	65.53 ± 32.35	9,809	63.44 ± 31.76	9,826	67.56 ± 32.78	230	67.68 ± 33.56
	Conduction Velocity (m/s)[e]	19,927	38.68 ± 5.10	9,837	38.57 ± 5.17	9,858	38.77 ± 5.02	232	39.41 ± 5.30
	No Responses[f]	129	-	64	-	65	-	0	-

[a] Hands = Total number of hands per group.
[b] SD = Standard deviation.
[c] ms = milliseconds
[d] µV = microvolts
[e] m/s = meters/second
[f] No Response = The technician was not able to evoke an action potential.

Table 9. Summary statistics of the 14 cm antidromic median and ulnar sensory nerve conduction outcomes stratified by hand.

		All Workers		Dominant Hand		Nondominant Hand		Unknown	
Nerve	**Nerve Conduction Outcome (units)**	**Hands[a]**	**Mean ± SD[b]**	**Hands**	**Mean ± SD**	**Hands**	**Mean ± SD**	**Hands**	**Mean ± SD**
Median	Peak Latency (ms)[c]	8,806	3.43 ± 0.47	4,370	3.45 ± 0.48	4,428	3.42 ± 0.45	8	3.40 ± 0.42
	Amplitude (µV)[d]	8,726	57.19 ± 24.35	4,335	55.13 ± 23.24	4,383	59.21 ± 25.22	8	70.88 ± 30.8
	Conduction Velocity (m/s)[e]	8,806	41.43 ± 4.95	4,370	41.24 ± 4.97	4,428	41.62 ± 4.92	8	41.73 ± 4.85
	No Responses[f]	58	-	29	-	29	-	0	-
Ulnar	Peak Latency (ms)	8,793	3.34 ± 0.40	4,373	3.33 ± 0.40	4,413	3.34 ± 0.41	7	3.19 ± 0.41
	Amplitude (µV)	8,685	43.29 ± 23.4	4,324	41.83 ± 22.86	4,354	44.73 ± 23.83	7	45.55 ± 31.47
	Conduction Velocity (m/s)	8,793	42.51 ± 4.65	4,373	42.52 ± 4.53	4,413	42.49 ± 4.76	7	44.45 ± 5.26
	No Responses	64	-	22	-	41	-	1	-
MUD[g]		8,751	0.10 ± 0.42	4349	0.12 ± 0.44	4395	0.07 ± 0.40	7	0.23 ± 0.37

[a] Hands = Total number of hands per group.
[b] SD = Standard deviation.
[c] ms = milliseconds
[d] µV = microvolts
[e] m/s = meters/second
[f] No Response = The technician was not able to evoke an action potential
[g] MUD = Median-Ulnar Difference, the difference between the median sensory peak latency and ulnar sensory peak latency.

2.4.4 Results of the Linear Quantile Mixed Models

Parameter estimates from the linear quantile mixed model and their respective confidence intervals and standard errors for the 5th, 50th, and 95th percentile nerve conduction outcomes are provided in Table 10, Table 11, Table 12, and Table 13. The 95th percentile was presented for sensory peak latency as increases in peak latency indicate poorer nerve function. The 5th percentile was presented for sensory amplitude and velocity as decreases in these outcomes indicate poorer nerve function. The percentiles presented at the upper and lower end of the distribution were selected to define threshold to be used to classify a value as likely to be the result of a disease state. The coefficients from the models presented in Tables 10-13 can be used to estimate the upper or lower (95th or 5th percentile) of the nerve conduction outcome's distribution for an individual based on the demographic information included in the model. For example, the regression equation for the 8 cm orthodromic NCS technique's 95th percentile of median sensory peak latency is:

$$95th\ \%tile\ median\ sensory\ peak\ latency\ = 1.684 + (0.011 * age) + (0.062 * sex) + (0.002 * height) + (0.011 * BMI) + (-0.015 * temp) + (-0.003 * hand) \quad \text{(Equation 1)}$$

with age in units of years, sex as either 0 (female) or 1 (male), height in units of cm, BMI in units of kg/m^2, temp was hand surface temperature in units of C°, and hand was coded as either 0 (dominant) or 1 (nondominant, ND). To illustrate further, using Equation 1 for the 95th percentile presented above, the 95th percentile value of the median sensory peak latency is 2.27 ms for an average male[a] in the present study. The quantile regression equation for the 95th percentile of the 14 cm antidromic median-ulnar peak latency difference is:

---

[a] The average male in the present study had an age of 31 years, height of 170 cm, BMI of 29, and hand temperature of 32 °C. The calculation was based on their dominant hand.

$$\text{95th \%tile Median} - \text{Ulnar Difference} = -0.589 + (0.009 * age) + (0.027 * sex)$$

$$-(0.001 * height) + (0.014 * BMI) + (0.014 * temp) - (0.042 * hand). \qquad \text{(Equation 2)}$$

Using Equation 2, the 95th percentile value for the median-ulnar difference is 0.40 ms for an average male[b] in the present study. The parameter estimates from fitting the linear quantile mixed model and their respective standard errors for a larger range of percentiles are provided in Tables I1 to Table I10 (in Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.).

[b] The average male in the present study had an age of 31 years, height of 170 cm, BMI of 29, and hand temperature of 32 °C. The calculation was based on their dominant hand.

Table 10. Summary of parameter estimates from the linear quantile mixed models for the median sensory nerve 50th Percentile and 5th/95th Percentile for the 8 cm orthodromic nerve conduction outcomes (Peak Latency Hands = 19,215 and N = 9,649, Amplitude Hands = 19,156 and N = 9,639, and Conduction Velocity Hands = 19,215 and N = 9,649).

	8 cm Orthodromic (Median Sensory)					
Variable	**Peak Latency (ms) (50th Percentile)**	**Amplitude (µV) (50th Percentile)**	**Conduction Velocity (m/s) (50th Percentile)**	**Peak Latency (ms) (95th Percentile)**	**Amplitude (µV) (5th Percentile)**	**Conduction Velocity (m/s) (5th Percentile)**
Intercept						
Estimate	**1.905**	**144.906**	**42.012**	**1.684**	**159.021**	**40.324**
(95% CI)	(1.015, 2.795)	(120.1, 169.711)	(36.817, 47.207)	(1.103, 2.264)	(124.888, 193.153)	(34.224, 46.425)
SE	0.448	12.501	2.618	0.293	17.202	3.075
Age						
Estimate	**0.009**	**-0.521**	**-0.156**	**0.011**	**-0.373**	**-0.178**
(95% CI)	(0.006, 0.012)	(-0.579, -0.463)	(-0.175, -0.137)	(0.009, 0.014)	(-0.469, -0.277)	(-0.208, -0.148)
SE	0.002	0.029	0.009	0.001	0.048	0.015
Sex (Male =1)						
Estimate	**0.072**	**-6.729**	**-1.273**	**0.062**	**-3.005**	**-0.881**
(95% CI)	(-0.071, 0.215)	(-8.465, -4.994)	(-1.766, -0.78)	(-0.022, 0.147)	(-5.39, -0.62)	(-1.806, 0.045)
SE	0.072	0.875	0.248	0.043	1.202	0.466
Height						
Estimate	**0.002**	**0.039**	**-0.042**	**0.002**	**-0.143**	**-0.045**
(95% CI)	(-0.007, 0.011)	(-0.064, 0.141)	(-0.071, -0.014)	(0.000, 0.005)	(-0.262, -0.023)	(-0.084, -0.005)
SE	0.005	0.052	0.015	0.001	0.06	0.02
BMI						
Estimate	**0.004**	**-0.594**	**-0.051**	**0.011**	**-0.567**	**-0.106**
(95% CI)	(-0.003, 0.01)	(-0.699, -0.488)	(-0.085, -0.016)	(0.007, 0.014)	(-0.705, -0.429)	(-0.146, -0.065)
SE	0.003	0.053	0.017	0.002	0.069	0.02
Temp[a]						
Estimate	**-0.018**	**-1.648**	**0.332**	**-0.015**	**-2.071**	**0.364**
(95% CI)	(-0.071, 0.035)	(-2.245, -1.051)	(0.209, 0.456)	(-0.032, 0.002)	(-2.976, -1.165)	(0.173, 0.555)
SE	0.027	0.301	0.062	0.009	0.456	0.096
Hand (ND = 1)						
Estimate	**-0.004**	**3.534**	**0.126**	**-0.003**	**2.921**	**0.157**
(95% CI)	(-0.034, 0.026)	(2.943, 4.125)	(0.055, 0.197)	(-0.013, 0.007)	(2.114, 3.728)	(-0.024, 0.338)
SE	0.015	0.298	0.036	0.005	0.407	0.091

[a] Temp = Hand temperature

Table 11. Summary of parameter estimates from the linear quantile mixed models for the median sensory nerve 50th Percentile and 5th/95th Percentile for the 14 cm antidromic nerve conduction outcomes (Peak latency Hands = 8,640 and N = 4,335, Amplitude Hands= 8,564 and N = 4,323, and Conduction velocity Hands = 8,640 and N = 4,335).

14 cm Antidromic (Median Sensory)

Variable	Peak Latency (ms) (50th Percentile)	Amplitude (µV) (50th Percentile)	Conduction Velocity (m/s) (50th Percentile)	Peak Latency (ms) (95th Percentile)	Amplitude (µV) (5th Percentile)	Conduction Velocity (m/s) (5th Percentile)
Intercept						
Estimate	**4.308**	**193.4**	**25.832**	**5.038**	**159.395**	**30.20**
(95% CI)	(3.375, 5.241)	(176.6, 210.2)	(20.477, 31.187)	(3.76, 6.317)	(122.5, 196.3)	(24.356, 36.04)
SE	0.47	8.485	2.699	0.644	18.602	2.945
Age						
Estimate	**0.014**	**-0.659**	**-0.149**	**0.019**	**-0.590**	**-0.159**
(95% CI)	(0.012, 0.015)	(-0.716, -0.603)	(-0.165, -0.133)	(0.014, 0.023)	(-0.721, -0.46)	(-0.191, -0.126)
SE	0.001	0.029	0.008	0.002	0.066	0.017
Sex (Male=1)						
Estimate	**0.066**	**-4.383**	**-0.641**	**0.147**	**-2.459**	**-0.543**
(95% CI)	(0.012, 0.121)	(-6.081, -2.685)	(-1.158, -0.124)	(0.01, 0.283)	(-7.096, 2.178)	(-1.76, 0.674)
SE	0.027	0.856	0.260	0.069	2.337	0.613
Height						
Estimate	**0.005**	**-0.127**	**-0.05**	**0.003**	**-0.101**	**-0.028**
(95% CI)	(0.002, 0.008)	(-0.197, -0.057)	(-0.071, -0.029)	(-0.002, 0.008)	(-0.302, 0.101)	(-0.066, 0.011)
SE	0.002	0.035	0.011	0.003	0.102	0.019
BMI						
Estimate	**0.003**	**-0.425**	**-0.012**	**0.006**	**-0.404**	**-0.052**
(95% CI)	(-0.001, 0.006)	(-0.521, -0.33)	(-0.043, 0.019)	(-0.001, 0.013)	(-0.61, -0.198)	(-0.108, 0.003)
SE	0.002	0.048	0.015	0.004	0.104	0.028
Temp[a]						
Estimate	**-0.071**	**-2.573**	**0.920**	**-0.084**	**-2.269**	**0.62**
(95% CI)	(-0.091, -0.052)	(-3.027, -2.12)	(0.758, 1.081)	(-0.13, -0.039)	(-3.067, -1.47)	(0.416, 0.824)
SE	0.01	0.229	0.081	0.023	0.402	0.103
Hand (ND=1)						
Estimate	**-0.030**	**3.913**	**0.345**	**-0.027**	**2.505**	**0.302**
(95% CI)	(-0.039, -0.022)	(3.302, 4.525)	(0.243, 0.448)	(-0.05, -0.005)	(1.138, 3.871)	(0.049, 0.555)
SE	0.004	0.308	0.052	0.011	0.689	0.128

[a] Temp = Hand temperature

Table 12. Summary of parameter estimates from the linear quantile mixed models for the 14 cm antidromic ulnar sensory nerve 50th and 5th/95th Percentiles (Peak Latency Hands = 8,628 and N = 4,345, Amplitude Hands = 8,525 and N = 4,326, and Conduction Velocity Hands = 8,628 and N = 4,345).

14 cm Antidromic (Ulnar Sensory)

Variable	**Peak Latency (ms) (50th Percentile)**	**Amplitude (µV) (50th Percentile)**	**Conduction Velocity (m/s) (50th Percentile)**	**Peak Latency (ms) (95th Percentile)**	**Amplitude (µV) (5th Percentile)**	**Conduction Velocity (m/s) (5th Percentile)**
Intercept						
Estimate	**5.502**	**212.416**	**18.253**	**6.014**	**193.618**	**16.431**
(95% CI)	(4.992, 6.011)	(195.487, 229.344)	(13.662, 22.845)	(4.68, 7.347)	(158.009, 229.227)	(12.427, 20.435)
SE	0.257	8.532	2.314	0.672	17.946	2.018
Age						
Estimate	**0.007**	**-0.505**	**-0.081**	**0.012**	**-0.445**	**-0.116**
(95% CI)	(0.006, 0.008)	(-0.547, -0.463)	(-0.104, -0.059)	(0.008, 0.016)	(-0.536, -0.354)	(-0.142, -0.089)
SE	0.001	0.021	0.011	0.002	0.046	0.013
Sex (Male=1)						
Estimate	**0.066**	**-5.849**	**-0.952**	**0.155**	**-4.196**	**-1.31**
(95% CI)	(0.036, 0.096)	(-7.126, -4.572)	(-1.351, -0.553)	(0.033, 0.276)	(-6.675, -1.716)	(-2.282, -0.338)
SE	0.015	0.644	0.201	0.061	1.25	0.490
Height						
Estimate	**0.004**	**-0.367**	**-0.067**	**0.003**	**-0.271**	**-0.042**
(95% CI)	(0.003, 0.006)	(-0.436, -0.299)	(-0.084, -0.0500)	(0.000, 0.006)	(-0.434, -0.108)	(-0.081, -0.003)
SE	0.001	0.035	0.008	0.002	0.082	0.02
BMI						
Estimate	**-0.010**	**-0.586**	**0.154**	**-0.008**	**-0.352**	**0.099**
(95% CI)	(-0.013, -0.008)	(-0.655, -0.517)	(0.124, 0.184)	(-0.013, -0.002)	(-0.5, -0.204)	(0.052, 0.145)
SE	0.001	0.035	0.015	0.003	0.075	0.023
Temp[a]						
Estimate	**-0.090**	**-2.301**	**1.076**	**-0.100**	**-3.049**	**1.02**
(95% CI)	(-0.101, -0.078)	(-2.658, -1.945)	(0.939, 1.212)	(-0.14, -0.061)	(-3.831, -2.266)	(0.822, 1.218)
SE	0.006	0.18	0.069	0.020	0.394	0.100
Hand (ND=1)						
Estimate	**0.001**	**2.61**	**-0.049**	**0.017**	**2.423**	**-0.127**
(95% CI)	(-0.006, 0.008)	(2.024, 3.196)	(-0.144, 0.046)	(-0.005, 0.038)	(1.122, 3.723)	(-0.34, 0.087)
SE	0.003	0.295	0.048	0.011	0.656	0.108

[a] Temp = Hand temperature

Table 13. Summary of parameter estimates from the linear quantile mixed models for the difference between the median and ulnar peak latency (MUD) 5th, 50th, and 90th Percentiles for the 14 cm antidromic technique (Hands = 8,588 and N = 4,333).

Variable	**5th Percentile (ms)**	**50th Percentile (ms)**	**95th Percentile (ms)**
Intercept			
Estimate	**-0.951**	**-0.294**	**-0.589**
(95% CI)	(-2.052, 0.149)	(-0.733, 0.145)	(-1.252, 0.074)
SE	0.555	0.221	0.334
Age			
Estimate	**0.000**	**0.006**	**0.009**
(95% CI)	(-0.003, 0.004)	(0.004, 0.007)	(0.005, 0.013)
SE	0.002	0.001	0.002
Sex (Male=1)			
Estimate	**-0.057**	**-0.007**	**0.027**
(95% CI)	(-0.165, 0.051)	(-0.039, 0.024)	(-0.126, 0.18)
SE	0.055	0.016	0.077
Height			
Estimate	**0.000**	**-0.001**	**-0.001**
(95% CI)	(-0.006, 0.007)	(-0.003, 0.000)	(-0.006, 0.005)
SE	0.003	0.001	0.003
BMI			
Estimate	**0.006**	**0.012**	**0.014**
(95% CI)	(0.001, 0.011)	(0.009, 0.014)	(0.008, 0.021)
SE	0.003	0.001	0.003
Temp[a]			
Estimate	**0.017**	**0.003**	**0.014**
(95% CI)	(-0.033, 0.067)	(-0.007, 0.013)	(-0.018, 0.045)
SE	0.025	0.005	0.016
Hand (ND=1)			
Estimate	**-0.020**	**-0.033**	**-0.042**
(95% CI)	(-0.043, 0.003)	(-0.043, -0.023)	(-0.069, -0.016)
SE	0.012	0.005	0.013

[a] Temp = Hand temperature

2.4.4.1 Age

The association between age and sensory peak latency was positive and the association between age and sensory amplitude, and sensory velocity was negative for the majority of the median and ulnar nerve conduction outcomes (Table 10-13). As the percentile of the distribution increases, the effect of age increased monotonically for the median and ulnar sensory peak latencies and velocities whereas the effect of age decreased monotonically for the median and ulnar sensory amplitude (see Figures I1-I5 in Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.). For example, the effect of age on sensory peak latency was slightly greater at the upper end of the distribution (95^{th} percentile) when compared to the 50^{th} percentile for the median and ulnar nerves and both NCS techniques (orthodromic and antidromic) (Figure 3). In contrast, the effect of age on sensory amplitude at the 50^{th} percentile was slightly less than the 5^{th} percentile for both nerves and NCS screening techniques (Figure 4). At the 50^{th} percentile for the median sensory nerve, a 10-year increase in age was associated with an average of 0.10 ms increase in peak latency, 5.62 microvolt decrease in amplitude, and 1.29 m/s decrease in velocity. At the 95^{th} percentile for the median sensory nerve, a 10-year increase in age was associated with an average of 0.14 ms increase in peak latency, 4.69 microvolt decrease in amplitude, and 1.51 m/s decrease in conduction velocity. The 95^{th} percentile of the 14 cm antidromic median sensory peak latency, ulnar sensory peak latency, and median-ulnar difference distributions for a range of ages is provided in Table 14. While holding all other covariates constant, an increase in age is associated with an increase (i.e., poorer performance) in median sensory peak latency, ulnar sensory peak latency, and median-ulnar difference for the 95^{th} percentile.

Table 14. The 95th percentile of the 14 cm antidromic median sensory peak latency, ulnar sensory peak latency, and the difference between the median and ulnar sensory peak latency varied by age.

14 cm Antidromic Technique, 95th Percentile[a]			
Age (years)	**Median Sensory Peak Latency (ms)**	**Ulnar Sensory Peak Latency (ms)**	**Median-Ulnar Difference (ms)**
20	3.54	3.48	0.32
30	3.72	3.60	0.41
40	3.90	3.72	0.50
50	4.08	3.84	0.59
60	4.26	3.96	0.68

[a] 95th percentile values were computed from the regression coefficients presented in Table 12, 13, and 14. All covariates other than age were held constant with a sex of male, height of 170 cm, BMI of 30 kg/m^2, hand temperature of 32 °C, and for the dominant hand.

2.4.4.2 Body Mass Index

Increased BMI was associated with a longer sensory peak latency and slower sensory velocity for the median nerve using both techniques (orthodromic and antidromic). Conversely, for the ulnar nerve (antidromic technique only), increased BMI was associated with a shorter sensory peak latency and faster sensory velocity. BMI was negatively associated with amplitude for both nerves and techniques. The median-ulnar difference also increased with an increase in BMI. The effect of BMI on the sensory peak latency, median-ulnar difference, and sensory conduction velocity was slightly greater at the 5^{th} or 95^{th} percentile when compared to the 50^{th} percentile for all except the ulnar sensory conduction velocity (Figure 3). In contrast, the effect of BMI on the sensory amplitude was greater at the 50^{th} percentile when compared to the 5^{th} or 95^{th} percentile (Figure 4). The effect of BMI on all nerve conduction outcomes was statistically significantly except the 8 cm orthodromic 50^{th} percentile median sensory peak latency, and 14 cm antidromic percentiles for the median sensory peak latency and velocity.

2.4.4.3 Height

Increased height was associated with a longer sensory peak latency and slower sensory velocity, and a smaller amplitude for both median and ulnar nerves, for both screening techniques (orthodromic and antidromic), and most of the percentiles of the distributions. The 50th percentile orthodromic median sensory amplitude was the only amplitude where a 10 cm increase in height was associated with an increase in amplitude size. The effect of height was relatively constant between the 5th, 50th, and 95th percentiles of the distribution (and was constant across other parts of the distribution as well, see Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.). Depending on the specific nerve conduction outcome, an increase in height of 10 cm (approximately 1 SD) affected the nerve conduction outcome similarly to a 2 to 7.7-year increase in age. For the 8 cm orthodromic results, the effect of height on all nerve conduction outcomes were statistically significantly except for the 50th percentile median sensory peak latency and amplitude. For the 14 cm antidromic results, the effect of height on all nerve conduction outcomes were statistically significantly except for the 95th percentile for the median sensory peak latency, 5th percentile for the median sensory amplitude, 5th percentile for the median sensory velocity, 95th percentile for the ulnar sensory peak latency, and all percentiles of the median-ulnar difference.

2.4.4.4 Sex

Unexpectedly, a positive effect of male sex was observed for the sensory peak latency whereas a negative effect of male sex was observed for the sensory amplitude and sensory velocity for the median and ulnar nerves and NCS screening techniques. The effect of sex was relatively constant between the 5th, 50th, and 95th percentiles of the distribution (and was constant across other parts of the distribution as well, see Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.). The effect of male sex on 5th and 50th percentile of the median-ulnar difference was negative whereas for the 95th percentile the effect was positive. For the 5th, 50th, and 95th percentiles, the effect of male sex on the nerve conduction outcomes was equivalent to an average of an 8-year increase in age. For 8 cm orthodromic results, the effect of male sex and all nerve conduction outcomes was statistically significant except for both percentiles of the median sensory peak latency and 5th percentile median sensory conduction velocity. For the 14 cm antidromic results, the effect of male sex on all nerve conduction outcomes was statistically significant except the 5th percentile median sensory amplitude, 5th percentile median sensory velocity, and all percentiles of the median-ulnar difference.

2.4.4.5 Hand Surface Temperature

As expected, an increase in hand temperature was associated with a shorter sensory peak latency, faster sensory conduction velocity, and reduced sensory amplitude for both nerves and screening techniques. An increase in hand temperature was also associated with an increase median-ulnar difference. The effect of hand temperature was similar between the 5th, 50th, and 95th percentile for all the nerve conduction outcomes. The effect of hand surface temperature was statistically significant for all outcomes except the 8 cm orthodromic median sensory peak latency and 14 cm antidromic median-ulnar difference.

2.4.4.6 Hand (Dominant versus Nondominant)

The nondominant hand was associated with a larger sensory amplitude for both nerves, regardless of screening technique, and all percentiles. For the median nerve, the nondominant hand was associated with a slightly shorter sensory peak latency and faster sensory velocity for both screening techniques and at all percentiles. In contrast, for the ulnar nerve, the nondominant hand was associated with a slightly longer sensory peak latency and slower sensory velocity at all percentiles. The nondominant hand was observed to have a smaller median-ulnar difference. The effect of hand dominance was greater at the 50th percentile (when compared to the 5th and 95th percentile) at the majority of the nerve conduction outcomes except the 8 cm orthodromic median sensory conduction velocity, 14 cm antidromic ulnar sensory peak latency, 14 cm antidromic ulnar sensory conduction velocity, and median-ulnar difference. For the 8 cm orthodromic results, the effect of the nondominant hand on all nerve conduction outcomes was statistically significant except all percentiles of the median sensory peak latency, and 5th percentile of the median sensory velocity. For the 14 cm antidromic results, the effect of the nondominant hand on all nerve conduction outcomes was statistically significant except the all percentiles of the median sensory peak latency and velocity, and the 5th percentile of the median-ulnar difference.

2.5 Discussion

The majority of the published nerve conduction reference values are limited by (1) small sample sizes, (2) the use of unsuitable statistical methods for the non-Gaussian distribution of nerve conduction outcomes, and (3) absence of adjustment for individual characteristics that have been previously associated with nerve conduction outcomes (Aroori & Spence, 2008; Becker et al., 2002; Boz et al., 2004; Buschbacher, 1999b, 1999a; Chen et al., 2016; Esteves et al., 2020; Herbert et al., 2000; Kouyoumdjian et al., 2002; Letz & Gerr, 1994; Pourmemari & Shiri, 2016; Shiri et al., 2015; Solomon et al., 1999; Werner et al., 1997; Zambelis et al., 2010). To the investigator's knowledge, the results of the present study provide the first reference values for the median and ulnar nerve NCS results for newly hired workers. The large sample sizes (n = 10,038 workers evaluated with orthodromic methods and n = 4,433 workers evaluated with antidromic methods) and use of semi-parametric analytical methods improves the validity of reference value estimations at the upper and lower bounds of the nerve conduction outcomes' distributions.

2.5.1 Reference Values

Access to relevant nerve conduction reference values is essential for accurate interpretation of electrophysiological test results in healthcare. Typically, a "normal" range is defined by values within an explicitly defined upper (commonly the 95th, 97.5th or 99th percentiles) and lower (5th, 2.5th, or 1st percentiles) bounds of the distribution. The upper and lower bounds of the distribution then serve as thresholds to classify a nerve conduction outcome as "normal" or "abnormal". Many statistical methods have been used to define nerve conduction outcome upper and lower bound values. The statistical methods range from the mean +/- 2 standard deviations of the distribution to multiple regression analyses. The mean +/- 2 standard deviations or the percentile of the distribution are used most frequently to define nerve conduction reference values. However, the same threshold is generally then applied to all members of the population. In contrast, regression analyses enable adjustment for important covariates and can be used to estimate individualized nerve conduction outcome upper and lower bound values likely to be more valid for most members of the population. More recently, quantile regression has been used to develop nerve conduction reference values as it can directly model the upper or lower bound of the distribution (Benatar et al., 2009; Esteves et al., 2020). Although the investigators of the present study used quantile regression to develop reference values, they compare the nerve conduction reference values in the present study to those not only developed using quantile regression but also to those developed using legacy statistical methods.

2.5.1.1 Currently Used Reference Values

Currently, clinicians, technicians, and researchers use a single threshold to define "normal" versus "abnormal" nerve conduction outcomes. In contrast, the upper and lower bound values provided in the present study vary from person to person due to adjustment for individual characteristics (age, BMI, height, sex, hand temperature, and hand). The range of nerve conduction outcome upper and lower bound values estimated from the quantile regression models in the present study were similar to the ranges of previously reported upper and lower bound values (Anton et al., 2014; Benatar et al., 2009; Buschbacher, 1999b, 1999a; Esteves et al., 2020; Jackson & Clifford, 1989; Johnson et al., 1981; Salerno et al., 1998; Stevens, 1987). For example, the upper bound values for the median sensory peak latency in the literature range from 1.84 to 2.85 ms for the 8 cm orthodromic technique and 2.50 to 4.00 ms for the 14 cm antidromic technique (Anton et al., 2014; Benatar et al., 2009; Buschbacher, 1999b, 1999a; Esteves et al., 2020; Jackson & Clifford, 1989; Johnson et al., 1981; Salerno et al., 1998; Stevens, 1987). In the present study, the 95th percentile for the median sensory peak latency for the 8 cm orthodromic technique ranged from 1.87 to 3.06 ms[c] and 3.32 to 4.20 ms[c] for the 14 cm antidromic technique. The median nerve latency, amplitude, and velocity have been used to identify median mononeuropathy consistent with CTS; however, more often the median sensory latency and ulnar sensory latency are compared on the ipsilateral side to produce a median-ulnar latency difference measure (Atroshi et al., 2003; Werner, 2006; Werner & Andary, 2011).

[c] The coefficients from Table 10-13 were used to calculate the ranges of values presented above. The 95th percentile for the median sensory peak latency ranges were calculated based on the upper and lower limits of the demographic characteristics. The lower bound was calculated for an 18-year-old female, with a height of 132.1 cm, BMI of 16 kg/m^2, hand temperature of 30 °C, and for their dominant hand. The upper bound was calculated for a 75-year-old male, with a height of 203.2 cm, BMI of 65, hand temperature of 38°C, and for their dominant hand.

The difference between the median sensory peak latency and ulnar sensory peak latency is commonly used to identify persons with median mononeuropathy consistent with CTS (Jablecki et al., 2002). This is because the median nerve passes through the carpal tunnel and the ulnar nerve does not. The investigators of the present study are the first to report reference values for the median-ulnar difference that can be adjusted for the effects of individual characteristics, such as age. Previous researchers typically reported a single median-ulnar difference upper bound value to be used with all persons, regardless of other individual characteristics. Values of the median-ulnar difference recommended for identifying an abnormal result (typically the 95th percentile value) reported in the literature range from 0.20 to 0.93 ms for the 8 cm orthodromic technique and 0.40 and 0.80 ms for the 14 cm antidromic technique (Anton et al., 2014; Jackson & Clifford, 1989; Johnson et al., 1981; Salerno et al., 1998; Stevens, 1987). Although a wide range of thresholds have been reported, a commonly used median-ulnar difference upper bound value in epidemiologic research is 0.50 ms (Bingham et al., 1996; Cartwright et al., 2012; Musolin & Ramsey, 2017; Patil et al., 2012; Redmond & Rivner, 1988; Rosecrance et al., 2013; Werner et al., 2005, 2001). In the present study, the 95th percentile for the median-ulnar difference ranged from approximately 0.10 to 1.32 ms[d] (14 cm antidromic technique only) depending on individual characteristics (age, sex height, BMI, hand temperature, and hand dominance). Of relevance is the investigator's observation that the median-ulnar difference varied substantially across age (Table 14), and other individual characteristics. For example, the 95th percentile value of the median-ulnar latency difference for a 20-year-old male would be

[d] 95th percentile values were computed from the regression coefficients presented in Table 14. All covariates other than age were held constant with a sex of male, height of 170 cm, BMI of 30 kg/m^2, hand temperature of 32 °C, and for the dominant hand.

different than a 60-year-old male even if all other covariates were held constant[e]. Using the 95th percentile median-ulnar difference modeled with quantile regression in the present study:

$$\text{95th \%tile Median} - \text{Ulnar Difference} = -0.589 + (0.009 * age) + (0.027 * sex) - (0.001 * height) + (0.014 * BMI) + (0.014 * temp) - (0.042 * hand) \quad \text{(Equation 3)}$$

The 95th percentile value of the median-ulnar difference was 0.32 ms[e] for the 20-year-old and 0.68 ms[e] for the 60-year-old (Equation 3). The 20-year-old had an observed median-ulnar difference of 0.40 ms, and the 60-year-old had an observed median-ulnar difference of 0.58 ms. Based on the currently used median-ulnar difference upper bound value of 0.50 ms, the 20-year-old *would not* be categorized as having median mononeuropathy whereas the 60-year-old *would*. Using the median-ulnar difference upper bound value in the present study, the opposite occurs where the 20-year-old *would* be categorized as having median mononeuropathy whereas the 60-year-old *would not*. The 0.50 ms median-ulnar difference upper bound value could potentially result in failing to identify younger persons with median mononeuropathy (i.e., low sensitivity) and over identifying those with median mononeuropathy at the older age groups (i.e., low specificity). Thus, there is a need for adjusting for variables like age and BMI when estimating upper and lower bound thresholds for defining an abnormal result.

2.5.1.2 Reference Values obtained through Quantile Regression

Recently, a few researchers have used quantile regression to develop nerve conduction reference values (Benatar et al., 2009; Esteves et al., 2020). The present study includes reference values for an 8 cm orthodromic and 14 cm antidromic technique. However, previous researchers

---

[e] 95th percentile values were computed from the regression coefficients presented in Table 14. All covariates other than age were held constant with a sex of male, height of 170 cm, BMI of 30 kg/m^2, hand temperature of 32 °C, and for the dominant hand.

have only used a 14 cm antidromic technique when developing median and ulnar nerve reference values using quantile regression (Benatar et al., 2009; Esteves et al., 2020). The sensory peak latency and amplitude 95th and 5th percentile values in the present study were greater than those presented by other researchers using quantile regression. The sensory velocity 5th percentile value was less than previously reported by other researchers (Benatar et al., 2009; Esteves et al., 2020). For example, Esteves et al. (2020) reported that the 97th percentile value of the median sensory latency for 40-49-year old's was 3.4 ms. In contrast, the researchers in the present study reported 95th percentile value of the median sensory peak latency for male 40-49-year old's that ranged from 3.89 ms to 4.05 ms[f]. The upper and lower bound values in the present study may have been greater and less than those previously reported because of some key methodological differences.

A common limitation of currently published reference values is a small or modest sample size which affects the precision of the estimates. Statistical power, or the probability of confirming the alternative hypothesis when it is true, can be increased by decreasing the variability of the sample (i.e., adjusting for covariates) and increasing the sample size. Improved precision of the outcome's estimates is evidence of increased power. Previous researchers using quantile regression to define nerve conduction reference values (1) only adjusted for age in their analyses, and (2) had much smaller sample sizes compared to the present study (n < 250) (Benatar et al., 2009; Esteves et al., 2020). In the present study, the reference value models adjusted for a variety of individual characteristics (age, sex, height, BMI, hand temperature, and hand), and had much larger sample sizes (n > 4000 workers). The confidence intervals for age

---

[f] The 95th percentile values of the median sensory peak latency for 40-49 year old's was based on an average worker in the present study who was male with a height of 170 cm, BMI of 29 kg/m^2, hand temperature of 32 °C, and for their dominant hand. Forty years old was used for the lower bound of the range, and 49 years old was used for the upper bound of the range.

were smaller in the present study compared to Benatar et al. (2009) which means adjusting for essential covariates beyond age and use of a larger sample size improved the precision of the nerve conduction upper and lower bound estimates.

The method used to select the current study sample was another difference between previous studies and the present study that could potentially account for the differences in the reported reference values. Previous researchers recruited study participants independent of occupational status to represent population-base reference values whereas the reference values in the present study were developed from a sample of newly hired workers (Benatar et al., 2009; Esteves et al., 2020). In addition, Esteves et al. (2020) had a more stringent exclusion criteria than the present study. For example, the researchers inquired about medications (e.g. chemotherapeutic agents) to ensure the sample from which the reference values were estimated contained no persons with drug related neuropathies whereas those questions were not included in the present study (Esteves et al., 2020). The reference values in the present study may have had a larger proportion of individuals with focal or diffuse neuropathies which may explain the differences in the upper and lower bound values when compared to those by previous researchers (Benatar et al., 2009; Esteves et al., 2020). The methodological differences regarding covariates, sample sizes, and sample selection may explain why the upper and lower bound values in the present vary from those published in previous research.

2.5.2 Individual Characteristics

The reference values in the present study allow for adjustment for individual characteristics (age, BMI, height, sex, hand surface temperature, and hand). The majority of the individual characteristics selected *a priori* were statistically significant predictors of the nerve conduction outcomes. Age, BMI, height, and male sex were generally associated with a longer sensory peak latency, slower sensory nerve conduction velocity, and smaller sensory amplitude. Increases in hand surface temperature and the non-dominant hand were associated with a shorter sensory peak latency, faster sensory velocity, and smaller amplitude. Overall, the 50th percentile magnitude and direction of the effect of most covariates (age, BMI, height, hand surface temperature, and hand) on the nerve conduction outcomes were within the ranges reported by other researchers (Anton et al., 2014; Campbell & Robinson, 1993; Letz & Gerr, 1994; Rempel et al., 2015; Salerno et al., 1998; Stetson, Albers, Barbara, & Wolfe, 1992).

Male sex was the only covariate that the investigators of the present study consistently observed the opposite direction and larger magnitude in effect on all NCS outcomes than expected. Male sex was associated with poorer median and ulnar nerve conduction outcomes including longer sensory peak latency, slower sensory velocity, and smaller sensory amplitude. There is an inconsistency in the literature on the effect of sex. Some researchers have observed similar findings to the present study where males had decrements in nerve conduction outcomes compared to females; however, the vast majority of previous researchers have reported that females tended to have poorer nerve conduction outcomes (Anton et al., 2014; Rempel et al., 2015; Salerno et al., 1998). Male sex may have been associated with poorer nerve function because a larger proportion of men included in the reference values may have had systemic neuropathies.

The effects of age and BMI varied systematically across the nerve conduction outcome distribution. Consequently, the effects of age and BMI may be estimated poorly by ordinary linear regression methods that provide only a single estimate of effect magnitude across the entire distribution of the dependent variable (Figure 3). Quantile regression captures the differences in the magnitude of change in the dependent variable across the percentiles of the distribution and offers a more accurate description of the upper and lower bounds of the distribution used for reference values. For example, the 50th percentile effect of age on the median sensory peak latency was less than the 95th percentile effect of age (Figure 3). In contrast, the 50th percentile effect of age on the median sensory amplitude was less than the 5th percentile effect of age (Figure 4). The differences observed between the 5th, 50th, and 95th percentiles suggest that quantile regression is advantageous in reference value applications.

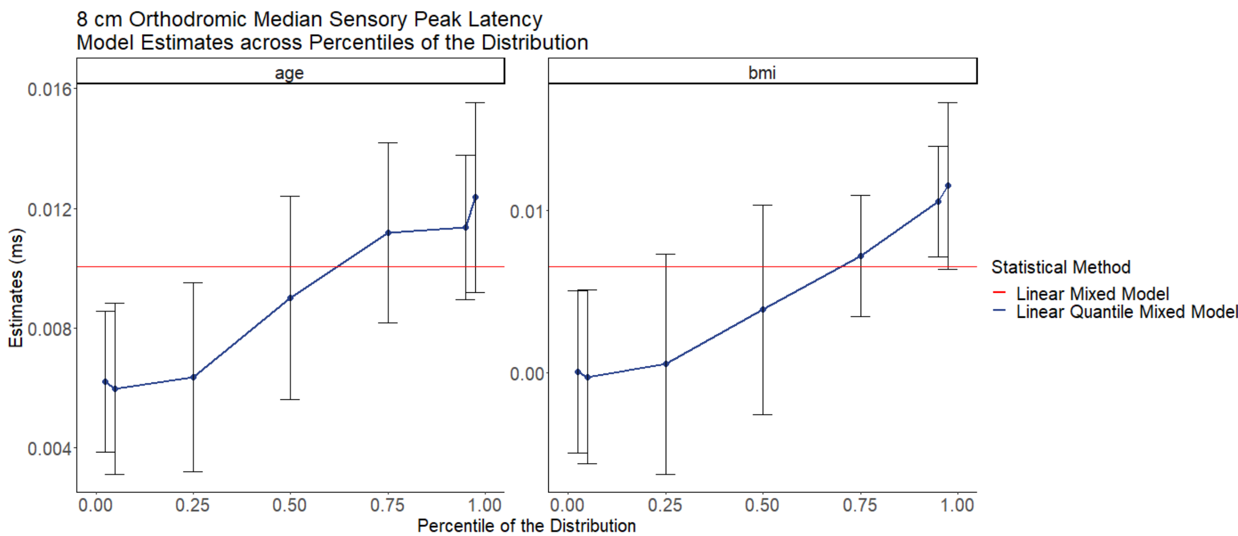


Figure 3. The graphs presented are the age and BMI estimates across a range of percentiles of the median sensory peak latency distribution from a regression model. For the regression model, the dependent variable was the median sensory peak latency. The fixed effects were age, BMI, height, sex, hand temperature, and hand, and the random effect was person. The red line is the linear mixed model whereas the blue line is the linear quantile mixed model. For the linear quantile mixed model, the effect sizes for age and BMI increase as the percentile of the median sensory peak latency increases. The 50th and 95th percentile coefficients for age and BMI can be found in Table 10. The remaining percentiles of the distribution can be found in the Appendix I (Tables I1-I10, and Figures I1-I5).

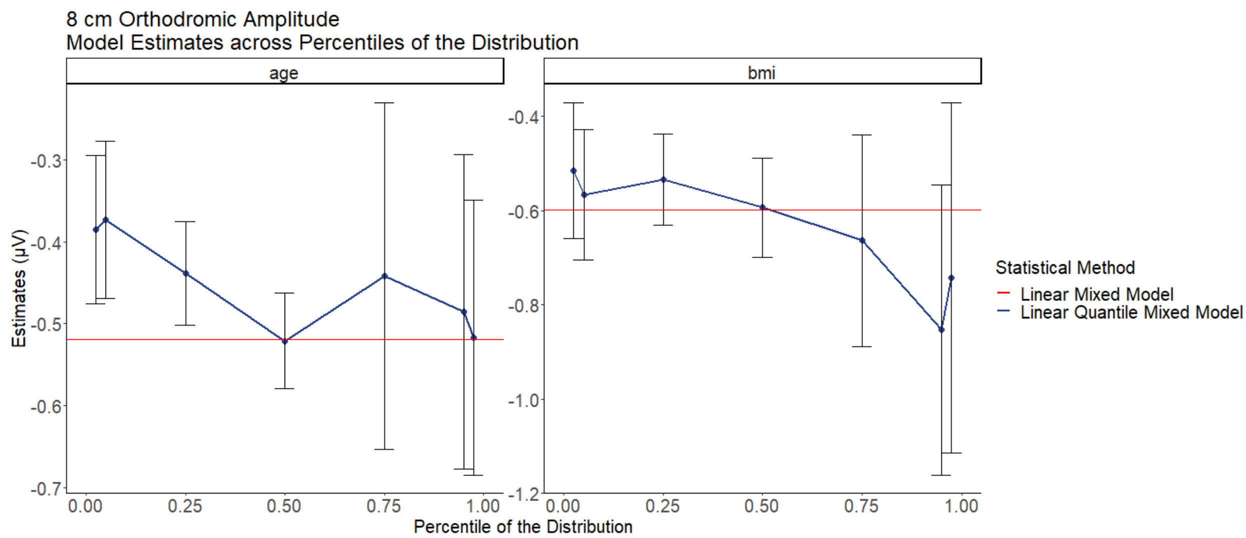


Figure 4. The graphs presented are the age and BMI estimates across a range of percentiles of the median sensory amplitude distribution from a regression model. For the regression model, the dependent variable was the median amplitude. The fixed effects were age, BMI, height, sex, hand temperature, and hand, and the random effect was person. The red line is the linear mixed model whereas the blue line is the linear quantile mixed model. For the linear quantile mixed model, the effect sizes for age and BMI decreases as the percentile of the median sensory amplitude increases. The 50th and 95th percentile coefficients for age and BMI can be found in Table 10. The remaining percentiles of the distribution can be found in the Appendix I (Tables I1-I10, and Figures I1-I5).

Currently published reference values that use quantile regression only present the upper and lower bounds of the distribution, typically the 5th and 95th percentiles. They do not allow for estimation of different effects of covariates on the outcome across the full range of outcome values (Benatar et al., 2009; Esteves et al., 2020). The phenomenon of certain independent variables having a different effect sizes as a function of value of the dependent variable has been reported in studies using quantile regression to investigate factors that affect infant birthweight (Abrevaya, 2001; Koenker & Hallock, 2001). In particular, race, education, and prenatal care were stronger predictors of birthweight at lower percentiles of the birthweight distribution compared to higher percentiles of the birthweight distribution (Abrevaya, 2001; Koenker & Hallock, 2001). Quantile regression is useful in applications where the researcher is more interested in estimating the effect of independent variables on specific strata of the dependent variable rather than solely on the mean response. The findings of the present study provide further evidence that quantile regression is an appropriate statistical method for developing reference values for neurophysiological data.

The reference values for newly hired workers provided in the present study address many of the sample size, statistical technique, and practical relevance limitations of currently published reference values. A number of the individual characteristics investigated were significant predictors of the nerve conduction outcomes. In addition, the effects of age and BMI increased or decreased monotonically across the nerve conduction outcome percentiles of the distribution highlighting the need for statistical methods that can characterize associations in the part of the distribution of interest. The parameter estimates in the present study can be used to calculate individualized estimates of the upper and lower bound of the nerve conduction outcome's distribution.

2.6 Limitations

The reference values in the present study were developed from a sample of newly hired workers. The newly hired workers were seeking employment in an industry with blue collar jobs that often have high repetitive hand/wrist exposures. Although hired into an industry with hand intensive job tasks, the investigators did not know the newly hired worker's employment history. Nonetheless, the findings of the present study may not be generalizable to other populations.

It is possible that the reference values in the present study were estimated from a sample of workers who may have had health conditions that may influence the nerve conduction measures. The inclusion of those with comorbidities associated with NCS outcomes in the reference values may have resulted in estimates that have the potential to bias toward decreased sensitivity and increased specificity. Although these limitations exist, the investigators used the available data regarding some of the most influential comorbidities and symptom reporting. At minimum, those workers with evidence of the disease of interest (CTS, CTS surgery, and symptoms consistent with CTS) were excluded. In addition to those with CTS, for the orthodromic results, those with other conditions that could negatively influence the reference values were also excluded from the analyses (diabetes, thyroid disease, previous hand/wrist fracture, previous hand/wrist surgery, and symptoms characteristics of distal upper extremity neuropathic conditions). Excluding those with these conditions produced reference values more representative of values that would be expected within a population.

The investigators observed inconsistent results for the sensory velocity and sensory peak latency even though sensory velocity was calculated as distance divided by sensory peak latency. The inconsistencies between the sensory velocity and peak latency may have been due to the non-differential error introduced while measuring the distance between the stimulation site and recording electrodes. Nonetheless, the investigators wanted to provide the reference values for sensory conduction velocity as it is independent of the distance between the stimulating and recording electrodes.

To the investigator's knowledge, the present study provides the first reference values of the median and ulnar nerve available for use with newly hired workers. The findings demonstrate the strengths of quantile regression and the importance of adjusting for select individual characteristics when developing population reference values.

2.7 Conclusions

The reference values provided in the present study emphasize the importance of quantitative adjustment for age, BMI, height, sex, hand temperature, and hand (either dominant or nondominant). The magnitude of the effect that some individual characteristics had on the NCS outcomes was greater at the upper and lower bounds of the distribution compared to the 50^{th} percentile. The effect sizes were also greater than those previously reported by researchers using linear regression models. The greater magnitude at the upper and lower bounds of the distribution suggests the statistics traditionally used in the past have underestimated the effect of certain individual characteristics. The present study involved the largest compilation of upper limb NCS outcomes ever published for orthodromic NCS (n = 10,038 workers) and antidromic NCS (n = 4,433 workers). The investigators were the first to develop reference values for nerve conduction outcomes of the distal limb among a sample of newly hired workers. Additionally, the investigators used a more suitable statistical method, linear quantile mixed model regression, for describing neurophysiological parameters that provides individualized reference values. Future studies are needed to evaluate reference values presented in Specific Aim 1 compared to those currently used in the field and research before individualized reference values serve as a viable replacement to current practices.

4. Chapter 4: Comorbidities associated with nerve conduction outcomes collected during a post-offer pre-placement job screening for CTS among newly hired workers

Specific Aim 2: To examine the relationship between select comorbid conditions and NCS outcomes among a sample of newly hired workers.

Objectives:

1. Quantify the associations between 8 cm palm-to-wrist median sensory orthodromic NCS outcomes and select comorbidities (diabetes, thyroid disease, previous fracture of the hand/wrist, previous CTS diagnosis, previous hand surgery, previous CTS surgery, and symptoms characteristic of CTS) while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand). The NCS outcomes of interest were the median sensory peak latency, amplitude, and velocity.
2. Quantify the associations between 14 cm wrist-to-finger median sensory antidromic NCS outcomes and select comorbidities (previous CTS diagnosis, previous CTS surgery, and symptoms characteristic of CTS) while adjusting for individual characteristics (age, sex, height, BMI, hand temperature, and hand). The NCS outcomes of interest were the median sensory peak latency, amplitude, and velocity as well as the difference between the median-ulnar sensory peak latencies.

4.1 Summary

Objective: To investigate the association between comorbid conditions self-reported during a post-offer pre-placement job screening for median mononeuropathy and median nerve conduction outcomes.

Methods: Seventeen thousand six-hundred and eighty-two (N = 17,682) newly hired workers had received post-offer pre-placement job screenings for the median mononeuropathy associated with CTS. Ten thousand and thirty-eight workers (N = 10,038) were included in the analyses that had an NCS using an 8 cm orthodromic technique, and 4,433 workers were included that had a NCS using a 14 cm antidromic technique. Linear quantile mixed regression models were fit where the nerve conduction outcomes were the dependent variable. The nerve conduction outcomes were the median and ulnar sensory peak latencies, amplitudes, and velocities as well as the difference between the median and ulnar peak latencies. The independent variables were the comorbid conditions (previous CTS diagnosis, CTS surgery, symptoms consistent with CTS, diabetes, thyroid disease, hand/wrist fracture, and hand/wrist surgery) while also adjusting for individual characteristics (age, height, BMI, sex, hand temperature, and hand). The upper and lower bound of the distribution was presented (5^{th} or 95^{th} percentile).

Results: A previous diagnosis of CTS, CTS surgery, symptoms consistent with CTS, and diabetes were statistically significantly associated with the majority of the median nerve conduction outcomes. Thyroid disease, hand/wrist fracture, and hand/wrist surgery were not statistically significant associated with the median nerve conduction outcomes.

Conclusions: Other health conditions beyond CTS should be considered when evaluating those with median mononeuropathy and developing reference values for a population.

4.2 Introduction

The first Specific Aim focused on establishing NCS reference values using quantile regression excluding individuals with selected comorbid conditions. In contrast, the purpose of Specific Aim 2 was to evaluate the association between select comorbid conditions and the median sensory nerve conduction outcomes in the distal upper limb.

Working populations, particularly those in industries with hand-intensive tasks, have an increased risk of developing physiological evidence of mononeuropathy of the median nerve and subsequent CTS (Barcenilla et al., 2012; Burt et al., 2011; Garg et al., 2012; Gell et al., 2005; Gerr et al., 2014; Harris-Adamson et al., 2015; Kapellusch et al., 2014; Violante et al., 2016). Because of the higher prevalence of CTS in certain industries, employers have adopted a strategy of conducting post-offer pre-placement job screenings using NCS to identify workers with the median neuropathy that is characteristic of CTS (Dale et al., 2014; Werner et al., 2001). NCS are an important tool to assess distal upper limb peripheral neuropathy; however, an abnormal result is not the only indicator of the neuropathy in question. Understanding individual characteristics, existing health conditions, occupational exposures, and NCS testing conditions are important in accurately characterizing nerve conduction abnormalities for optimal prevention and treatment. Some conditions that have been previously associated with distal upper extremity neuropathy include diabetes, thyroid disease, hand/wrist fracture, and hand/wrist surgery (Ahmad et al., 2016; Aroori & Spence, 2008; Herbert et al., 2000; Pope & Tang, 2018; Pourmemari & Shiri, 2016; Solomon et al., 1999; Werner et al., 2005). Researchers have investigated the relationship between NCS outcomes and comorbidities; however, none have analyzed the relationship using quantile regression and modeling the upper or lower bounds of the distribution. The purpose of Specific Aim 2 was to investigate the relationship between nerve conduction outcomes and self-reported comorbidities collected during a post-offer pre-placement job screening of newly hired workers using quantile regression. The investigators sought to identify the most important to exclude for reference values and ask during a post-offer pre-placement job screening.

4.3 Methods

The participant sample and post-offer pre-placement screening methods (for assessing the median mononeuropathy associated with CTS) that were used in Specific Aim 2 are described in detail in Chapter 3 under Specific Aim 1. As with Specific Aim 1, the investigators examined two datasets for assessing the distal median neuropathy of the upper limb. On dataset had NCS outcomes using the 8 cm orthodromic technique while the other had NCS outcomes using the 14 cm antidromic technique. For the orthodromic dataset, a total of 12,821 workers had a post-offer pre-placement screening. For the antidromic dataset, a total of 4,861 workers had a post-offer pre-placement screening. All data cleaning steps were completed using RStudio Version 3.6.1. and those that did not diverge from Specific Aim 1 are described in detail in Chapter 3.

4.3.1 Data Analysis

4.3.1.1 Exclusions

The exclusion criterion for the demographic values (age, height, weight, BMI, and hand temperature – see Table 15) were based on extreme values that were unlikely. The values were so extreme that they were likely an error during the original data collection. Of the 12,821 newly hired workers in the orthodromic dataset, 39 (0.30%) were excluded from the analyses (Table 15). Of the 4,861 newly hired workers in the antidromic dataset, 17 (0.35%) were excluded from the analyses (Table 15).

Table 15. Participant exclusion criterion.

Exclusion Criterion	Orthodromic N (%)	Antidromic N (%)
Age < 18	6 (0.05)	3 (0.06)
Age > 75	3 (0.02)	3 (0.06)
Height < 132.1 cm	8 (0.06)	0 (0.00)
Height > 203.2 cm	4 (0.03)	1 (0.02)
Weight < 40.8 kg	4 (0.03)	6 (0.12)
Weight > 192.8 kg	2 (0.02)	0 (0.00)
BMI < 16 kg/m^2	6 (0.05)	4 (0.08)
BMI > 65 kg/m^2	1 (0.01)	0 (0.00)
Hand temperature < 30 °C	5 (0.04)	0 (0.00)
Hand temperature > 38°C	0 (0.00)	0 (0.00)

For the orthodromic dataset, a total of 39 (0.30%) out of 12,821 workers were excluded, and 12,787 (99.7%) were included in the analysis.
For the antidromic dataset, a total of 17 (0.35%) out of 4,861 were excluded, and 4,844 (99.6%) were included in the analysis.

4.3.1.2 Statistical Methods

The regression analyses were conducted using R and the lqmm package (Geraci, 2014; Geraci & Bottai, 2014). Linear quantile mixed models were used with the nerve conduction outcome as the dependent variable (either peak latency, amplitude, velocity, or median-ulnar sensory peak latency difference). The linear quantile mixed models allows for both fixed and random effects (Geraci, 2014; Geraci & Bottai, 2014). Because each worker had an NCS conducted on their dominant and non-dominant hand, subject was included as a random effect. For the orthodromic models, the fixed effects were age, sex, height, BMI, hand temperature, hand (either dominant or non-dominant), diabetes, thyroid disease, hand/wrist fracture, hand/wrist surgery, previous diagnosis of CTS, CTS surgery, and symptoms characteristic of

CTS (Table 16). Fewer questions regarding comorbid conditions were asked during the 14 cm antidromic screening. Comorbid conditions not included in the screening tool during the 14 cm antidromic technique were a history of diabetes, thyroid disease, hand/wrist fracture, and hand/wrist surgery. Thus, for the antidromic models, the fixed effects were age, sex, height, BMI, hand temperature, hand (either dominant or non-dominant), previous diagnosis of CTS, CTS surgery, and symptoms characteristic of CTS (Table 16). Symptoms characteristic of CTS was defined as workers that reported numbness, tingling, or pain in two fingers innervated by the median nerve (thumb, index, middle, or ring) within the past year that persisted for at least 2 weeks (Armstrong et al., 2008; Franzblau, Werner, et al., 1993; Patil et al., 2012; Shrivastava & Szabo, 2008; Werner et al., 2005).

Linear quantile mixed models were only fit for the three median nerve conduction outcomes and the median-ulnar latency difference (a total of 3 models for the NCS performed with orthodromic techniques and 4 for the NCS performed with antidromic techniques). The upper bound of the distribution (95^{th} percentile) was presented for the median sensory peak latency and median-ulnar sensory peak latency difference because an increase in these outcomes have been associated with the distal median neuropathy associated with CTS. In contrast, the lower bound of the distribution (5^{th} percentile) was presented for the median sensory velocity and amplitude as reductions in the magnitude and velocity is indicative of nerve impairment. Although the individual characteristics were included in the models, the results presented were limited to the relationships between the select comorbidities and nerve conduction outcomes. The individual characteristic (age, sex, height, BMI, hand temperature, hand (either dominant or non-dominant)) results are described in detail in Chapter 3 under Specific Aim 1.

Table 16. The individual characteristics and comorbid conditions included in the model for Specific Aim 2.

Model Covariates	8 cm Orthodromic Screening (N = 12,787)	14 cm Antidromic Screening (N = 4,844)
Individual Characteristics		
Age	X	X
Sex	X	X
Height	X	X
Weight	X	X
Handedness (Dominant or Nondominant)	X	X
Hand Temperature	X	X
Comorbid Conditions		
Previous CTS diagnosis	X	X
Previous CTS surgery	X	X
Symptoms consistent with CTS	X	X
Diabetes	X	
Thyroid Disease	X	
Hand/wrist Fracture	X	
Hand/Wrist Surgery	X	

4.4 Results

4.4.1 Description of Worker Demographics

Demographic characteristics of all workers in the analyses of the NCS performed with orthodromic and antidromic techniques are presented in Table 17 and 18, respectively. For both orthodromic and antidromic datasets, the workers were predominately male (approximately 60%) and relatively young (mean approximately 30 years old) for both orthodromic and antidromic datasets. The majority (90%) of the workers were right-hand dominant. Workers with comorbid conditions tended to be slightly older and heavier than those without comorbid conditions (Table 17 and 18). Approximately 21% of workers who received an NCS using the 8 cm orthodromic technique reported a medical condition and 8.5% of workers in the who received an NCS using the 14 cm antidromic technique reported a medical condition. The higher percentage of comorbidities for workers who received an 8 cm orthodromic NCS dataset compared to workers who received the 14 cm antidromic NCS was likely due to the additional questionnaire items included in the procedure for the orthodromic screenings. For the orthodromic dataset, the three most common health conditions reported were hand/wrist fracture with 1524 (11. 9%) workers, hand/wrist surgery with 584 (4.57%) workers, and diabetes with 319 workers (2.5%) (Table 19). For the antidromic dataset, the most common health condition reported was symptoms consistent with CTS with 58 (1.2%) out of 4,844.

Table 17. Summary statistics of worker demographics for those who received the 8 cm orthodromic NCS stratified by those without comorbidities and those with comorbidities that could influence nerve conduction outcomes.

Characteristics	**Value (units)**	**All Workers (N[a] = 12,782)**	**Without Comorbidities (N = 10,038)**	**With Comorbidities (N = 2,744)**
Sex:	Male n[b] (%)[c]	7,921 (62)	6,160 (61.4)	1,761 (64.2)
	Female n (%)	4,859 (38)	3,877 (38.6)	982 (35.8)
	Unknown n (%)	2 (0)	1 (0)	1 (0)
Age:	Average ± SD[d] (years)	30.8 ± 11.1	30.1 ± 10.8	33.6 ± 11.8
	Range (min-max)[e] (years)	18-74	18-74	18-70
Height:	Average ± SD (cm)	170.2 ± 10.1	169.8 ± 10.2	171.6 ± 9.9
	Range (min-max) (cm)	132.1-203.2	132.1-203.2	132.1-203.2
Mass:	Average ± SD (kg)	83.7 ± 22	82.6 ± 21.8	87.7 ± 22.1
	Range (min-max) (kg)	40.8-190.5	40.8-190.5	41.3-181.4
BMI:	Average ± SD (kg/m^2)	28.8 ± 6.9	28.6 ± 6.8	29.8 ± 7.2
	Range (min-max) (kg/m^2)	16-64.6	16-64.6	16.6-61.3
Handedness:	Right n (%)	11,377 (89)	8,950 (89.2)	2,427 (88.4)
	Left n (%)	1,256 (9.8)	960 (9.6)	296 (10.8)
	Unknown n (%)	135 (1.1)	116 (1.2)	19 (0.7)
Hand Temperature	Mean ± SD (°C)	32.3 ± 1.08	32.3 ± 1.09	32.4 ± 1.08
	Range (min-max) (°C)	30-38	30-38	30-37

[a] N = Total number of subjects per group.
[b] n = Total number
[c] % = Percentage.
[d] SD = Standard deviation.
[e] (min-max) = Minimum value of the range and maximum value of the range.

Table 18. Summary statistics of worker demographics for those who received the 14 cm antidromic NCS stratified by those without comorbidities and those with comorbidities that could influence nerve conduction outcomes.

Characteristics	**Value (units)**	**All Workers (N[a] = 4,844)**	**Without Comorbidities (N = 4,433)**	**With Comorbidities (N = 411)**
Sex:	Male n[b] (%)[c]	2914 (60.2)	2717 (61.3)	197 (47.9)
	Female n (%)	1929 (39.8)	1715 (38.7)	214 (52.1)
	Unknown n (%)	1 (0)	1 (0)	0 (0)
Age:	Mean ± SD[d] (years)	31.8 ± 11.2	31.4 ± 11.1	36.3 ± 11.6
	Range (min-max)[e] (years)	18-75	18-75	18-68
Height:	Mean ± SD (cm)	169.7 ± 10.2	169.8 ± 10.2	169.1 ± 9.8
	Range (min-max) (cm)	132.1-203.2	132.1-203.2	137.2-195.6
Mass:	Mean ± SD (kg)	84.3 ± 24.2	83.7 ± 24.1	91.3 ± 24.3
	Range (min-max) (kg)	40.8-192.8	40.8-192.8	45.4-167.8
BMI:	Mean ± SD (kg/m^2)	29.1 ± 7.4	28.9 ± 7.3	31.8 ± 7.6
	Range (min-max) (kg/m^2)	16.1-63.6	16.1-63.6	17.3-56.3
Handedness:	Right n (%)	4390 (90.6)	4036 (91)	354 (86.1)
	Left n (%)	416 (8.6)	364 (8.2)	52 (12.7)
	Unknown n (%)	5 (0.1)	4 (0.1)	1 (0.2)
Hand Temperature	Mean ± SD (°C)	31.9 ± 1.31	31.9 ± 1.31	32.3 ± 1.20
	Range (min-max) (°C)	30-35	30-35	30-35

[a] N = Total number of subjects per group.
[b] n = Total number
[c] % = Percentage.
[d] SD = Standard deviation.
[e] (min-max) = Minimum value of the range and maximum value of the range.

Table 19. Summary of comorbid conditions for the 8 cm orthodromic and 14 cm antidromic NCS techniques.

NCS Technique	Comorbidity	Total N	Right Hand Only	Left Hand Only	Both Hands
8 cm Orthodromic	Diabetes	319	-	-	-
	Thyroid	163	-	-	-
	Fracture of Hand/Wrist	1524	862	496	166
	Hand/Wrist Surgery	584	298	247	39
	Previous CTS Diagnosis	193	65	30	98
	Previous CTS Surgery	86	38	0	48
	Symptoms characteristic of CTS	96	34	23	39
14 cm Antidromic	Previous CTS Diagnosis	38	12	5	21
	Previous CTS Surgery	27	11	0	16
	Symptoms characteristic of CTS	58	28	12	18

4.4.2 Description of Nerve Conduction Outcomes

The number of hands included in the analyses, means, standard deviations, and number of no responses for the nerve conduction outcomes for the orthodromic and antidromic measures are found in Table 20 and Table 21, respectively. The workers with comorbid conditions had a longer median sensory peak latency, slower median sensory velocity, and smaller median sensory amplitude than those without comorbidities (Table 20 and 21). Those with comorbid conditions tended to have greater differences between the median and ulnar peak latency (Table 21).

The reason the number of hands varied across the nerve conduction outcomes was in part due to the voiding procedure. The amplitudes have the smallest sample sizes as these values were most frequently voided due to the high signal-to-noise ratio observed on the original waveform. In addition, a small proportion of the missing observations for the sensory peak latency, amplitude, and velocity were due to nerves that the technicians could not elicit a response.

Table 20. Summary statistics of the 8 cm Orthodromic median sensory nerve conduction outcomes stratified by those without comorbidities and those with comorbidities that could influence nerve conduction outcomes.

		Without Comorbidities		**With Comorbidities[a]**	
Nerve	**Nerve Conduction Outcome (units)**	**Hands[b]**	**Mean ± SD[c]**	**Hands**	**Mean ± SD**
Median	Peak Latency (ms)[d]	19,927	2.11 ± 0.33	5,395	2.24 ± 0.41
	Amplitude (µV)[e]	19,865	65.53 ± 32.35	5,363	58.99 ± 30.67
	Conduction Velocity (m/s)[f]	19,927	38.68 ± 5.10	5,395	36.81 ± 5.76
	No Responses[g]	129	-	108	-

[a] Workers with at least one comorbid condition.
[b] Hands = Total number of hands per group.
[c] SD = Standard deviation.
[d] ms = milliseconds
[e] µV = microvolts
[f] m/s = meters/second
[g] No Response = The technician was not able to evoke an action potential.

Table 21. Summary statistics of the 14 cm antidromic median and ulnar sensory nerve conduction outcomes stratified by those without comorbidities and those with comorbidities that could influence nerve conduction outcomes.

		Without Comorbidities		With Comorbidities[a]	
Nerve	**Nerve Conduction Outcome (units)**	**Hands[b]**	**Mean ± SD[c]**	**Hands**	**Mean ± SD**
Median	Peak Latency (ms)[d]	8,914	3.43 ± 0.47	671	3.81 ± 0.84
	Amplitude (μV)[e]	8,833	57.19 ± 24.35	659	45.64 ± 22.79
	Conduction Velocity (m/s)[f]	8,914	41.43 ± 4.95	671	38.15 ± 6.66
	No Responses[g]	58	-	72	-
Ulnar	Peak Latency (ms)[d]	8,897	3.34 ± 0.40	698	3.30 ± 0.48
	Amplitude (μV)[e]	8,789	43.29 ± 23.4	682	37.51 ± 22.20
	Conduction Velocity (m/s)[f]	8,897	42.51 ± 4.65	698	43.18 ± 5.28
	No Responses[g]	64	-	17	-
MUD[h]		8,897	0.10 ± 0.42	661	0.50 ± 0.86

[a] Workers with at least one comorbid condition.
[b] Hands = Total number of hands per group.
[c] SD = Standard deviation.
[d] ms = milliseconds
[e] μV = microvolts
[f] m/s = meters/second
[g] No Response = The technician was not able to evoke an action potential.
[h] MUD = Median-Ulnar Difference, the difference between the median sensory peak latency and ulnar sensory peak latency.

4.4.3 Results of the Linear Quantile Mixed Models

Parameter estimates from fitting the linear quantile mixed models, and their respective confidence intervals and standard errors for 5th or 95th percentile of the nerve conduction outcomes are in Table 22 and Table 23. The 95th percentile was presented for sensory peak latency as increases in peak latency are often indicative of nerve impairment. The 5th percentile was presented for sensory amplitude and sensory velocity as decreases in these outcomes are often indicative of nerve impairment. Age, BMI, height, sex, hand surface temperature, and handedness were included in the models. Although individual characteristics (age, sex, BMI, height, hand temperature, and handedness) were included in the models, the primary focus of Specific Aim 2 was to investigate the association between comorbidities and NCS outcomes. Only the comorbid condition parameter estimates (previous CTS diagnosis, CTS surgery, symptoms consistent with CTS, diabetes, thyroid disease, hand/wrist fracture, and hand/wrist surgery) are presented in the Results Section (Table 22 and 23). All (individual characteristics and comorbid conditions) linear quantile mixed model parameter estimates for Specific Aim 2 can be found in Appendix J.

Table 22. Summary of linear quantile mixed models for the median sensory nerve 5th or 95th Percentiles for both NCS techniques.

	8 cm Orthodromic with Comorbidities (Median)			14 cm Antidromic with Comorbidities (Median)		
Variable	**Peak Latency (ms) (95th Percentile)** Hands = 23,970 N = 12,163	**Amplitude (μV) (5th Percentile)** Hands = 24,062 N = 12,144	**Conduction Velocity(m/s) (5th Percentile)** Hands = 23,970 N = 12,163	**Peak Latency (ms) (95th Percentile)** Hands = 9,306 N = 4,684	**Amplitude (μV) (5th Percentile)** Hands = 9,218 N = 4,669	**Conduction Velocity(m/s) (5th Percentile)** Hands = 9,306 N = 4,684
Diabetes (1)						
Estimate	**0.31*****	**-7.44****	**-1.811***	-	-	-
(95% CI)	(0.143, 0.477)	(-12.839, -2.041)	(-3.54, -0.081)			
SE	0.084	2.721	0.871			
Thyroid (1)						
Estimate	0.129	-4.387	0.664	-	-	-
(95% CI)	(-0.069, 0.326)	(-11.67, 2.896)	(-1.049, 2.376)			
SE	0.100	3.671	0.863			
Hand/Wrist Fracture (1)						
Estimate	0.007	-0.745	0.475	-	-	-
(95% CI)	(-0.018, 0.031)	(-2.697, 1.207)	(-0.307, 1.256)			
SE	0.012	0.984	0.394			
CTS (1)						
Estimate	**0.281***	**-7.623****	-1.408	**0.856****	-13.77	-3.381
(95% CI)	(0.014, 0.549)	(-12.482, -2.763)	(-3.326, 0.51)	(0.252, 1.46)	(-30.721, 3.182)	(-7.641, 0.879)
SE	0.135	2.449	0.967	0.304	8.543	2.147
CTS Surgery (1)						
Estimate	-0.078	6.620	0.920	**-0.873***	14.863	**7.284****
(95% CI)	(-0.36, 0.203)	(-0.053, 13.294)	(-1.785, 3.624)	(-1.587, -0.16)	(-5.057, 34.783)	(2.025, 12.543)
SE	0.142	3.363	1.363	0.36	10.039	2.65
Hand/Wrist Surgery (1)						
Estimate	-0.011	-0.004	0.301	-	-	-
(95% CI)	(-0.078, 0.056)	(-2.666, 2.659)	(-0.491, 1.093)			
SE	0.034	1.342	0.399			
Symptomatic (1)						
Estimate	**0.28****	-3.54	**-4.13*****	**0.677****	**-6.977*****	**-3.495****
(95% CI)	(0.074, 0.485)	(-9.451, 2.371)	(-6.003, -2.257)	(0.226, 1.129)	(-13.823, -0.131)	(-5.852, -1.138)
SE	0.103	2.979	0.944	0.227	3.45	1.188

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 23. Summary of LQMM for the 95th Percentile of the Median-Ulnar Difference for the 14 cm antidromic nerve conduction outcomes.

	With Comorbid Conditions
Variable	**Median-Ulnar Difference (ms) (95th Percentile)** Hands = 9,239 N = 4,679
CTS (1)	
Estimate	**0.588***
(95% CI)	(0.109, 1.067)
SE	0.242
CTS Surgery (1)	
Estimate	-0.324
(95% CI)	(-0.977, 0.33)
SE	0.329
Symptomatic (1)	
Estimate	0.344
(95% CI)	(-0.069, 0.756)
SE	0.208

* p < 0.05, ** p < 0.01, *** p < 0.001

4.4.3.1 Previous Diagnosis Carpal Tunnel Syndrome

Previous diagnosis of CTS was included as a covariate in the model for both NCS techniques (Tables 23 and 24). The effect of a previous diagnosis of CTS on the median sensory peak latency was statistically significant ($p < 0.05$) for both NCS techniques. Whereas, the effect on the median sensory velocity was not statistically significant for both NCS techniques ($p > 0.05$). The effect of a previous diagnosis of CTS on the median sensory amplitude was only statistically significant for the 8 cm orthodromic technique ($p < 0.05$). Overall, a previous diagnosis of CTS was associated with a longer median sensory peak latency, slower sensory velocity, and smaller median sensory amplitude. As expected, the relationship between a previous diagnosis of CTS and the difference between the median and ulnar sensory peak latency was positive.

4.4.3.2 Carpal Tunnel Syndrome Surgery

Previous history of CTS surgery was included as a covariate in the model for both NCS techniques (Tables 23 and 24). The effect of a previous CTS surgery was not consistently statistically significant between the orthodromic and antidromic techniques. The relationship between previous CTS surgery, 14 cm antidromic median sensory peak latency, and 14 cm antidromic median sensory velocity were the only statistically significant associations ($p < 0.05$). For both techniques (although not statistically significant for the orthodromic technique median sensory amplitude), a previous CTS surgery was associated with a longer median sensory peak latency, slower sensory velocity, and larger sensory amplitude. A previous CTS surgery was associated with a reduction in median-ulnar difference although the finding was not statistically significant.

4.4.3.3 Symptoms Consistent with Carpal Tunnel Syndrome

Symptoms consistent with CTS was included as a covariate in the model for both NCS techniques (Tables 23 and 24). The relationship between symptoms consistent with CTS and the median sensory nerve conduction outcomes was statistically significant ($p < 0.05$) for all outcomes except the 8 cm orthodromic median sensory amplitude and 14 cm antidromic median-ulnar latency difference. Overall, symptoms consistent with CTS were associated with a longer median sensory peak latency, slower velocity, smaller amplitude, and greater difference between the median and ulnar sensory peak latency. The effect of having symptoms consistent with CTS on the nerve conduction outcomes was similar to diabetes or a previous diagnosis of CTS. The median sensory peak latency estimate for the 95th percentile of an average worker[g] who reported symptoms characteristic of CTS was 2.57 ms for the orthodromic technique and 4.43 ms for the antidromic technique. In contrast, the same average worker[g] without reported symptoms characteristic of CTS had a 95th percentile median sensory peak latency estimate of 2.29 ms for the orthodromic technique and 3.76 ms for the antidromic technique.

4.4.3.4 Diabetes

Diabetes was only included as a covariate in the model for the 8 cm orthodromic technique (Table 23) as the question was not asked during the screening that used the 14 cm antidromic technique. The effect of diabetes on all nerve conduction outcomes was statistically significant ($p < 0.05$). The effect size of diabetes was the largest observed among all individual characteristics (age, height, BMI, sex, hand temperature and hand) and comorbidities (previous diagnosis of CTS, CTS surgery, symptoms, thyroid disease, hand/wrist fracture, and hand/wrist surgery). Diabetes was associated with a longer median sensory peak latency, slower velocity, and a reduction in amplitude. An average worker[g] in the present study *without* diabetes had a 95th percentile median sensory peak latency of 2.29 ms, amplitude of 36.94 microvolts, and velocity of 34.86 m/s. An average worker[g] in the present study *with* diabetes had a 95th percentile median sensory peak latency of 2.60 ms, amplitude of 29.50 microvolts, and velocity of 33.05 m/s. The change in magnitude of the estimates for the median sensory peak latency and conduction velocity between those with and without diabetes was approximately one standard deviation of the mean response (Table 20). The change in magnitude of the estimate for the median sensory

[g] An average worker was 30 years old, male, 170 cm, with a BMI of 30 kg/m^2, and hand temperature of 32 °C. The estimations were based on the worker's dominant hand. The average worker was assumed to have none of the other comorbid conditions included in the model (see Table 22).

amplitude between those with and without diabetes was less than the peak latency and conduction velocity at approximately a quarter of a standard deviation of the mean response (Table 20).

4.4.3.5 Thyroid Disease

A thyroid disease was only included as a covariate in the model for the 8 cm orthodromic technique (Table 23) as the question was not asked during the screening that used the 14 cm antidromic NCS technique. The effect of thyroid disease on all the nerve conduction outcomes was not statistically significant ($p > 0.05$). Nonetheless, a thyroid condition was associated with a longer median sensory peak latency and smaller amplitude. Unexpectedly, a thyroid condition was associated with a faster conduction velocity.

4.4.3.6 Hand/Wrist Fracture

Hand/wrist fracture was only included as a covariate in the model for the 8 cm orthodromic technique (Table 23) as the question was not asked during the screening that used the 14 cm antidromic technique. The effect of a hand or wrist fracture on all the nerve conduction outcomes was not statistically significant ($p > 0.05$). A hand/wrist fracture was associated with a slightly longer median sensory peak latency, slight reduction in amplitude, and a faster conduction velocity. A hand/wrist fracture had a relatively smaller effect on the nerve conduction outcomes when compared to other comorbid conditions and individual characteristics. For example, a hand/wrist fracture would influence the median sensory peak latency and amplitude the same amount as a 1 and 2-month increase in age, respectively.

4.4.3.7 Hand/Wrist Surgery

Hand/wrist surgery was only included as a covariate in the model for the 8 cm orthodromic technique (Table 23) as the question was not asked during the screening that used the 14 cm antidromic technique. Similar to hand/wrist fracture, the effect of a hand or wrist surgery on all the nerve conduction outcomes was not statistically significant ($p > 0.05$). A hand/wrist surgery was associated with a slightly longer median sensory peak latency and slower conduction velocity, and a very small decrement in median sensory amplitude. The nerve conduction outcome estimates between those with and without a hand/wrist surgery were very similar. For example, an average worker[h] in the present study *without* a hand/wrist surgery had a 95th percentile median sensory peak latency of 2.29 ms, amplitude of 36.94 microvolts, and conduction velocity of 34.86 m/s. An average worker[h] in the present study *with* a hand/wrist surgery had almost identical 95th percentile estimates of the nerve conduction outcomes as those without a hand/wrist surgery, with an estimate of the median sensory peak latency of 2.28 ms, amplitude of 36.94 microvolts, and conduction velocity of 35.16 m/s.

4.5 Discussion

Employers frequently use post-offer pre-placement job screenings with NCS to identify workers with impaired median nerve function making them more susceptible to developing CTS in jobs tasks with high hand/wrist biomechanical exposures (Dale et al., 2014; Werner et al., 2001). However, an abnormal NCS result is a non-specific indicator of a neurological disease as many comorbid conditions have been associated with abnormal median NCS (Aroori & Spence, 2008; Herbert et al., 2000; Pourmemari & Shiri, 2016; Solomon et al., 1999; Werner et al., 2005). For example, abnormal median nerve responses could be due to diffuse neuropathies, like those resulting from diabetes, not necessarily the focal median nerve entrapment characteristic of CTS (J. Kimura, 1989; Pourmemari & Shiri, 2016; Solomon et al., 1999; Werner et al., 2005).

[h] An average worker was 30 years old, male, 170 cm, with a BMI of 30 kg/m^2, and hand temperature of 32 °C. The estimations were based on the worker's dominant hand. The average worker was assumed to have none of the other comorbid conditions included in the model (see Table 22).

Understanding existing health conditions helps isolate the neuropathy to the median nerve at the carpal canal.

Specific comorbidities may have a greater influence than others on NCS outcomes, which potentially influence the interpretation of post-offer pre-placement job screenings for median mononeuropathy. Specific Aim 2 was designed to investigate the relationship between selected comorbid conditions and median NCS outcomes. The investigators sought to understand which health history items were not only most important to ask during a post-offer pre-placement job screening for median mononeuropathy but also which were most critical to use as exclusion criteria for reference values.

The present study was the first to use quantile regression to investigate the associations between comorbid conditions and nerve conduction outcomes. The investigators examined the relationship at the upper and lower ends of the nerve conduction distribution that are relevant for developing reference values. In contrast, other studies have relied on traditional parametric statistics (i.e., logistic regression) with dichotomized dependent variables (Pourmemari & Shiri, 2016; Solomon et al., 1999; Werner et al., 2005). For example, Werner et al. (2005) used a combination of symptomology and the median sensory peak latency to classify whether or not participants had CTS. The investigators of the present study used nerve conduction outcomes as a continuous response for the dependent variable which provided greater statistical power. Although previous researchers have used statistical procedures that differed from the present study, the investigators of the present study still observed similar findings with regards to the comorbid conditions associated with NCS outcomes (Ahmad et al., 2016; Dhong, Han, Lee, & Kim, 2000; Palumbo, Szabo, & Olmsted, 2000; Pope & Tang, 2018; Schrijver et al., 2005; Stevens, 1987).

The major comorbid conditions associated with nerve conduction outcomes in the present study were diabetes, previous diagnosis of CTS, CTS surgery (antidromic results only), and symptoms consistent with CTS. The other comorbid conditions with no statistically significant relationship with the nerve conduction outcomes were thyroid disease, hand/wrist fracture, and hand/wrist surgery. Thus, diabetes, previous diagnosis of CTS, CTS surgery, and symptoms consistent with CTS should be included as health history questions for post-offer pre-placement screenings involving median neuropathy. Additionally, these are the most significant comorbidities to use as exclusion criteria when developing normative reference values for distal median neuropathy.

4.5.1 Previous Diagnosis of Carpal Tunnel Syndrome

A previous diagnosis of CTS was positively associated with the median sensory peak latency and median-ulnar difference, and negatively associated with the median sensory amplitude and velocity. Three (out of seven) nerve conduction outcomes were not statistically significantly associated with a previous CTS diagnosis. The nerve conduction outcomes not significantly associated with a previous CTS diagnosis were the 8 cm orthodromic median sensory velocity, 14 cm antidromic median sensory velocity, and 14 cm antidromic median sensory amplitude.

Because velocity was calculated as distance divided by peak latency, the investigators of the present study anticipated similar results for the median sensory peak latency and velocity. However, the relationship between the median sensory peak latency and previous CTS diagnosis was statistically significant, whereas the relationship between the median sensory velocity and previous CTS diagnosis was not. The investigators suspect the inconsistency between the median sensory velocity and peak latency findings may have been partially due to random error introduced during the measurement (8 cm or 14 cm) of the distance between the stimulation site and recording electrodes at the time of testing.

The relationship between the median sensory amplitude and previous CTS diagnosis was not statistically significant for the 14 cm antidromic technique. The AANEM recommends using the nerve conduction speed instead of amplitude when interpreting NCS results because the amplitude is less a less sensitive measure (Jablecki et al., 1993). Some researchers have reported a reduction in median sensory amplitudes with CTS (I. Kimura & Ayyar, 1985; Stevens, 1987); however, this does not always occur (Jackson & Clifford, 1989). Although CTS can result in amplitude decrements, the findings in the present study are consistent with previous research in that there is not always a strong relationship between the two.

4.5.2 Carpal Tunnel Syndrome Surgery

The relationship between CTS surgery and median sensory nerve conduction outcomes was not consistently statistically significant; however, the direction was consistent with a CTS surgery being associated with slightly improved NCS outcomes. The only statistically significant relationships were between CTS surgery and 14 cm antidromic median sensory peak latency and velocity. Researchers have cautioned against using NCS alone to evaluate the treatment efficacy of patients who have undergone CTS release surgery as the NCS results indicate variable levels of improvement with the surgical procedure (Schrijver et al., 2005).The inconsistencies observed in the present study may be due to the variation in neurophysiologic response to CTS release surgery.

4.5.3 Symptoms consistent with Carpal Tunnel Syndrome

There was a positive association between symptoms consistent with CTS and median sensory peak latency. There was a negative association between symptoms consistent with CTS and median sensory amplitude and velocity. The investigators of the present study observed a statistically significant relationship between symptoms, median sensory peak latency, and median sensory velocity similar to other researchers (Dhong et al., 2000). Dhong et al. (2000) reported a significant relationship between median motor latency, median motor velocity and CTS symptoms. The associations between median sensory amplitude (14 cm antidromic only) and symptoms consistent with CTS appear to be the first reported.

Interestingly, there was not a statistically significant relationship between the median-ulnar latency difference and symptoms. The median-ulnar difference and symptoms are often used together to define CTS cases in epidemiologic research (Atroshi et al., 2003; Werner, 2006; Werner & Andary, 2011). Thus, in studies where workers are not hesitant to report symptoms a statistically significant relationship between symptoms and median neuropathy would be expected. One possibility as to why the relationship between the median-ulnar difference and median nerve symptoms was not significant is that symptoms consistent with CTS are often non-specific. It is possible that pathology in more proximal aspects of the median nerve may be the source of the numbness and tingling in the hands/fingers (Atroshi et al., 1999; Franzblau, Blitz, et al., 1993; Werner et al., 2005). The investigators also suspect the relationship was diluted because newly hired workers (as in the present study) may be less forthcoming with symptoms for fear of losing employment or unfavorable job placement (Dale et al., 2016). The investigators observed a CTS symptom prevalence of 0.9% among all 17,682 newly hired works. Other researchers have reported prevalence rates of 15.2-19.0% of active workers have symptoms consistent with CTS (Dale et al., 2013; Harris-Adamson et al., 2013; Patil et al., 2012; Rempel et al., 2015). The investigators of the present study suspect workers undergoing a post-offer pre-placement screening are not as forthcoming with symptoms compared to those already actively working. Although symptoms are commonly used in other scenarios in combination with NCS, symptoms consistent with CTS should be interpreted with caution when collected during a post-offer pre-placement job screening with newly hired workers.

4.5.4 Diabetes

Diabetes was positively related to the median sensory peak latency and negatively related to the median sensory velocity and amplitude. The magnitude and direction for the effect of diabetes on median sensory velocity was similar to previous research (Ahmad et al., 2016). Many researchers have reported diabetes as a significant risk factor for CTS and hypothesize that diabetes increases the likelihood that nerves will undergo pathophysiological changes when subject to compression (Ahmad et al., 2016; Aroori & Spence, 2008; Herbert et al., 2000; Rempel et al., 1999; Solomon et al., 1999; Werner et al., 2005). The finding of the present study adds to the existing body of literature supporting that diabetes is associated with decrements in median nerve function.

4.5.5 Thyroid disease

Thyroid disease was not significantly associated with the median nerve conduction outcomes. Researchers have observed that the majority of patients receiving thyroid replacement therapy to maintain thyroid levels have normal median NCS results even though they still experience symptoms characteristic of CTS (Palumbo et al., 2000). In the present study, those workers who self-reported thyroid disease were likely undergoing treatment; therefore, were anticipated to have nerve conduction outcomes within a range that would be expected for this population. The results observed in the present study should be used with caution as the investigators anticipate those with untreated thyroid disease to have decrements in nerve conduction outcomes when compared to those with treated thyroid disease (Palumbo et al., 2000).

4.5.6 Hand/Wrist Fracture and Surgery

Previous hand/wrist fracture and surgery were not associated with the median nerve conduction outcomes. Previous hand/wrist fracture and surgery were the most frequently reported comorbid conditions; however, the type of hand/wrist fracture or surgery was unknown. Thus, the hand/wrist fractures or surgeries could range from small metacarpal fractures to distal radial surgeries, many of which do not affect the median nerve. Distal radial fractures are more impactful to the median nerve than other types of hand/wrist fractures. Previous researchers have reported that those with distal radius fractures can experience acute CTS (Pope & Tang, 2018). The level of median nerve impairment is dependent on temporality and type of fracture or surgery. Since type of fracture or surgery was not specified in the present study, the investigators cannot conclude for certain all hand/wrist fractures and surgeries have no association with nerve conduction outcomes.

4.2 Limitations

The results of the present study may not be generalizable beyond newly hired workers seeking employment or employed in relatively low-skilled jobs. In addition, the present study was a cross sectional design; therefore, casual inferences cannot be made about the relationship between the selected comorbid conditions and median nerve conduction outcomes.

The previous health conditions were self-reported which could be subject to self-reporting bias. Further, the health history conditions were asked during a post-offer pre-placement job screening where workers may have felt disincentivized to report existing health conditions or symptoms. Other researchers have reported up to 15 – 19% of workers report symptoms characteristic of CTS and 4% of workers report a history of diabetes (Dale et al., 2013; Harris-Adamson et al., 2013; Rempel et al., 2015). In contrast, the present study observed 0.75-1.2% of the workers with symptoms consistent with CTS and 2.5% with diabetes suggesting that worker's may underreport their health history during a post-offer pre-placement job screening.

Two different methods were used when collecting information about previous diagnosis of CTS and previous CTS surgery. For the orthodromic dataset, there were specific items on the questionnaire regarding a previous diagnosis of CTS and CTS surgery. For the antidromic dataset, the occupational nurses asked and recorded if a worker had a previous diagnosis of CTS and previous CTS surgery. The information was then written in the comments section, which was then coded by the investigators. It was possible that nurses did not always remember to ask about the pre-existing health conditions.

There are other health conditions or behaviors associated with nerve conduction outcomes such as alcoholism, smoking, rheumatoid arthritis, and pregnancy that were not included in the health history screening (Herbert et al., 2000; Solomon et al., 1999). Although this limitation exists, the investigators of the present study analyzed the available worker health history which included comorbidities that arguably had the most influence on the nerve conduction outcomes.

4.3 Conclusions

The investigators determined the associations between select comorbid conditions and nerve conduction outcomes while adjusting for individual factors (age, sex, height, BMI, handedness, and hand temperature) in a large sample of newly hired workers. As expected, decrements in median nerve conduction outcomes were associated with CTS (symptoms, surgery, and diagnosis). Diabetes was the only additional comorbid condition associated with the median nerve conduction outcomes. These comorbid conditions should be considered during post-offer pre-placement job screenings for better interpretation of NCS findings. Further, those with these comorbid conditions should be omitted when developing reference values so they do not alter the range of median nerve outcomes expected within a population. Caution is advised when generalizing the results of the present study to additional populations as this was a sample of newly hired workers undergoing a post-offer pre-placement job screening.

5. Chapter 5: Performance classification of symptoms collected during a post-offer pre-placement job screening for median mononeuropathy

Specific Aim 3: To determine the performance classification of hand-related symptoms to identify newly hired workers with abnormal NCS outcomes.

Objectives:

1. To determine the sensitivity and specificity of CTS symptoms relative to a median mononeuropathy as determined by 8 cm orthodromic NCS conducted during a post-offer pre-placement screening.
2. To determine the sensitivity and specificity of CTS symptoms relative to a median mononeuropathy as determined by 14 cm antidromic NCS conducted during a post-offer pre-placement screening.

5.1 Summary

Objective: Determine the sensitivity and specificity of CTS symptoms relative to a median mononeuropathy.

Methods: Seventeen thousand six-hundred and eighty-two (N = 17,682) newly hired workers had received post-offer pre-placement job screenings for the median mononeuropathy that is often associated with CTS. Ten thousand and thirty-eight workers (N = 10,038) were included in the analyses that had an NCS using an 8 cm orthodromic technique, and 4,433 workers were included that had a NCS using a 14 cm antidromic technique. Sensitivity and specificity for symptoms characteristic of CTS were computed for each hand (dominant and nondominant). The reference case definitions were based on the median and ulnar NCS. Workers were classified as

having median mononeuropathy if their NCS result exceeded the median and ulnar normative values developed using quantile regression (described in Specific Aim 1).

Results/Conclusions: Sensitivity of symptoms consistent with CTS was low (2.0% -3.6%) across the various NCS references, and specificity was high (99.5%-99.8%) across the various NCS references. Symptoms consistent with CTS collected during a post-offer pre-placement screening should not be the only variable used to identify workers with median mononeuropathy.

5.2 Introduction

Post-offer pre-placement job screenings have been used to identify workers with median mononeuropathy in the distal upper limb, which is often associated with of CTS. The screenings often consist of median and ulnar NCS as well as inquiries about symptoms consistent with CTS. Symptoms of numbness and tingling in the fingers innervated by the median nerve and NCS outcomes are often used by employers to identify workers that may be at higher risk for developing future CTS. Using symptomology alone instead of in combination with NCS would reduce the resources required to screen employees for the median mononeuropathy. Other researchers have investigated the usefulness of hand symptoms as a screening tool for identifying workers with CTS (Franzblau et al., 1994). However, little is known about the performance classification of symptoms characteristic of CTS among newly hired workers. The purpose of Specific Aim 3 was to determine the sensitivity and specificity of symptoms characteristic of CTS using the median and ulnar nerve normative values developed in Specific Aim 1 as the reference case definitions.

5.3 Methods

Participant selection and post-offer pre-placement screening procedure were identical to those in Specific Aim 1. All data cleaning steps were completed using RStudio Version 3.6.1. and described in detail in Specific Aim 1.

5.3.1 Data Analysis

5.3.1.1 Exclusions

As described previously in Specific Aim 1 and 2, the investigators excluded workers with demographics (age, height, weight, BMI, and hand temperature) exceeding thresholds limits defined for values considered errors during data collection at the work setting. For example, BMI cutoffs of less than 16 kg/m^2 or greater than 65 kg/m^2 were selected to exclude those from the analyses that have a BMI that would be outside of the expected range. Of the 12,821 potential workers in the orthodromic dataset, 39 (0.30%) were excluded from the analyses for ages, heights, weights, BMI, or hand temperatures outside of the defined expected ranges. Of the 4,861 potential workers in the antidromic dataset, 17 (0.35%) were excluded from the analyses due to the values outside of the expected ranges.

5.3.1.2 Case Definitions

Symptoms characteristic of CTS was defined as workers that reported numbness, tingling, or pain of two of the first four digits within the past year, which lasted for at least 2 weeks (Armstrong et al., 2008; Franzblau, Werner, et al., 1993; Patil et al., 2012; Shrivastava & Szabo, 2008; Werner et al., 2005) (the same case definition used in Specific Aim 2). The NCS outcomes served as the reference case definitions in the analyses. An abnormal NCS response characteristic of median mononeuropathy was based on the median and ulnar sensory nerve reference values developed using quantile regression described in Specific Aim 1. An abnormal median nerve response is a nonspecific indicator of underlying pathophysiologic dysfunction. Therefore, the ulnar nerve was used (when available for the orthodromic measures) to identify those that met the case definition of a median mononeuropathy. For the orthodromic measures, the reference case definition for median mononeuropathy characteristic of CTS was either (1) a median peak latency greater than the 95th percentile using quantile regression modeling and an ulnar peak latency less than 2.3 ms or (2) an unresponsive median nerve with an ulnar peak latency less than 2.3 ms. The cutoff for the ulnar peak latency (2.3 ms) was selected based on previously reported reference values (Buschbacher, 1999b; Esteves et al., 2020; Jackson & Clifford, 1989). For the antidromic measures, two case definitions were included in the analysis based on the cutoffs defined by the 95th percentile quantile regression models of the nerve conduction outcomes presented in Specific Aim 1. The first reference case definition was defined as (1) a median peak latency greater than the 95th percentile and an ulnar peak latency less than the 95th percentile or (2) an unresponsive median nerve with an ulnar peak latency less than the 95th percentile. The second case definition used for the antidromic measures was defined as either (1) median-ulnar sensory latency difference greater than the 95th percentile or (2) an unresponsive median nerve with an ulnar peak latency less than the 95th percentile.

5.3.1.3 Statistical Methods

The analyses were completed using R and the caret package (Kuhn, 2020). The reference measurements discussed previously were the case definitions for an abnormal median NCS. Two-by-two tables were created with groups of workers classified according to the reference case definition (NCS outcomes) in the columns, and according to the test (symptoms characteristic of CTS) in the rows. The reference case definition for the orthodromic measures were based on the median and ulnar sensory peak latency. A total of two 2x2 tables were created for the orthodromic measures corresponding to the dominant and nondominant hand. The reference case definitions for the antidromic measures were based on the median and ulnar sensory peak latency and the difference between the median and ulnar peak latency. Four 2x2 tables were created for the antidromic measures corresponding to two case definitions and two hands in the analyses (dominant and nondominant). Sensitivity and specificity were computed. The sensitivity of a test is the proportion of positive symptomatic cases that were correctly classified. The specificity of a test is the proportion of negative symptomatic cases that were correctly classified.

5.4 Results

The summary of the worker demographics and nerve conduction outcomes were presented previously in Chapters 3 and 4. The two-by-two matrices, sensitivity, and specificity for both NCS techniques are outlined in Table 24. For the orthodromic measures, 1,785 of 11,384 (15.7%) hands on the dominant extremity had an abnormal NCS indicating median neuropathy and 1,562 hands (13.8%, N = 11,355) had an abnormal for the nondominant hand. For the antidromic measures using the absolute median and ulnar sensory peak latency as the reference, 513 hands (11.0%, N = 4,668) and 521 hands (11.0%, N = 4,740) had an abnormal NCS for the dominant and nondominant hand, respectively. For the antidromic measures using the median-ulnar latency difference as the reference, 843 hands (18.1%, N = 4,653) and 829 hands (17.5%, N = 4,732) had an abnormal NCS for the dominant and nondominant hand, respectively. The percentage of hands that met the case definition for symptoms consistent with CTS ranged from 0.48% to 1.0% for the orthodromic and antidromic measures. The sensitivity was extremely poor for symptoms consistent with CTS ranging from 2.0% to 3.6% (Table 24). The specificity for symptoms consistent with CTS was higher than the sensitivity, ranging from 98.6% to 99.8%

(Table 24). The investigators completed a sensitivity analysis to ensure the observed sensitivities and specificities were robust across a range of percentile values for the reference method (results presented in Appendix K: Sensitivity analysis). The reference case definition for median mononeuropathy using NCS was analyzed for the 75th percentile and 97.5th percentile value for the median and ulnar nerve conduction outcomes (whereas the 95th percentile value is presented in Specific Aim 3). The investigators observed no meaningful changes in the results.

Table 24. Sensitivity and Specificity of symptoms reported during a post-offer pre-placement job screening.

Technique	Reference	Hand	Confusion Matrix: Symptoms	Confusion Matrix: Reference 0	Confusion Matrix: Reference 1	Sensitivity	Specificity
8 cm Orthodromic	Quantile Regression, 95th Percentile Median Sensory Peak Latency, and Ulnar Sensory Peak Latency < 2.3 ms	Dominant	0	9565	1745	2.2%	98.6%
			1	34	40		
		Nondominant	0	9770	1531	2.0%	99.8%
			1	23	31		
14 cm Antidromic	Quantile Regression, 95th Percentile Median & Ulnar Sensory Peak Latency	Dominant	0	4133	488	2.3%	99.5%
			1	22	25		
		Nondominant	0	4204	509	3.6%	99.6%
			1	15	12		
	Quantile Regression, 95th Percentile Median-Ulnar Difference	Dominant	0	3794	813	3.6%	99.6%
			1	16	30		
		Nondominant	0	3893	812	2.1%	99.7%
			1	10	17		

5.5 Discussion

A combination of symptoms and NCS findings are typically used in screenings, surveillance, case definitions, and diagnoses for CTS. However, as indicated in the present study, symptoms alone may be of limited value in the identification of median distal neuropathy during a post-offer pre-placement job screening. Previous researchers have suggested that workers, especially newly hired workers, may be hesitant to report of any symptoms to the employer (Binghan et al., 1996; Dale et al., 2016; Taylor Moore et al., 2013). The purpose of the present study was to investigate the performance classification of hand symptomology collected during a post-offer pre-placement job screening for median mononeuropathy. NCS outcomes served as the reference case definition to determine the sensitivity and specificity of symptoms consistent with CTS. The investigators of the present study observed that CTS symptoms have low sensitivity and high specificity suggesting that symptoms offer very little information to employers when collected during these type of screenings. The high specificity was likely due to the low percentage (0.48%-1.0%) of workers who reported symptoms consistent with CTS and relatively low percentage (11.0%-18.1%) of workers with an abnormal median NCS.

The percentage of workers who had an abnormal NCS ranged from 11.0% -18.1% depending on the NCS technique (orthodromic versus antidromic) and case definition for median mononeuropathy. Bingham et al. (1996) reported 17.5% of all workers had a distal median neuropathy across the carpal tunnel at the time of hire. Additionally, very few of the workers with a median neuropathy had symptoms consistent with CTS (Bingham et al., 1996). Both the investigators of the present study and Bingham et al. (1996) collected hand-related symptoms, conducted NCS with newly hired workers in industrial jobs, and classified workers with median mononeuropathy based on the median and ulnar peak latencies (Bingham et al., 1996). The sample sizes were larger in the present study (N = 12,782 and N = 4,844 workers for the orthodromic and antidromic datasets, respectively) compared to Bingham et al. (1996) (N = 1,021 workers). Although the sample sizes were substantially different, the prevalence of median mononeuropathy was comparable between the present study and other research (Bingham et al., 1996).

The results of the present study are consistent with what other studies regarding the low sensitivity and high specificity of using symptoms alone to detect median mononeuropathy (Atroshi et al., 1999; Franzblau, Blitz, et al., 1993; Werner et al., 2005). The pathophysiology that results in numbness and tingling in the hands and fingers is not unique to CTS. Nerve entrapment in the cervical region can lead to a radiculopathy that also produces numbness and tingling in the hands and fingers (Duncan & Kakinoki, 2017). Although symptomology supplements NCS findings in the assessment of CTS, NCS are the only quantitative method to differentiate between various neurological impairments.

Although the results of Specific Aim 3 are consistent with other research, the investigators observed sensitivities much smaller than those previously reported. Researchers who have investigated using hand-related symptomology as a surveillance or screening tool for CTS with current employees have reported relatively low sensitivities (19% -40%) and high specificities (50%-100%) (Franzblau et al., 1994). Franzblau et al. (1994) investigated the performance classification of symptoms characteristic of CTS for 411 active workers. The present study also investigated the performance classification of symptoms characteristic of CTS; however, the investigators did so with a large sample of *newly hired* workers. The much smaller sensitivities reported in the present study (2.0% to 3.6%) could be due to the assumption that newly hired workers are not as forthcoming with symptoms during a post-offer pre-placement job screenings compared to those who are already actively working. Other researchers also reported an underreporting of hand-related symptoms during post-offer pre-placement job screenings for the median mononeuropathy characteristic of CTS (Bingham et al., 1996; Dale et al., 2016). The present study was not designed to provide quantitative evidence of underreporting of symptoms; however, the investigators suspect there was low symptom reporting with newly hired workers during this type of CTS job screening. Another key methodological difference between the study by Franzblau et al. (1994) and the present study in terms of the differences in symptomology sensitivity are the differences in case definition of median mononeuropathy. Franzblau et al. (1994) reference method was based on a single cutoff of 0.80 ms for the median-ulnar peak latency difference to classify a worker with median mononeuropathy. In contrast, rather than using a single cutoff to define median mononeuropathy, the investigators in the present study used reference values for the median peak latency, ulnar peak latency, and median-ulnar latency difference derived by quantile regression allowing for quantitative adjustment for important individual characteristics (age, sex, height, BMI, hand temperature, and hand). Additional studies are needed to compare the performance classification of symptoms using both traditional nerve conduction outcome reference values and those presented in Specific Aim 1 using quantile regression.

Another possible explanation of the low sensitivity when using symptomology to identify median neuropathy may be related to the natural history of CTS. Newly hired asymptomatic workers with a median mononeuropathy across the carpal canal could be experiencing early electrophysiologic evidence of nerve impairment that precedes the experience of symptoms characteristic of CTS (Keir & Rempel, 2005; J. Kimura, 1989; Rempel et al., 1999). Other researchers have also reported a high prevalence of abnormal median NCS findings among asymptomatic workers (Bingham et al., 1996; Dale et al., 2013; Jacklitsch et al., 2016; Musolin & Ramsey, 2017). Other studies have reported that a significant number of asymptomatic workers with median mononeuropathy develop CTS (Dale et al., 2014; Werner et al., 2001). If workers with a moderate to severe median mononeuropathy across the carpal canal are subjected to hand intensive occupational or non-occupational activities, they may progress to experiencing symptoms, and ultimately, developing clinical CTS (Dale et al., 2014; Werner et al., 2001).

5.6 Limitations

Unfortunately, the investigators did not have reference values developed using quantile regression (described in detail in Specific Aim 1) for the ulnar nerve using an 8 cm orthodromic NCS technique. Although though the median-ulnar difference is the most frequently used NCS outcome to classify median nerve function, the investigators could not compute the median-ulnar difference for the NCS data using the 8 cm orthodromic technique as they did not have ulnar sensory peak latencies for every worker. For the antidromic dataset, the investigators did have all median and ulnar sensory peak latencies. The investigators observed 5.2%-7.1% (approximately 600 to 800) more hands were classified as an abnormal NCS result with the median-ulnar difference definition compared to the median and ulnar sensory definition. Using the median and ulnar difference may have slightly improved the sensitivity. However, based on the results of the antidromic NCS reference case definitions, the investigators do not suspect the sensitivity would have improved enough that the interpretation of the results would be different. Thus, the absolute latencies were a more conservative method to classify an abnormal median sensory NCS result.

5.7 Conclusions

Symptoms consistent with CTS had a low sensitivity (2.0% -3.6%) and high specificity (99.5%-99.8%). Thus, symptoms should not be used in isolation to identify newly hired workers with median mononeuropathy. The low sensitivities may have been observed because hand-related symptoms are not unique to CTS or workers were experiencing the neurophysiologic changes that precedes any symptoms. The investigators also suspect another reason they observed low sensitivities for hand-related symptoms was because the newly hired workers were not forthcoming with symptoms during the post-offer pre-placement job screening. Although symptomology is typically used alongside NCS, symptomology should be interpreted with caution when collected during a post-offer pre-placement job screening for median mononeuropathy.

6. Chapter 6: Conclusion

6.1 Limitations

All three Specific Aims were accomplished using the same datasets. In addition to the individual limitations discussed previously under each specific aim, there are limitations that span across all three Specific Aims. These data were collected over the course of 16 years at three facilities as part of a post-offer pre-placement job screening for median mononeuropathy. Every newly hired worker at the facilities was screened and considered a sample population of convenience. The workers self-reported their health history including hand symptoms, which are subject to recall bias. Additionally, because questions related to symptoms were asked during an initial employment health screening, workers may have not been forthcoming their complete health history and symptomology.

The study was cross-sectional and retrospective where the purpose was to estimate the nerve conduction outcomes rather than provide causal inferences about the associations reported. The screening questionnaires and methodologies were not designed a priori for research purposes but were rather conducted under actual work conditions within a variety of workplaces. There were limitations with the availability of NCS and health history information.

6.2 Strengths

This study represents the largest sample of NCS ever published. A total of 17,630 newly hired workers were assessed to establish reference values for the median and/or ulnar nerve conduction outcomes using AANEM criteria as a guide. Although the AANEM recommends a minimum of 100 subjects to establish quality reference values, the proposed study had large samples to draw from when deriving normative median and ulnar nerve conduction values for both the 8 cm and 14 cm distal nerve conduction outcomes. The study population represented a large age-span of workers including older adults, which are insufficiently represented in the current NCS literature (Benatar et al., 2009; Buschbacher, 1999a, 1999b; Esteves et al., 2020). Another innovative aspect of the Specific Aims outlined in this dissertation is using linear quantile mixed models for the statistical analysis. Quantile regression is only beginning to gain traction in health-related fields, and this study is one of few that uses quantile regression with nerve conduction outcomes (Benatar et al., 2009; Esteves et al., 2020).

6.3 Summary

This dissertation contains the largest compilation of NCS from newly hired workers. The purpose of this project was to analyze an existing dataset from post-offer pre-placement job screenings for median mononeuropathy to (1) establish reference values for the median and ulnar sensory nerve, (2) investigate the relationship between comorbid conditions and NCS outcomes, and (3) determine the performance classification (i.e., sensitivity and specificity) of symptoms collected during a post-offer pre-placement job screening for median mononeuropathy.

In Specific Aim 1, the investigators were the first to develop reference values for a sample of newly hired workers, and median and ulnar nerve conduction outcomes using linear quantile mixed model regression. The reference values presented in Specific Aim 1 vary from person to person due to adjustment for individual characteristics, which, although preferable, contrasts the single threshold currently used in practice to classify NCS results. Future studies are needed to evaluate the reference values presented in this dissertation compared to those currently used in the field and research before individualized reference values serve as a viable replacement to current practices.

Previous diagnosis of CTS, previous CTS surgery, symptoms consistent with CTS, and diabetes were statistically significantly associated with the majority of the nerve conduction outcomes (Specific Aim 2). These finding provide further evidence reference values should be developed using robust exclusion criteria to ensure the estimations are not artificially influenced by other health conditions.

Symptoms are typically useful when evaluating persons for median mononeuropathy; however, symptoms had a low sensitivity and high specificity when collected during post-offer pre-placement job screenings (Specific Aim 3). Thus, using only symptomology is not recommended to classify persons as having median mononeuropathy, especially during job placement screenings.

The investigators used novel statistical techniques throughout this dissertation to provide more precise nerve conduction reference values to improve the classification of NCS in occupational health research and practice.

References

Abrevaya, J. (2001). The effects of demographics and maternal behavior on the distribution of birth outcomes. *Empirical Economics*, *26*(1), 247–257. https://doi.org/10.1007/s001810000052

Ahmad, A., Moinuddin, A., Ahsan, A., & Goel, A. (2016). Study of electrophysiological changes in sensory nerves among diabetic smokers. *Journal of Clinical and Diagnostic Research*, *10*(1), CC09-CC11. https://doi.org/10.7860/JCDR/2016/16673.7103

American Association of Electrodiagnostic Medicine. (2002). Practice parameter for electrodiagnostic studies in carpal tunnel syndrome: Summary statement. *Muscle and Nerve*, *25*(6), 918–922. https://doi.org/10.1002/mus.10185

Anton, D., Gerr, F., Merlino, L. A., & Rosecrance, J. (2014). Normative median and ulnar nerve conduction values among a rural aged population. *Work*, *49*(1), 5–14. https://doi.org/10.3233/WOR-131764

Armstrong, T., Dale, A. M., Franzblau, A., & Evanoff, B. (2008). Risk factors for Carpal tunnel syndrome and median neuropathy in a working population. *Journal of Occupational and Environmental Medicine*, *50*(12), 1355–1364. https://doi.org/10.1097/JOM.0b013e3181845fb1

Aroori, S., & Spence, R. (2008). Carpal tunnel syndrome. *Ulster Med J*, *77*(1), 6–17. https://doi.org/10.1007/s001320050272

Atroshi, I., Gummesson, C., Johnsson, R., & Ornstein, E. (2003). Diagnostic properties of nerve conduction tests in population-based carpal tunnel syndrome. *BMC Musculoskeletal Disorders*, *4*, 1–7. https://doi.org/10.1186/1471-2474-4-9

Atroshi, I., Gummesson, C., Johnsson, R., Ornstein, E., Ranstam, J., & Rosen, I. (1999). Prevalence of carpal tunnel syndrome in a general population. *Journal of American Medical Association*, *281*(2), 153–158.

Barcenilla, A., March, L. ., Chen, J. S., & Sambrook, P. N. (2012). Carpal tunnel syndrome and its relationship to occupation: A meta-analysis. *Rheumatology*, *51*(2), 250–261. https://doi.org/10.1093/rheumatology/ker108

Becker, J., Nora, D. B., Gomes, I., Stringari, F. F., Seitensus, R., Panosso, J. S., & Ehlers, J. A. C. (2002). An evaluation of gender , obesity , age and diabetes mellitus as risk factors for carpal tunnel syndrome. *Clinical Neurophysiology*, *113*, 1429–1434.

Benatar, M., Wuu, J., & Peng, L. (2009). Reference data for commonly used sensory and motor nerve conduction studies. *Muscle & Nerve*, *40*, 772–794. https://doi.org/10.1002/mus.21490

Beyerlein, A. (2014). *Quantile Regression - Opportunities and challenges from a user's perspective* (Vol. 180, pp. 330–331). Vol. 180, pp. 330–331. https://doi.org/10.1093/aje/kwu178

Bhattacharya, A. (2014). Costs of occupational musculoskeletal disorders (MSDs) in the United

States. *International Journal of Industrial Ergonomics*, *44*(3), 448–454. https://doi.org/10.1016/j.ergon.2014.01.008

Bingham, R. C., Rosecrance, J., & Cook, T. (1996). Prevalence of abnormal median nerve conduction in applicants for industrial jobs. *American Journal of Industrial Medicine*, *30*(3), 355–361. https://doi.org/10.1002/(SICI)1097-0274(199609)30:3<355::AID-AJIM15>3.0.CO;2-V

Bonfiglioli, R., Mattioli, S., Spagnolo, M. R., & Violante, F. S. (2006). Course of symptoms and median nerve conduction values in workers performing repetitive jobs at risk for carpal tunnel syndrome. *Occupational Medicine*, *56*(2), 115–121. https://doi.org/10.1093/occmed/kqj007

Boz, C., Ozmenoglu, M., Altunayoglu, V., Velioglu, S., & Alioglu, Z. (2004). Individual risk factors for carpal tunnel syndrome: An evaluation of body mass index, wrist index and hand anthropometric measurements. *Clinical Neurology and Neurosurgery*, *106*(4), 294–299. https://doi.org/10.1016/j.clineuro.2004.01.002

Burt, S., Crombie, K., Jin, Y., Wurzelbacher, S., Ramsey, J. G., & Deddens, J. A. (2011). Workplace and individual risk factors for carpal tunnel syndrome. *Occupational and Environmental Medicine*, *68*(12), 928–933. https://doi.org/10.1136/oem.2010.063677

Buschbacher, R. M. (1999a). Median 14-cm and 7-cm antidromic sensory studies to digits two and three. *American Journal of Physical Medicine and Rehabilitation*, *78*(6). https://doi.org/10.1097/00002060-199911001-00011

Buschbacher, R. M. (1999b). Ulnar 14-cm and 7-cm antidromic sensory studies to the fifth digit: Reference values derived from a large population of normal subjects. *American Journal of Physical Medicine and Rehabilitation*, *78*(6). https://doi.org/10.1097/00002060-199911001-00012

Campbell, W. W., & Robinson, L. R. (1993). Deriving reference values in electrodiagnostic medicine. *Muscle & Nerve*, *16*, 424–428.

Cartwright, M. S., Walker, F. O., Blocker, J. N., Schulz, M. R., Arcury, T. ., Grzywacz, J. G., … Quandt, S. A. (2012). The prevalence of carpal tunnel syndrome in latino poultry-processing workers and other latino manual workers. *Journal of Occupational and Environmental Medicine*, *54*(2), 198–201. https://doi.org/10.1097/JOM.0b013e31823fdf53.The

Chaudhry, V., Cornblath, D. R., Mellits, E. D., Avila, O., Freimer, M. L., Glass, J. D., … Kunci, R. W. (1991). Inter- and intraexaminer reliability of nerve conduction measurements in patients with diabetic neuropathy. *Annals of Neurology*, *30*(6), 841–843. https://doi.org/10.1002/ana.410300614

Chen, S., Andary, M., Buschbacher, R. M., Del Toro, D., Smith, B., So, Y., … Dillingham, T. R. (2016). Electrodiagnostic reference values for upper and lower limb nerve conduction studies in adult populations. *Muscle and Nerve*, *54*(3), 371–377. https://doi.org/10.1002/mus.25203

Dale, A. M., Descatha, A., Coomes, J., Franzblau, A., & Evanoff, B. (2011). Physical examination has a low yield in screening for carpal tunnel syndrome. *American Journal of Industrial Medicine*, *54*(1), 1–9.

Dale, A. M., Gardner, B. T., Buckner-petty, S., Strickland, J. R., & Evanoff, B. (2016). Post-Offer Pre-Placement Screening for Carpal Tunnel Syndrome in Newly Hired Manufacturing Workers. *Journal of Occupational and Environmental Medicine*, *58*(12), 1212–1216. https://doi.org/10.1097/JOM.0000000000000891.Post-Offer

Dale, A. M., Gardner, B. T., Zerigue, A., Werner, R., Franzblau, A., & Evanoff, B. (2014). The effectiveness of post-offer pre-placement nerve conduction screening for carpal tunnel syndrome. *Journal of Occupational and Environmental Medicine*, *56*(8), 840–847. https://doi.org/10.1097/JOM.0000000000000185

Dale, A. M., Harris-Adamson, C., Rempel, D. M., Gerr, F., Hegmann, K., Silverstein, B. A., … Evanoff, B. (2013). Prevalence and incidence of carpal tunnel syndrome in US working populations: pooled analysis of six prospective studies. *Scandinavian Journal of Work, Environment and Health*, *39*(5), 495–505. https://doi.org/10.5271/sjweh.3351

Dhong, E., Han, S., Lee, B., & Kim, W. (2000). Correlation of Electrodiagnostic Findings with Subjective Symptoms in Carpal Tunnel Syndrome. *Annals of Plastic Surgery*, *45*, 127–131.

Dillingham, T. R., Chen, S., Andary, M., Buschbacher, R. M., Del Toro, D., Smith, B., … Yuen, S. O. (2016). Establishing high-quality reference values for nerve conduction studies: A report from the normative data task force of the American Association Of Neuromuscular & Electrodiagnostic Medicine. *Muscle and Nerve*, *54*(3), 366–370. https://doi.org/10.1002/mus.25204

Division of Population Health National Center for Chronic Disease Prevention and Health Promotion. (2020). Work-Related Musculoskeletal Disorders & Ergonomics. Retrieved January 20, 2021, from Centers for Disease Control and Prevention website: https://www.cdc.gov/workplacehealthpromotion/health-strategies/musculoskeletal-disorders/index.html

Dorfman, L. J., & Robinson, L. R. (1997). Normative Data in Electrodiagnostic Medicine. *Muscle & Nerve*, *20*, 4–14.

Duncan, S. F. M., & Kakinoki, R. (2017). Carpal Tunnel Syndrome and Related Median Neuropathies: Challenges and Complications. In *Carpal Tunnel Syndrome and Related Median Neuropathies: Challenges and Complications*. https://doi.org/10.1007/978-3-319-57010-5

Elveback, L. (1973). The population of healthy persons as a source of reference information. *Human Pathology*, *4*(1), 9–16.

Esteves, E. A., Guio, S. P., de los Reyes-Guevara, C. A., Cantor, E., Habeych, M. E., & Malagón, A. L. (2020). Reference values of upper extremity nerve conduction studies in a Colombian population. *Clinical Neurophysiology Practice*, *5*, 73–78. https://doi.org/10.1016/j.cnp.2020.02.001

Foley, M., Silverstein, B. A., & Polissar, N. (2007). The Economic Burden of Carpal Tunnel Syndrome : Long-Term Earnings of CTS Claimants in Washington State. *American Journal* *of Industrial Medicine*, *50*, 155–172. https://doi.org/10.1002/ajim.20430.

Ford, C. (2015). Getting started with quantile regression. Retrieved from Research Data Services + Sciences website: https://data.library.virginia.edu/getting-started-with-quantile-regression/

Franzblau, A., Blitz, S., Flaschner, D., Werner, R., Albers, J. W., & Armstrong, T. J. (1993). Medical screening of office workers for upper extremity cumalitve trauma disorders. *Archives of Environmental Health*, *48*(3), 164–170.

Franzblau, A., Werner, R., Albers, J. W., Grant, C. L., Olinski, D., & Johnston, E. (1994). Workplace surveillance for carpal tunnel syndrome using hand diagrams. *Journal of Occupational Rehabilitation*, *4*(4), 185–198. https://doi.org/10.1007/BF02331615

Franzblau, A., Werner, R., Valle, J., & Johnston, E. (1993). Workplace surveillance for carpal tunnel syndrome: A comparison of methods. *Journal of Occupational Rehabilitation*, *3*(1), 1–14. https://doi.org/10.1007/BF01076738

Franzblau, A., Werner, R., & Yihan, J. (2004). Preplacement nerve testing for carpal tunnel syndrome: Is it cost effective? *Journal of Occupational and Environmental Medicine*, *46*(7), 714–719. https://doi.org/10.1097/01.jom.0000131798.48162.63

Garg, A., Kapellusch, J., Hegmann, K., Wertsch, J., Merryweather, A., Deckow-Schaefer, G., & Malloy, E. J. (2012). The Strain Index (SI) and Threshold Limit Value (TLV) for Hand Activity Level (HAL): Risk of carpal tunnel syndrome (CTS) in a prospective cohort. *Ergonomics*, *55*(4), 396–414.

Gell, N., Werner, R., Franzblau, A., Ulin, S. S., & Armstrong, T. J. (2005). A longitudinal study of industrial and clerical workers: Incidence of carpal tunnel syndrome and assessment of risk factors. *Journal of Occupational Rehabilitation*, *15*(1), 47–55. https://doi.org/10.1007/s10926-005-0873-0

Geraci, M. (2014). Linear Quantile Mixed Models : The lqmm Package for Laplace Quantile Regression. *Journal of Stastistical Software*, *57*(13), 1–29. Retrieved from http://www.jstatsoft.org/v57/i13/

Geraci, M., & Bottai, M. (2014). Linear quantile mixed models. *Statistics and Computing*, *24*(3), 461–479. https://doi.org/10.1007/s11222-013-9381-9

Gerr, F., Fethke, N. B., Merlino, L. A., Anton, D., Rosecrance, J., Jones, M. P., … Meyers, A. R. (2014). A prospective study of musculoskeletal outcomes among manufacturing workers: I. effects of physical risk factors. *Human Factors*, *56*(1), 112–130.

Gerr, F., & Letz, R. (1998). The sensitivity and specificity of tests for carpal tunnel syndrome vary with the comparison subjects. *The Journal of Hand Surgery*, *23B*(2), 151–155.

Hallgren, K. A. (2012). Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial. *Tutor Quant Methods Psychol*, *8*(1), 23–24. https://doi.org/10.1080/11035896009449194

Harris-Adamson, C., Eisen, E. A., Dale, A. M., Evanoff, B., Hegmann, K. T., Thiese, M. S., … Rempel, D. M. (2013). The impact of gender on personal, health and workplace psychosocial risk factors for carpal tunnel syndrome: A pooled study cohort. *Proceedings of* *the Human Factors and Ergonomics Society Annual Meeting, HFES 2013*, 911–914. https://doi.org/10.1177/1541931213571202

Harris-Adamson, C., Eisen, E. A., Kapellusch, J., Garg, A., Hegmann, K. T., Thiese, M. S., … Rempel, D. M. (2015). Biomechanical risk factors for carpal tunnel syndrome: A pooled study of 2474 workers. *Occupational and Environmental Medicine*, *72*(1), 33–41. https://doi.org/10.1136/oemed-2014-102378

Herbert, R., Gerr, F., & Dropkin, J. (2000). Clinical evaluation and management of work-related carpal tunnel syndrome. *American Journal of Industrial Medicine*, *37*(1), 62–74. https://doi.org/10.1002/(sici)1097-0274(200001)37:1<62::aid-ajim6>3.0.co;2-d

Jablecki, C., Andary, M., Floeter, M., Miller, R., Quartly, C., Vennix, M., & Wilson, J. (2002). Practice parameter: Electrodiagnostic studies in carpal tunnel syndrome: Report of the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*, *58*(11), 1589–1592. https://doi.org/10.1212/WNL.58.11.1589

Jablecki, C., Andary, M., So, Y., Wilkins, D., & Williams, F. (1993). Literature review of the usefulness of nerve conduction studies and electromyography for the evaluation of patients with carpal tunnel syndrome. *Muscle & Nerve*, *16*(12), 1392–1414. https://doi.org/10.1002/mus.880161220

Jacklitsch, B., Williams, W., Musolin, K., Coca, A., Kim, J.-H., & Turner, N. (2016). NIOSH criteria for a recommended standard: occupational exposure to heat and hot environments. *US Department of Health and Human Services*, Publication 2016-106.

Jackson, D. A., & Clifford, J. C. (1989). Electrodiagnosis of mild carpal tunnel syndrome. *Journal of Chemical Information and Modeling*, *70*(3), 199–204.

Johnson, E. W., Kukla, R. D., Wongsam, P. E., & Piedmonth, A. (1981). Sensory latencies to the ring finger: Normal Values and Relation to Carpal Tunnel Syndrome. *Archives of Physical Medicine and Rehabilitation*, *62*, 206–208.

Kapellusch, J., Gerr, F., Malloy, E. J., Garg, A., Harris-Adamson, C., Bao, S., … Rempel, D. M. (2014). Exposure-response relationships for the ACGIH threshold limit value for handactivity level: Results from a pooled data study of carpal tunnel syndrome. *Scandinavian Journal of Work, Environment and Health*, *40*(6), 610–620. https://doi.org/10.5271/sjweh.3456

Katz, J. N., Stirrat, C. R., Larson, M. G., Fossel, A. H., Eaton, H. M., & Liang, M. H. (1990). A self-administered hand symptom diagram for the diagnosis and epidemiologic study of carpal tunnel syndrome. *The Journal of Rheumatology*, *17*(11), 1495–1498.

Keir, P. J., & Rempel, D. M. (2005). Pathomechanics of peripheral nerve loading: Evidence in carpal tunnel syndrome. *Journal of Hand Therapy*, *18*(2), 259–269. https://doi.org/10.1197/j.jht.2005.02.001

Kimura, I., & Ayyar, D. (1985). The carpal tunnel syndrome: electrophysiological aspects of 639 symptomatic extremities. *Electromyography Clin. Neurophysiology*, *25*, 151–164.

Kimura, J. (1989). *Electrodiagnosis in Disease of Nerve and Muscle: Principles and Practice*

(2nd ed.). United States of America: F. A. Davis Company.

Koenker, R., & Hallock, K. F. (2001). Quantile Regression. *J Econ Perspect*, *15*(4), 143–156.

Kouyoumdjian, J. A., Zanetta, D. M. T., & Morita, M. P. A. (2002). Evaluation of age, body mass index, and wrist index as risk factors for carpal tunnel syndrome severity. *Muscle and Nerve*, *25*(1), 93–97. https://doi.org/10.1002/mus.10007

Kuhn, M. (2020). *caret: Classification and Regression Training*. Retrieved from https://cran.r-project.org/package=caret

Letz, R., & Gerr, F. (1994). Covariates of human peripheral nerve function: I. Nerve conduction velocity and amplitude. *Neurotoxicology and Teratology*, *16*(1), 95–104. https://doi.org/10.1016/0892-0362(94)90014-0

Mattioli, S., Baldasseroni, A., Curti, S., Cooke, R. M. T., Mandes, A., Zanardi, F., … Violante, F. S. (2009). Incidence rates of surgically treated idiopathic carpal tunnel syndrome in blue- and white-collar workers and housewives in Tuscany, Italy. *Occupational and Environmental Medicine*, *66*(5), 299–304. https://doi.org/10.1136/oem.2008.040212

Musolin, K., & Ramsey, J. (2017). Carpal tunnel syndrome prevalence: an evaluation of workers at a raw poultry processing plant. *International Journal of Occupational and Environmental Health*, *23*(4), 282–290. https://doi.org/10.1080/10773525.2018.1474420

Musolin, K., Ramsey, J. G., Wassell, J. T., & Hard, D. L. (2014). Prevalence of carpal tunnel syndrome among employees at a poultry processing plant. *Applied Ergonomics*, *45*(6), 1377–1383. https://doi.org/10.1016/j.apergo.2014.03.005

National Research Council and Institute of Medicine. (2001). *Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities* (Panel on Musculoskeletal Disorders and the Workplace. Commission on Behavioral and Social Sciences and Education, Ed.). https://doi.org/10.17226/10032

Ott, R. L., & Longnecker, M. (2010). Multiple Regression and the General Linear Model. In *An Introduction to Statistical Methods and Data Analysis* (6th ed., pp. 664–762). Belmont, CA: Brooks/Cole.

Padua, L., Coraci, D., Erra, C., Pazzaglia, C., Paolasso, I., Loreti, C., … Hobson-Webb, L. D. (2016). Carpal tunnel syndrome: clinical features, diagnosis, and management. *The Lancet Neurology*, *15*(12), 1273–1284. https://doi.org/10.1016/S1474-4422(16)30231-9

Palmer, K. T., Harris, E. C., & Coggon, D. (2007). Carpal tunnel syndrome and its relation to occupation: A systematic literature review. *Occupational Medicine*, *57*(1), 57–66. https://doi.org/10.1093/occmed/kql125

Palumbo, C. F., Szabo, R. M., & Olmsted, S. L. (2000). The effects of hypothyroidism and thyroid replacement on the development of carpal tunnel syndrome. *Journal of Hand Surgery*, *25*(4), 734–739. https://doi.org/10.1053/jhsu.2000.8642

Patil, A., Rosecrance, J., Douphrate, D., & Gilkey, D. (2012). Prevalence of carpal tunnel syndrome among dairy workers. *American Journal of Industrial Medicine*, *55*(2), 127–135. https://doi.org/10.1002/ajim.21995

Peng, L., Wuu, J., & Benatar, M. (2009). Developing reference data for nerve conduction studies: an application of quantile regression. *Muscle & Nerve*, *40*, 763–771. https://doi.org/10.1002/mus.21489

Pope, D., & Tang, P. (2018). Carpal Tunnel Syndrome and Distal Radius Fractures. *Hand Clinics*, *34*(1), 27–32. https://doi.org/10.1016/j.hcl.2017.09.003

Pourmemari, M. H., & Shiri, R. (2016). Diabetes as a risk factor for carpal tunnel syndrome: A systematic review and meta-analysis. *Diabetic Medicine*, *33*(1), 10–16. https://doi.org/10.1111/dme.12855

Punnett, L., & Wegman, D. H. (2004). Work-related musculoskeletal disorders: The epidemiologic evidence and the debate. *Journal of Electromyography and Kinesiology*, *14*, 13–23. https://doi.org/10.1016/j.jelekin.2003.09.015

Redmond, M. D., & Rivner, M. H. (1988). False positive electrodiagnostic tests in carpal tunnel syndrome. *Muscle & Nerve*, *11*, 511–518.

Rempel, D. M., Dahlin, L., & Lundborg, G. (1999). Pathophysiology of Nerve Compression Syndromes : Response of Peripheral Nerves to Loading Current Concepts Review Pathophysiology of Nerve Compression Syndromes : Response of Peripheral Nerves to Loading *. *Bone Joint Surg Am*, *81*, 1600–1610.

Rempel, D. M., Evanoff, B., Amadio, P. C., De Krom, M., Franklin, G. M., Franzblau, A., … Pransky, G. (1998). Consensus criteria for the classification of carpal tunnel syndrome in epidemiologic studies. *American Journal of Public Health*, *88*(10), 1447–1451. https://doi.org/10.2105/AJPH.88.10.1447

Rempel, D. M., Gerr, F., Harris-Adamson, C., Hegmann, K. T., Thiese, M. S., Kapellusch, J., … Evanoff, B. (2015). Personal and workpalce factors and median nerve function in a pooled study of 2396 US workers. *J Occup Environ Med*, *57*(1), 98–104.

Romero-Ortega, M. (2015). Peripheral Nerves, Anatomy and Physiology of. In D. Jaeger & R. Jung (Eds.), *Encyclopedia of Comupational Neuroscience*. Retrieved from https://doi-org.ezproxy2.library.colostate.edu/10.1007/978-1-4614-6675-8_214

Rosecrance, J., Cook, T. M., Anton, D. C., & Merlino, L. A. (2002). Carpal tunnel syndrome among apprentice construction workers. *American Journal of Industrial Medicine*, *42*(2), 107–116. https://doi.org/10.1002/ajim.10093

Rosecrance, J., Marras, T., Murgia, L., Tartaglia, R., & Baldasseroni, A. (2013). Carpal tunnel syndrome among ewe dairy farmers in Sardinia, ITA. *American Journal of Industrial Medicine*, *56*(8), 889–896. https://doi.org/10.1002/ajim.22153

Salerno, D. F., Franzblau, A., Werner, R., Bromberg, M. B., Armstrong, T. J., & Albers, J. W. (1998). Median and ulnar nerve conduction studies among workers: Normative values. *Muscle and Nerve*, *21*(8), 999–1005. https://doi.org/10.1002/(SICI)1097-4598(199808)21:8<999::AID-MUS3>3.0.CO;2-0

Schrijver, H. M., Gerritsen, A. A. M., Strijers, R. L. M., Uitdehaag, B. M. J., Scholten, R. J. P. M., De Vet, H. C. W., & Bouter, L. M. (2005). Correlating nerve conduction studies and clinical outcome measures on carpal tunnel syndrome: Lessons from a randomized controlled trial. *Journal of Clinical Neurophysiology*, *22*(3), 216–221. https://doi.org/10.1097/01.WNP.0000167936.75404.C3

Shiri, R., Pourmemari, M. H., Falah-Hassani, K., & Viikari-Juntura, E. (2015). The effect of excess body mass on the risk of carpal tunnel syndrome: A meta-analysis of 58 studies. *Obesity Reviews*, *16*(12), 1094–1104. https://doi.org/10.1111/obr.12324

Shrivastava, N., & Szabo, R. (2008). Decision Making in Upper Extremity Entrapment Neuropathies. Retrieved from Rheumatology Netwrok website: https://www.rheumatologynetwork.com/view/decision-making-upper-extremity-entrapment-neuropathies

Silver, J. (2004). What is an EMG? In L. Weiss, J. Silver, & J. Weiss (Eds.), *Easy EMG* (pp. 1–4). Philadelphia, USA: Elsevier Inc.

Silverstein, B. A., Fan, Z. J., Bonauto, D. K., Bao, S., Caroline, K., Howard, N., … September, N. (2010). The natural course of carpal tunnel syndrome in a working population. *Scand J Work Environ Health*, *35*(5), 384–393.

Solomon, D. H., Katz, J. N., Bohn, R., Mogun, H., & Avorn, J. (1999). Nonoccupational risk factors for carpal tunnel syndrome. *Journal of General Internal Medicine*, *14*(5), 310–314. https://doi.org/10.1046/j.1525-1497.1999.00340.x

Stetson, D. S., Albers, J. W., Barbara, A., & Wolfe, R. A. (1992). Effects of age, sex, and anthropometric factors on nerve conduction measures. *Muscle & Nerve*, *15*, 1095–1104.

Stevens, J. C. (1987). AAEE Minimonograph #26: The Electrodiagnosis of Carpal Tunnel Syndrome. *Muscle & Nerve*, *10*, 99–113.

Taylor Moore, J., Cigularov, K. P., Sampson, J. M., Rosecrance, J., & Chen, P. Y. (2013). Construction workers' reasons for not reporting work-related injuries: An exploratory study. *International Journal of Occupational Safety and Ergonomics*, *19*(1), 97–105. https://doi.org/10.1080/10803548.2013.11076969

U.S. Bureau of Labor Statistics. (2019a). *2018 Survey of Occupational Injuries and Illnesses*. Retrieved from https://www.bls.gov/iif/soii-charts-2018.pdf

U.S. Bureau of Labor Statistics. (2019b). Survey of Occupational Injuries and Illnesses Data. Retrieved January 20, 2021, from https://www.bls.gov/iif/soii-data.htm

U.S. Equal Employment Opportunity Commission. (2013). *Fabricut to Pay $50,000 to Settle EEOC Disability and Genetic Information Discrimination Lawsuit: Federal Agency Files First Suit Enforcing Genetic Discrimination Law Against Fabric Distributor That Requested Family Medical History, Refused to Hire Woman.* Retrieved from https://www.eeoc.gov/newsroom/fabricut-pay-50000-settle-eeoc-disability-and-genetic-information-discrimination-lawsuit

Valls-Sole, J., Leote, J., & Pereira, P. (2016). Antidromic vs orthodromic sensory median nerve conduction studies. *Clinical Neurophysiology Practice*, *1*, 18–25. https://doi.org/10.1016/j.cnp.2016.02.004

Violante, F. S., Bonfiglioli, R., Isolani, L., & Raffi, G. B. (2004). Levels of agreement of nerve conduction studies and symptoms in workers at risk of carpal tunnel syndrome. *International Archives of Occupational and Environmental Health*, *77*(8), 552–558. https://doi.org/10.1007/s00420-004-0563-9

Violante, F. S., Farioli, A., Graziosi, F., Marinelli, F., Curti, S., Armstrong, T. J., … Bonfiglioli, R. (2016). Carpal tunnel syndrome and manual work: the OCTOPUS cohort, results of a ten-year longitudinal study. *Scandinavian Journal of Work, Environment & Health*, *42*(4), 280–290. https://doi.org/10.5271/sjweh.3566

Waldmann, E. (2018). Quantile regression: A short story on how and why. *Statistical Modelling*, *18*(3–4), 203–218. https://doi.org/10.1177/1471082X18759142

Weiss, L. (2004a). Carpal Tunnel Syndrome. In L. Weiss, J. Silver, & J. Weiss (Eds.), *Easy EMG2* (pp. 121–125). Philadelphia, USA: Elsevier Inc.

Weiss, L. (2004b). Injury to Peripheral Nerves. In L. Weiss, J. Silver, & J. Weiss (Eds.), *Easy EMG* (pp. 81–86). Philadelphia, USA: Elsevier Inc.

Weiss, L., Weiss, J., Pobre, T., & Kalman, A. (2004). Nerve Conduction Studies. In L. Weiss, J. Silver, & J. Weiss (Eds.), *Easy EMG* (pp. 17–39). Philadelphia, USA: Elsevier Inc.

Werner, R. (2006). Evaluation of work-related carpal tunnel syndrome. *Journal of Occupational Rehabilitation*, *16*(2), 207–222. https://doi.org/10.1007/s10926-006-9026-3

Werner, R., & Andary, M. (2011). Electrodiagnostic evaluation of carpal tunnel syndrome. *Muscle and Nerve*, *44*(4), 597–607. https://doi.org/10.1002/mus.22208

Werner, R., Franzblau, A., Albers, J. W., & Armstrong, T. J. (1997). Influence of body mass index and work activity on the prevalence of median mononeuropathy at the wrist. *Occupational and Environmental Medicine*, *54*(4), 268–271. https://doi.org/10.1136/oem.54.4.268

Werner, R., Franzblau, A., Gell, N., Hartigan, A. G., Ebersole, M., & Armstrong, T. J. (2005). Incidence of carpal tunnel syndrome among automobile assembly workers and assessment of risk factors. *Journal of Occupational and Environmental Medicine*, *47*(10), 1044–1050. https://doi.org/10.1097/01.jom.0000171065.17288.a0

Werner, R., Gell, N., Franzblau, A., & Armstrong, T. J. (2001). Prolonged median sensory latency as a predictor of future carpal tunnel syndrome. *Muscle and Nerve*, *24*(11), 1462–1467. https://doi.org/10.1002/mus.1169

Zambelis, T., Tsivgoulis, G., & Karandreas, N. (2010). Carpal tunnel syndrome: Associations between risk factors and laterality. *European Neurology*, *63*(1), 43–47. https://doi.org/10.1159/000268165

Zou, G. Y. (2012). Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. *Statistics in Medicine*, *31*(29), 3972–3981. https://doi.org/10.1002/sim.5466

Appendix A: Components of the action potential.

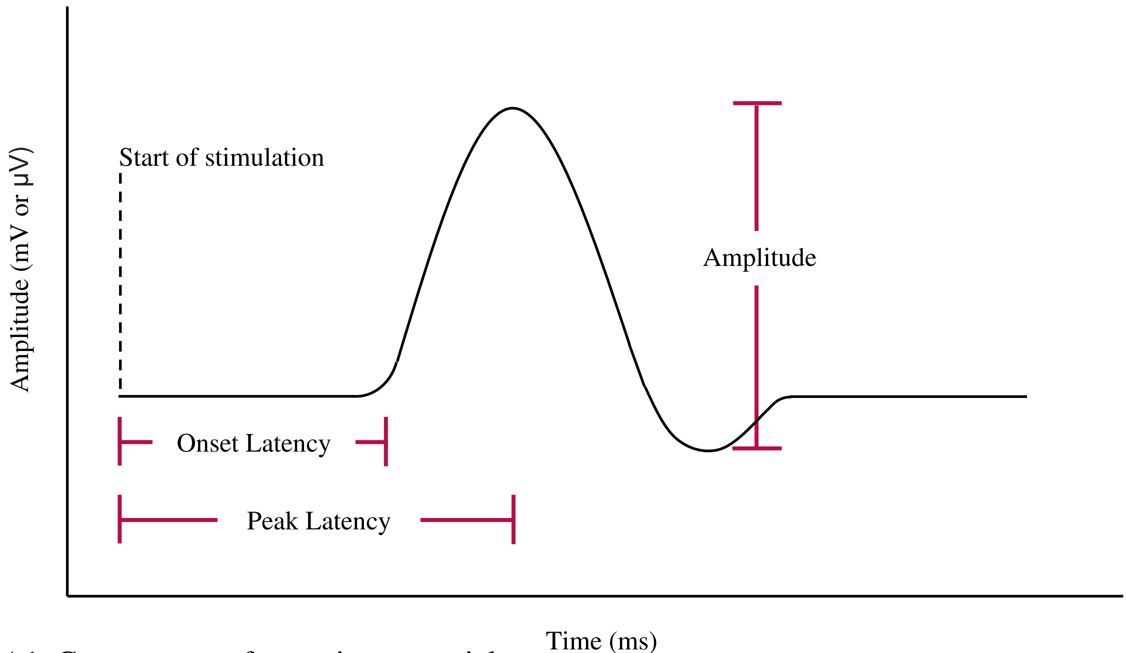


Figure A1. Components of an action potential.

Appendix B: Data Collection Sheet Example – 8 cm Orthodromic NCS

9/18/07 10:30:47 AM

Facility -1

Employee: Last, First
Age: 38 year
Height: 72"
Weight: 221
Gender: Male
Nurse: TERESA
Right Temp: 32
Left Temp: 32

Handedness: Right
[ ] Yes [X] No ---------- **Diabetes?**
[ ] Yes [X] No ---------- **Thyroid Disease?**

Please indicate "YES" or "NO"

[ ] Yes [X] No ---------- **Have you ever broken your hand or wrist?**
[ ] Right [ ] Left Date:
[ ] Yes [X] No---------- **Have you ever had carpal tunnel syndrome?**
[ ] Right [ ] Left Date:
[ ] Yes [X] No---------- **Have you ever had carpal tunnel surgery?**
[ ] Right [ ] Left Date:
[ ] Yes [X] No---------- **Have you ever had any hand or wrist surgery?**
[ ] Right [ ] Left Date:

[ ] Yes [X] No -------- **HAVE YOU EVER HAD numbness or tingling in your hands or fingers?**
[ ] RIGHT [ ] LEFT

SYMPTOM LOCATION - RIGHT
[ ] Palm [ ] Back [ ] Fingertips
[ ] thumb [ ] index [ ] long [ ] ring [ ] little
[ ] Severity of tingling or numbness on a scale of 1 to 10 *(1=Very little, 10=Severe)*

When was the last time you had numbness or tingling in you hands?
How long HAVE YOU HAD the numbness or tingling in your hands?

SYMPTOM LOCATION - LEFT
[ ] Palm [ ] Back [ ] Fingertips
[ ] thumb [ ] index [ ] long [ ] ring [ ] little
[ ] Severity of tingling or numbness on a scale of 1 to 10 *(1=Very little, 10=Severe)*

When was the last time you had numbness or tingling in you hands?
How long HAVE YOU HAD the numbness or tingling in your hands?

[ ] Yes [X] No --- **Are you currently having any pain in your hands?**
[ ] Right [ ] Left
[ ] Yes [X] No --- **Do you wake up with numbness or tingling in your hands or fingers?**
[ ] Right [ ] Left
[ ] Yes [X] No --- **Do any activities increase your hand pain, numbness, or tingling?**
[ ] Right [ ] Left
If Yes, what activity make it worse?

COMMENTS:

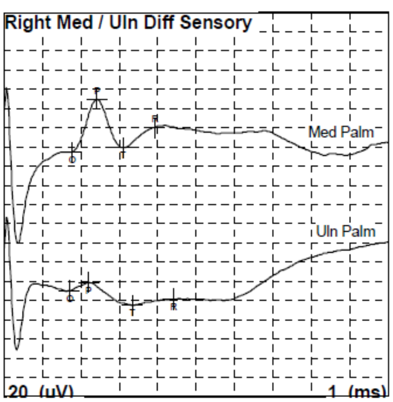
ELECTROPHYSIOLOGIC RESULTS:

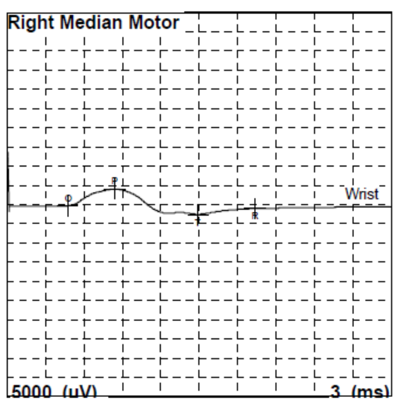
Motor Nerves

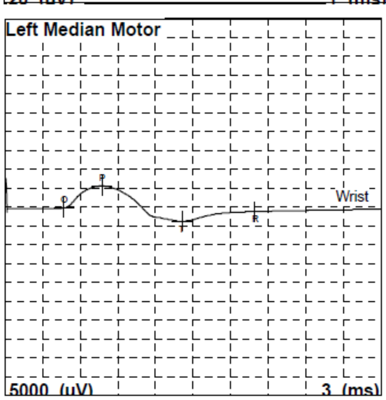
Site	NR	Onset (ms)	Norm Onset (ms)	O-P Amp (mV)	Norm Amp (mV)	Neg Dur (ms)	Segment Name	Delta-O (ms)	Dist (cm)	Vel (m/s)	Norm Vel (m/s)
Right Median (Abd Poll Brev)											
Wrist		4.78	<4.7	4.29	>5.0	6.42					
Left Median (Abd Poll Brev)											
Wrist		4.69	<4.7	5.82	>5.0	6.38					

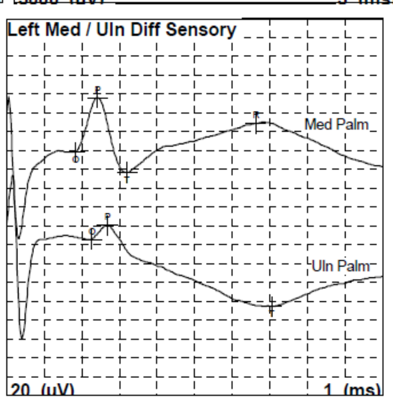
Sensory Nerves

Site	NR	Peak (ms)	Norm Peak (ms)	P-T Amp (µV)	Norm Amp (µV)	Segment Name	Delta-P (ms)	Dist (cm)	Vel (m/s)	Norm Vel (m/s)
Right Med / Uln Diff (Palm)										
Med Palm		2.42		50.24		Med Palm-Uln Palm	0.22	8 cm		
Uln Palm		2.20		23.41						
Left Med / Uln Diff (Palm)										
Med Palm		2.42		79.84		Med Palm-Uln Palm	-0.27	8 cm		
Uln Palm		2.69		86.55						









Appendix C: Data Collection Sheet Example – 14 cm Antidromic NCS

6/4/2015 10:08:46 AM

Facility 1

TEAM MEMBER:
Height: 65
Sex: Female
Age: 19 year
R-TEMP: 33 **L-TEMP:** 33
Handedness: RIGHT

DOB:1/16/1996
NURSE:MARCIE
Weight:97

****

HAVE YOU EVER HAD numbness or tingling in your hands or fingers?
[ ] Yes [X] No
[ ] RIGHT [ ] LEFT

SYMPTOM LOCATION - RIGHT
[ ] Palm [ ] Back [ ] Fingertips
[ ] thumb [ ] index [ ] long [ ] ring [ ] little
* Severity of tingling or numbness on a scale of 1 to 10 *(1=Very little, 10=Severe):*
* When was the last time you had numbness or tingling in your hands?:
* How long (months / years) have you had these symptoms?:

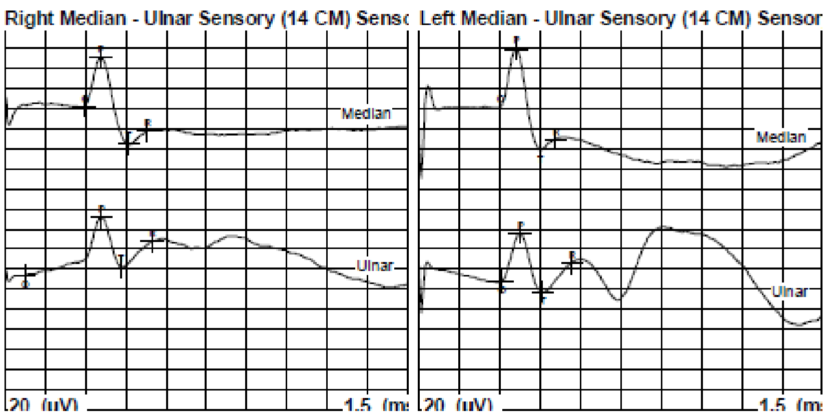
SYMPTOM LOCATION - LEFT
[ ] Palm [ ] Back [ ] Fingertips
[ ] thumb [ ] index [ ] long [ ] ring [ ] little
* Severity of tingling or numbness on a scale of 1 to 10 *(1=Very little, 10=Severe):*
* When was the last time you had numbness or tingling in your hands?:
* How long (months / years) have you had these symptoms?:

COMMENTS:

ELECTROPHYSIOLOGIC SCREENING RESULTS
14 cm Antidromic Sensory Latentcies (D2 to D5 Comparison)
7 cm Median Motor Latency (if preformed)

Sensory Nerves

Site	NR	Peak (ms)	Norm Peak (ms)	P-T Amp (µV)	Norm Amp (µV)	Segment Name	Delta-P (ms)	Dist (cm)
Right Median - Ulnar Sensory (14 CM) (2nd and 5th Digits)								
Median		3.59	<3.6	86.26	>10.0	Median-Ulnar	-0.02	
Ulnar		3.61	<3.6	50.32	>10.0			
Left Median - Ulnar Sensory (14 CM) (2nd and 5th Digits)								
Median		3.61	<3.6	100.11	>10.0	Median-Ulnar	-0.14	
Ulnar		3.75	<3.6	58.00	>10.0			



Appendix D: Sample sizes across age distribution categories

Table D1. Sample sizes across age distribution categories for all workers, those without comorbid conditions, and those with comorbid conditions.

	8 cm Orthodromic			**14 cm Antidromic**		
Age Category	**All Workers**	**Without Comorbid Conditions**	**With Comorbid Conditions**	**All Workers**	**Without Comorbid Conditions**	**With Comorbid Conditions**
19 - 29	7,023	5,796	1,227	2,455	2,324	131
30 - 39	2,714	2,088	626	1,214	1,088	126
40 - 49	1,945	1,384	561	718	630	88
50 - 59	861	586	275	334	286	48
≥ 60	124	85	39	88	75	13
Total	12,667	9,939	2,728	4,809	4,403	406

Appendix E: Distributions of the nerve conduction outcomes

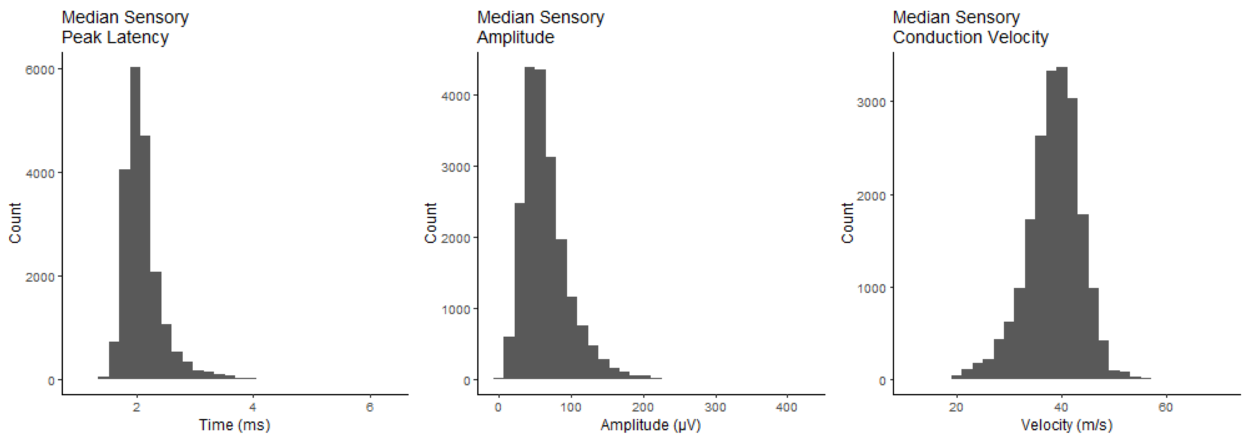


Figure E1. Distribution of the 8 cm orthodromic median sensory nerve conduction outcomes. The distributions of the nerve conduction outcomes were typically right skewed which is consistent with other physiologic data and observations from previous researchers (Dorfman & Robinson, 1997).

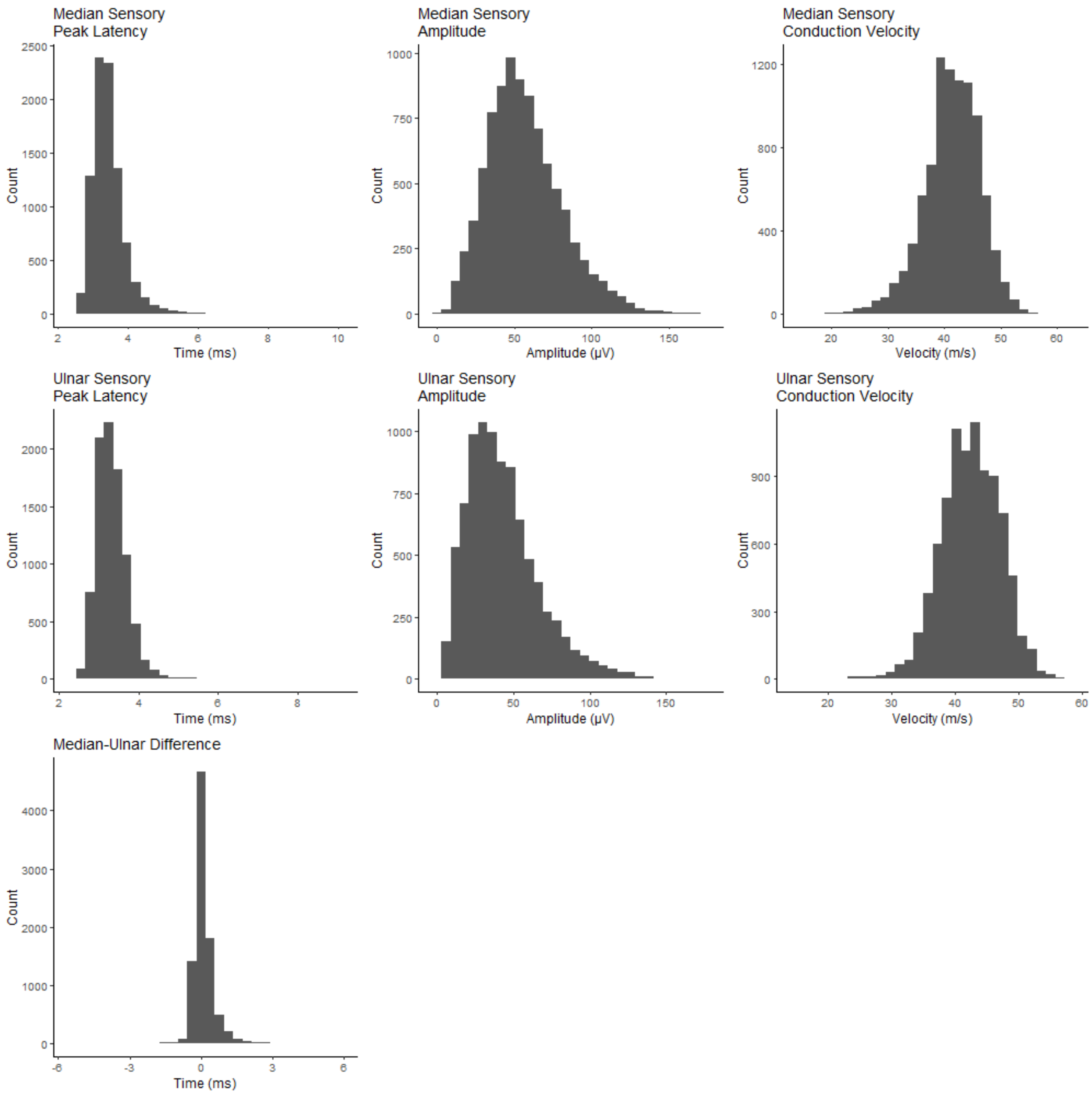


Figure E2. Distribution of the 14 cm orthodromic median and ulnar sensory nerve conduction outcomes. The distributions of the nerve conduction outcomes were typically right skewed which is consistent with other physiologic data and observations from previous researchers (Dorfman & Robinson, 1997).

Appendix F: Pairwise correlations between covariates.

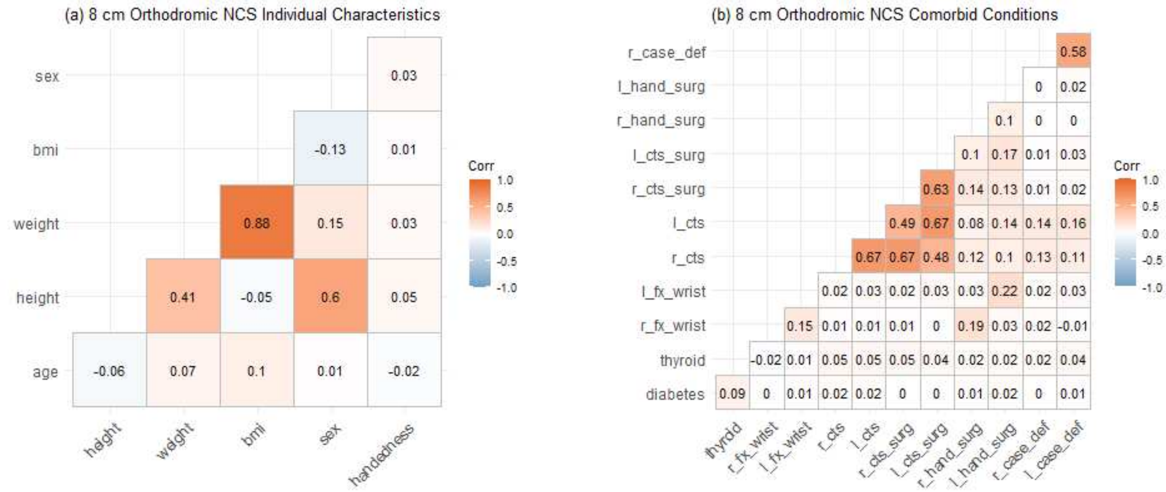


Figure F1. Pairwise correlation coefficients for (a) individual characteristics and (b) comorbid conditions included in the 8 cm orthodromic NCS screening questionnaire.

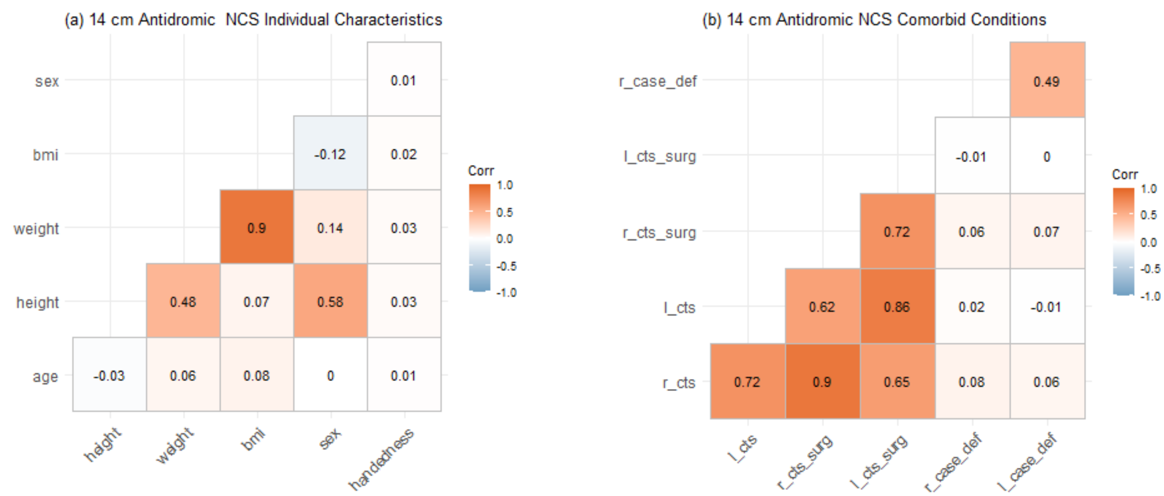


Figure F2. Pairwise correlation coefficients for (a) individual characteristics and (b) comorbid conditions included in the 14 cm antidromic screening questionnaire.

Appendix G: Data voiding example

ELECTROPHYSIOLOGIC SCREENING RESULTS

14 cm Antidromic Sensory Latentcies (D2 to D5 Comparison)

7 cm Median Motor Latency (if preformed)

Sensory Nerves

Site	NR	Peak (ms)	Norm Peak (ms)	P-T Amp (µV)	Norm Amp (µV)	Segment Name	Delta-P (ms)	Dist (cm)	Vel (m/s)
Right Median-Ulnar Sensory (14cm) (2nd and 5th Digis)									
Median		3.3	<3	65	>	Median-Ulnar			
		5	.6	.4	10.0		0.09		
Ulnar		3.2	<3	46	>				
		6	.6	.1	10.0				
Left Median-Ulnar Sensory (14cm) (2nd and 5th Digis)									
Median		3.2	<3	35	>	Median-Ulnar			
		1	.6	.9	10.0		0.31		
Ulnar		2.9	<3	~~13~~	>				
		1	.6	~~0.86~~	10.0				

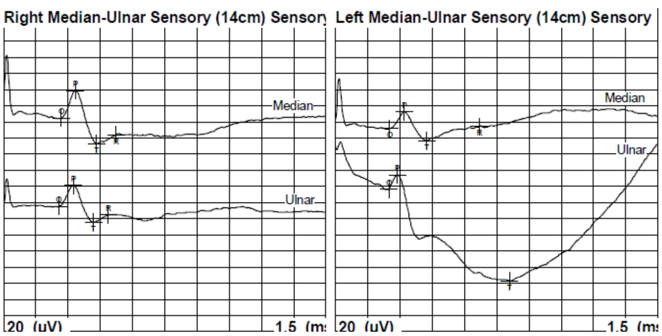


Figure G1. An image from the original NCS screening results. The left ulnar sensory amplitude (red horizontal line) was voided due to a high signal-to-noise ratio.

Appendix H: Intraclass correlation coefficient table.

Table H1. Intraclass correlation coefficients for the orthodromic and antidromic datasets.

	Orthodromic Dataset (N^a Raters = 4)			Antidromic Dataset (N* Raters = 5)		
		95% Confidence Interval			95% Confidence Interval	
Variable	**ICC**	**Lower Bound**	**Upper Bound**	**ICC**	**Lower Bound**	**Upper Bound**
Date	0.99	0.99	0.99	0.99	0.989	0.994
Age	0.99	0.99	0.99	0.99	0.989	0.994
Height (inches)	0.89	0.85	0.92	0.98	0.978	0.988
Weight (pounds)	0.98	0.98	0.99	0.99	0.99	0.99
Sex	0.99	0.985	0.99	1.00	1.00	1.00
Right Wrist Temperature	0.997	0.997	0.998	1.00	1.00	1.00
Left Wrist Temperature	1.00	1.00	1.00	1.00	1.00	1.00
Handedness	1.00	1.00	1.00	1.00	1.00	1.00
Diabetes	1.00	1.00	1.00	-	-	-
Thyroid	1.00	1.00	1.00	-	-	-
Right Hand/Wrist Fracture	0.98	0.97	0.98	-	-	-
Left Hand/Wrist Fracture	0.93	0.91	0.95	-	-	-
Right CTS	1.00	1.00	1.00	0.97[c]	0.97	0.97
Left CTS	1.00	1.00	1.00	0.98[c]	0.98	0.98
Right CTS Surgery	1.00	1.00	1.00	0.98[c]	0.98	0.98
Left CTS Surgery	1.00	1.00	1.00	1.00[c]	1.00	1.00
Right Hand/Wrist Surgery	0.80[b]	0.75	0.85	-	-	-
Left Hand/Wrist Surgery	0.91	0.88	0.93	-	-	-
Right Numbness/Tingling	1.00	1.00	1.00	0.98	0.97	0.98
Left Numbness/Tingling	1.00	1.00	1.00	0.97	0.95	0.98
Right Hand Thumb	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Index	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Long	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Ring	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Little	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Last Time Symptoms	1.00	1.00	1.00	1.00	1.00	1.00
Right Hand Symptom Duration (months)	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Thumb	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Index	1.00	1.00	1.00	1.00	1.00	1.00

	Orthodromic Dataset (N[a] Raters = 4)			Antidromic Dataset (N* Raters = 5)		
		95% Confidence Interval			95% Confidence Interval	
Variable	**ICC**	**Lower Bound**	**Upper Bound**	**ICC**	**Lower Bound**	**Upper Bound**
Left Hand Long	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Ring	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Little	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Last Time Symptoms	1.00	1.00	1.00	1.00	1.00	1.00
Left Hand Symptom Duration (months)	1.00	1.00	1.00	1.00	1.00	1.00
Right Median Sensory Peak Latency	0.999	0.999	0.999	0.999	0.999	0.999
Right Median Sensory Amplitude	0.999	0.999	0.999	0.99	0.99	0.99
Right Ulnar Sensory Peak Latency	-	-	-	0.97	0.96	0.98
Right Ulnar Sensory Amplitude	-	-	-	0.99	0.99	0.99
Left Median Sensory Peak Latency	0.96	0.95	0.97	0.99	0.99	0.99
Left Median Sensory Amplitude	0.99	0.997	0.998	0.99	0.99	0.99
Left Ulnar Sensory Peak Latency	-	-	-	0.99	0.98	0.99
Left Ulnar Amplitude	-	-	-	0.99	0.99	0.99
Comments	-	-	-	0.88[d]	0.85	0.91

[a] N = Total number of raters evaluated.
[b] The investigator randomly sampled 25 entries to review from the orthodromic dataset that had reported "1" for right hand/wrist surgery. The investigator found 100% accuracy in coding "1" for right hand/wrist surgery for the random sample of 25 original PDFs reviewed.
[c] The antidromic dataset right CTS, left CTS, right CTS surgery, and left CTS surgery were coded from the comments item (total comments reviewed = 429). Right CTS, left CTS, right CTS surgery, and left CTS surgery were coded by two coders. All inconsistencies (n = 4) between the two coders were reviewed and/or reconciled by the investigator.
[d] The investigator reviewed the errors in the comments item (data type = character). There were 7 errors in the comments item (out of 500 entries). Three errors were missing data. Four errors were spelling mistakes.

Appendix I: Summary of linear quantile mixed models for the nerve conduction outcomes for a range of quantiles.

Table I1. Summary of parameter estimates from the linear quantile mixed models for 8 cm orthodromic median sensory peak latency (Hands = 19,215) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**1.912**	**1.963**	**2.344**	**1.905**	**2.088**	**1.684**	**1.694**
(95% CI)	(0.562, 3.262)	(0.442, 3.483)	(1.359, 3.328)	(1.015, 2.795)	(1.204, 2.972)	(1.103, 2.264)	(0.277, 3.11)
SE	0.681	0.766	0.496	0.448	0.445	0.293	0.714
Age							
Estimate	**0.006**	**0.006**	**0.006**	**0.009**	**0.011**	**0.011**	**0.012**
(95% CI)	(0.004, 0.009)	(0.003, 0.009)	(0.003, 0.01)	(0.006, 0.012)	(0.008, 0.014)	(0.009, 0.014)	(0.009, 0.016)
SE	0.001	0.001	0.002	0.002	0.002	0.001	0.002
Sex (Male=1)							
Estimate	**0.013**	**0.052**	**0.088**	**0.072**	**0.102**	**0.062**	**0.119**
(95% CI)	(-0.07, 0.097)	(-0.045, 0.15)	(-0.112, 0.287)	(-0.071, 0.215)	(0.038, 0.167)	(-0.022, 0.147)	(0.000, 0.237)
SE	0.042	0.049	0.100	0.072	0.032	0.043	0.060
Height							
Estimate	**0.005**	**0.003**	**0.000**	**0.002**	**0.001**	**0.002**	**0.002**
(95% CI)	(-0.001, 0.012)	(-0.004, 0.01)	(-0.01, 0.01)	(-0.007, 0.011)	(-0.003, 0.005)	(0, 0.005)	(-0.004, 0.009)
SE	0.003	0.003	0.005	0.005	0.002	0.001	0.003
BMI							
Estimate	**0.000**	**0.000**	**0.001**	**0.004**	**0.007**	**0.011**	**0.012**
(95% CI)	(-0.005, 0.005)	(-0.006, 0.005)	(-0.006, 0.007)	(-0.003, 0.01)	(0.003, 0.011)	(0.007, 0.014)	(0.006, 0.017)
SE	0.003	0.003	0.003	0.003	0.002	0.002	0.003
Temp							
Estimate	**-0.036**	**-0.026**	**-0.019**	**-0.018**	**-0.018**	**-0.015**	**-0.017**
(95% CI)	(-0.095, 0.024)	(-0.09, 0.038)	(-0.076, 0.038)	(-0.071, 0.035)	(-0.041, 0.006)	(-0.032, 0.002)	(-0.057, 0.024)
SE	0.030	0.032	0.029	0.027	0.012	0.009	0.02
Hand (ND=1)							
Estimate	**-0.009**	**-0.005**	**-0.002**	**-0.004**	**-0.012**	**-0.003**	**-0.002**
(95% CI)	(-0.034, 0.015)	(-0.017, 0.007)	(-0.039, 0.035)	(-0.034, 0.026)	(-0.035, 0.01)	(-0.013, 0.007)	(-0.014, 0.011)
SE	0.012	0.006	0.019	0.015	0.011	0.005	0.006

Table I2. Summary of parameter estimates from the linear quantile mixed models for the 8 cm orthodromic median sensory amplitude (Hands = 19,156) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**140.0**	**159.0**	**138.1**	**145.0**	**166.9**	**167.0**	**182.2**
(95% CI)	(114.2, 165.8)	(124.9, 193.2)	(111.7, 164.5)	(120.1, 169.7)	(139.9, 194.0)	(142.2, 191.9)	(149.0, 215.4)
SE	13.01	17.20	13.30	12.50	13.65	12.52	16.75
Age							
Estimate	**-0.385**	**-0.373**	**-0.439**	**-0.521**	**-0.442**	**-0.486**	**-0.517**
(95% CI)	(-0.476, -0.295)	(-0.469, -0.277)	(-0.502, -0.375)	(-0.579, -0.463)	(-0.653, -0.230)	(-0.678, -0.293)	(-0.684, -0.349)
SE	0.046	0.048	0.032	0.029	0.107	0.097	0.085
Sex (Male=1)							
Estimate	**-3.133**	**-3.005**	**-5.014**	**-6.729**	**-8.621**	**-8.971**	**-5.449**
(95% CI)	(-5.780, -0.487)	(-5.390, -0.620)	(-6.561, -3.467)	(-8.465, -4.994)	(-12.487, -4.755)	(-14.821, -3.121)	(-11.704, 0.807)
SE	1.334	1.202	0.780	0.875	1.948	2.948	3.153
Height							
Estimate	**-0.089**	**-0.143**	**0.039**	**0.039**	**-0.065**	**0.036**	**-0.016**
(95% CI)	(-0.187, 0.010)	(-0.262, -0.023)	(-0.022, 0.100)	(-0.064, 0.141)	(-0.247, 0.117)	(-0.143, 0.214)	(-0.239, 0.206)
SE	0.050	0.060	0.031	0.052	0.092	0.09	0.112
BMI							
Estimate	**-0.515**	**-0.567**	**-0.534**	**-0.594**	**-0.664**	**-0.854**	**-0.743**
(95% CI)	(-0.659, -0.371)	(-0.705, -0.429)	(-0.631, -0.438)	(-0.699, -0.488)	(-0.888, -0.439)	(-1.161, -0.546)	(-1.115, -0.372)
SE	0.073	0.069	0.049	0.053	0.113	0.155	0.187
Temp							
Estimate	**-1.821**	**-2.071**	**-1.978**	**-1.648**	**-1.314**	**-1.258**	**-1.510**
(95% CI)	(-2.555, -1.087)	(-2.976, -1.165)	(-2.759, -1.198)	(-2.245, -1.051)	(-2.157, -0.471)	(-2.281, -0.234)	(-2.951, -0.07)
SE	0.37	0.456	0.393	0.301	0.425	0.516	0.726
Hand (ND=1)							
Estimate	**2.709**	**2.921**	**3.149**	**3.534**	**3.969**	**4.408**	**4.206**
(95% CI)	(1.596, 3.822)	(2.114, 3.728)	(2.533, 3.765)	(2.943, 4.125)	(3.143, 4.795)	(2.92, 5.897)	(2.828, 5.584)
SE	0.561	0.407	0.31	0.298	0.416	0.750	0.694

Table I3. Summary of parameter estimates from the linear quantile mixed models for the 8 cm orthodromic median sensory conduction velocity (Hands = 19,215) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**53.49**	**40.32**	**42.44**	**42.01**	**45.20**	**50.20**	**51.37**
(95% CI)	(46.61, 60.37)	(34.22, 46.43)	(37.72, 47.16)	(36.82, 47.21)	(39.59, 50.81)	(45.29, 55.12)	(46.73, 56.02)
SE	3.469	3.075	2.379	2.618	2.826	2.476	2.341
Age							
Estimate	**-0.157**	**-0.178**	**-0.161**	**-0.156**	**-0.148**	**-0.154**	**-0.150**
(95% CI)	(-0.189, -0.126)	(-0.208, -0.148)	(-0.187, -0.136)	(-0.175, -0.137)	(-0.168, -0.128)	(-0.173, -0.134)	(-0.17, -0.129)
SE	0.016	0.015	0.013	0.009	0.010	0.01	0.010
Sex (Male=1)							
Estimate	**-1.012**	**-0.881**	**-1.314**	**-1.273**	**-1.063**	**-1.028**	**-1.186**
(95% CI)	(-1.834, -0.191)	(-1.806, 0.045)	(-1.805, -0.822)	(-1.766, -0.78)	(-1.707, -0.419)	(-1.669, -0.386)	(-1.864, -0.508)
SE	0.414	0.466	0.248	0.248	0.325	0.323	0.342
Height							
Estimate	**-0.033**	**-0.045**	**-0.053**	**-0.042**	**-0.053**	**-0.085**	**-0.079**
(95% CI)	(-0.068, 0.003)	(-0.084, -0.005)	(-0.073, -0.032)	(-0.071, -0.014)	(-0.078, -0.028)	(-0.102, -0.067)	(-0.108, -0.05)
SE	0.018	0.020	0.01	0.015	0.013	0.009	0.015
BMI							
Estimate	**-0.139**	**-0.106**	**-0.093**	**-0.051**	**-0.084**	**-0.033**	**-0.038**
(95% CI)	(-0.201, -0.078)	(-0.146, -0.065)	(-0.143, -0.044)	(-0.085, -0.016)	(-0.123, -0.045)	(-0.076, 0.010)	(-0.073, -0.002)
SE	0.031	0.020	0.025	0.017	0.020	0.022	0.018
Temp							
Estimate	**-0.095**	**0.364**	**0.372**	**0.332**	**0.351**	**0.379**	**0.319**
(95% CI)	(-0.327, 0.136)	(0.173, 0.555)	(0.257, 0.486)	(0.209, 0.456)	(0.211, 0.492)	(0.241, 0.517)	(0.151, 0.488)
SE	0.117	0.096	0.058	0.062	0.071	0.069	0.085
Hand (ND=1)							
Estimate	**-0.067**	**0.157**	**0.116**	**0.126**	**0.130**	**0.004**	**-0.054**
(95% CI)	(-0.248, 0.113)	(-0.024, 0.338)	(0.043, 0.189)	(0.055, 0.197)	(0.056, 0.204)	(-0.152, 0.160)	(-0.202, 0.095)
SE	0.091	0.091	0.037	0.036	0.037	0.078	0.075

Table I4. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic median sensory nerve peak latency (Hands = 8,640) for a range of quantiles.

Variable	**2.5th Percentile**	**5th Percentile**	**25th Percentile**	**50th Percentile**	**75th Percentile**	**95th Percentile**	**97.5th Percentile**
Intercept							
Estimate	**4.877**	**4.596**	**5.120**	**4.308**	**5.069**	**5.038**	**5.821**
(95% CI)	(3.823, 5.932)	(3.604, 5.589)	(4.465, 5.775)	(3.375, 5.241)	(4.418, 5.72)	(3.76, 6.317)	(4.292, 7.35)
SE	0.532	0.500	0.33	0.470	0.328	0.644	0.771
Age							
Estimate	**0.010**	**0.010**	**0.011**	**0.014**	**0.012**	**0.019**	**0.015**
(95% CI)	(0.007, 0.013)	(0.007, 0.012)	(0.008, 0.013)	(0.012, 0.015)	(0.008, 0.015)	(0.014, 0.023)	(0.01, 0.02)
SE	0.001	0.001	0.001	0.001	0.002	0.002	0.003
Sex (Male=1)							
Estimate	**0.025**	**0.071**	**0.050**	**0.066**	**0.061**	**0.147**	**0.080**
(95% CI)	(-0.07, 0.12)	(-0.029, 0.171)	(-0.002, 0.102)	(0.012, 0.121)	(-0.021, 0.142)	(0.010, 0.283)	(-0.053, 0.214)
SE	0.048	0.05	0.026	0.027	0.041	0.069	0.067
Height							
Estimate	**0.007**	**0.004**	**0.004**	**0.005**	**0.006**	**0.003**	**0.000**
(95% CI)	(0.000, 0.014)	(-0.001, 0.010)	(0.002, 0.006)	(0.002, 0.008)	(0.003, 0.009)	(-0.002, 0.008)	(-0.006, 0.007)
SE	0.004	0.003	0.001	0.002	0.002	0.003	0.003
BMI							
Estimate	**-0.001**	**-0.002**	**-0.002**	**0.003**	**0.002**	**0.006**	**0.005**
(95% CI)	(-0.005, 0.003)	(-0.005, 0.002)	(-0.005, 0.001)	(-0.001, 0.006)	(-0.005, 0.009)	(-0.001, 0.013)	(0.000, 0.011)
SE	0.002	0.002	0.001	0.002	0.004	0.004	0.003
Temp							
Estimate	**-0.098**	**-0.076**	**-0.086**	**-0.071**	**-0.094**	**-0.084**	**-0.087**
(95% CI)	(-0.137, -0.060)	(-0.096, -0.057)	(-0.105, -0.068)	(-0.091, -0.052)	(-0.112, -0.075)	(-0.13, -0.039)	(-0.129, -0.045)
SE	0.019	0.010	0.009	0.010	0.009	0.023	0.021
Hand (ND=1)							
Estimate	**-0.027**	**-0.022**	**-0.024**	**-0.030**	**-0.027**	**-0.027**	**-0.035**
(95% CI)	(-0.047, -0.007)	(-0.038, -0.007)	(-0.034, -0.015)	(-0.039, -0.022)	(-0.037, -0.017)	(-0.05, -0.005)	(-0.061, -0.01)
SE	0.010	0.008	0.005	0.004	0.005	0.011	0.013

Table I5. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic median sensory nerve amplitude (Hands = 8,564) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**175.8**	**159.4**	**179.7**	**193.4**	**220.6**	**229.6**	**210.0**
(95% CI)	(141.5, 210.2)	(122.5, 196.3)	(155.4, 203.9)	(176.6, 210.2)	(191.5, 249.8)	(195.9, 263.4)	(177.0, 243.1)
SE	17.33	18.60	12.22	8.485	14.68	17.01	16.66
Age							
Estimate	**-0.585**	**-0.59**0	**-0.562**	**-0.659**	**-0.629**	**-0.643**	**-0.677**
(95% CI)	(-0.718, -0.452)	(-0.721, -0.46)	(-0.627, -0.498)	(-0.716, -0.603)	(-0.716, -0.541)	(-0.865, -0.421)	(-0.872, -0.481)
SE	0.067	0.066	0.033	0.029	0.044	0.112	0.099
Sex (Male=1)							
Estimate	**-4.508**	**-2.459**	**-2.514**	**-4.383**	**-4.247**	**-7.574**	**-6.657**
(95% CI)	(-9.851, 0.836)	(-7.096, 2.178)	(-4.703, -0.325)	(-6.081, -2.685)	(-7.77, -0.724)	(-11.55, -3.594)	(-11.479, -1.834)
SE	2.693	2.337	1.103	0.856	1.775	2.006	2.431
Height							
Estimate	**0.029**	**-0.101**	**-0.114**	**-0.127**	**-0.293**	**-0.214**	**-0.238**
(95% CI)	(-0.158, 0.216)	(-0.302, 0.101)	(-0.219, -0.010)	(-0.197, -0.057)	(-0.456, -0.129)	(-0.375, -0.053)	(-0.454, -0.022)
SE	0.094	0.102	0.053	0.035	0.083	0.081	0.109
BMI							
Estimate	**-0.390**	**-0.404**	**-0.369**	**-0.425**	**-0.455**	**-0.505**	**-0.516**
(95% CI)	(-0.65, -0.129)	(-0.61, -0.198)	(-0.494, -0.243)	(-0.521, -0.33)	(-0.549, -0.361)	(-0.753, -0.257)	(-0.765, -0.266)
SE	0.131	0.104	0.063	0.048	0.048	0.125	0.126
Temp							
Estimate	**-3.477**	**-2.269**	**-2.717**	**-2.573**	**-2.212**	**-2.531**	**-1.720**
(95% CI)	(-4.586, -2.368)	(-3.067, -1.47)	(-3.228, -2.205)	(-3.027, -2.12)	(-2.879, -1.545)	(-3.609, -1.453)	(-3.120, -0.320)
SE	0.559	0.402	0.258	0.229	0.336	0.543	0.705
Hand (ND=1)							
Estimate	**2.331**	**2.505**	**3.314**	**3.913**	**4.532**	**5.302**	**5.525**
(95% CI)	(0.676, 3.985)	(1.138, 3.871)	(2.632, 3.996)	(3.302, 4.525)	(3.627, 5.436)	(3.847, 6.756)	(3.599, 7.452)
SE	0.834	0.689	0.344	0.308	0.456	0.733	0.971

Table I6. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic median sensory nerve conduction velocity (Hands = 8,640) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**25.81**	**30.20**	**26.30**	**25.83**	**24.00**	**26.91**	**25.54**
(95% CI)	(21.02, 30.61)	(24.36, 36.04)	(20.11, 32.46)	(20.48, 31.19)	(18.28, 29.72)	(21.44, 32.38)	(19.90, 31.17)
SE	2.415	2.945	3.112	2.699	2.882	2.759	2.839
Age							
Estimate	**-0.137**	**-0.159**	**-0.160**	**-0.149**	**-0.126**	**-0.150**	**-0.130**
(95% CI)	(-0.177, -0.096)	(-0.191, -0.126)	(-0.196, -0.124)	(-0.165, -0.133)	(-0.16, -0.091)	(-0.179, -0.122)	(-0.171, -0.088)
SE	0.020	0.017	0.018	0.008	0.018	0.015	0.021
Sex (Male=1)							
Estimate	**-0.658**	**-0.543**	**-0.665**	**-0.641**	**-0.699**	**-0.094**	**-0.293**
(95% CI)	(-1.767, 0.451)	(-1.76, 0.674)	(-1.546, 0.217)	(-1.158, -0.124)	(-1.391, -0.007)	(-1.023, 0.835)	(-0.991, 0.405)
SE	0.559	0.613	0.444	0.26	0.349	0.468	0.352
Height							
Estimate	**-0.030**	**-0.028**	**-0.069**	**-0.050**	**-0.043**	**-0.085**	**-0.104**
(95% CI)	(-0.068, 0.008)	(-0.066, 0.011)	(-0.096, -0.041)	(-0.071, -0.029)	(-0.069, -0.017)	(-0.12, -0.051)	(-0.135, -0.072)
SE	0.019	0.019	0.014	0.011	0.013	0.017	0.016
BMI							
Estimate	**-0.038**	**-0.052**	**-0.028**	**-0.012**	**0.014**	**0.013**	**0.023**
(95% CI)	(-0.096, 0.02)	(-0.108, 0.003)	(-0.075, 0.019)	(-0.043, 0.019)	(-0.033, 0.061)	(-0.029, 0.055)	(-0.024, 0.069)
SE	0.029	0.028	0.024	0.015	0.024	0.021	0.024
Temp							
Estimate	**0.72**0	**0.620**	**0.991**	**0.920**	**0.935**	**1.13**	**1.246**
(95% CI)	(0.491, 0.949)	(0.416, 0.824)	(0.828, 1.155)	(0.758, 1.081)	(0.768, 1.102)	(0.927, 1.333)	(1.035, 1.458)
SE	0.116	0.103	0.082	0.081	0.084	0.102	0.107
Hand (ND=1)							
Estimate	**0.226**	**0.302**	**0.397**	**0.345**	**0.316**	**0.346**	**0.301**
(95% CI)	(-0.046, 0.499)	(0.049, 0.555)	(0.274, 0.52)	(0.243, 0.448)	(0.183, 0.448)	(0.147, 0.546)	(0.093, 0.508)
SE	0.137	0.128	0.062	0.052	0.067	0.101	0.105

Table I7. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic ulnar sensory peak latency (Hands = 8,640) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**5.212**	**5.011**	**6.183**	**5.502**	**5.623**	**6.014**	**6.213**
(95% CI)	(4.309, 6.116)	(3.874, 6.147)	(5.404, 6.962)	(4.992, 6.011)	(5.070, 6.175)	(4.68, 7.347)	(4.768, 7.659)
SE	0.455	0.573	0.393	0.257	0.278	0.672	0.728
Age							
Estimate	**0.006**	**0.006**	**0.006**	**0.007**	**0.008**	**0.012**	**0.013**
(95% CI)	(0.004, 0.008)	(0.004, 0.009)	(0.004, 0.007)	(0.006, 0.008)	(0.006, 0.010)	(0.008, 0.016)	(0.008, 0.018)
SE	0.001	0.001	0.001	0.001	0.001	0.002	0.002
Sex (Male=1)							
Estimate	**0.041**	**0.031**	**0.058**	**0.066**	**0.067**	**0.155**	**0.112**
(95% CI)	(-0.037, 0.12)	(-0.044, 0.106)	(0.004, 0.112)	(0.036, 0.096)	(0.011, 0.123)	(0.033, 0.276)	(-0.001, 0.224)
SE	0.04	0.038	0.027	0.015	0.028	0.061	0.057
Height							
Estimate	**0.004**	**0.007**	**0.004**	**0.004**	**0.004**	**0.003**	**0.005**
(95% CI)	(-0.001, 0.009)	(0.002, 0.012)	(0.001, 0.007)	(0.003, 0.006)	(0.002, 0.006)	(0.000, 0.006)	(0.001, 0.009)
SE	0.003	0.003	0.001	0.001	0.001	0.002	0.002
BMI							
Estimate	**-0.012**	**-0.011**	**-0.011**	**-0.010**	**-0.011**	**-0.008**	**-0.010**
(95% CI)	(-0.016, -0.008)	(-0.014, -0.008)	(-0.014, -0.009)	(-0.013, -0.008)	(-0.014, -0.008)	(-0.013, -0.002)	(-0.017, -0.003)
SE	0.002	0.002	0.001	0.001	0.001	0.003	0.003
Temp							
Estimate	**-0.084**	**-0.091**	**-0.110**	**-0.090**	**-0.090**	**-0.100**	**-0.115**
(95% CI)	(-0.118, -0.051)	(-0.12, -0.063)	(-0.134, -0.086)	(-0.101, -0.078)	(-0.105, -0.075)	(-0.14, -0.061)	(-0.154, -0.075)
SE	0.017	0.014	0.012	0.006	0.008	0.020	0.020
Hand (ND=1)							
Estimate	**0.000**	**-0.012**	**-0.006**	**0.001**	**0.002**	**0.017**	**0.025**
(95% CI)	(-0.019, 0.018)	(-0.029, 0.004)	(-0.016, 0.004)	(-0.006, 0.008)	(-0.009, 0.012)	(-0.005, 0.038)	(-0.003, 0.053)
SE	0.009	0.008	0.005	0.003	0.005	0.011	0.014

Table I8. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic ulnar sensory amplitude (Hands = 8,628) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**168.8**	**193.6**	**189.3**	**212.4**	**243.4**	**240.3**	**234.6**
(95% CI)	(142.2, 195.5)	(158.0, 229.2)	(170.0, 208.6)	(195.5, 229.3)	(218.9, 267.9)	(197.7, 282.9)	(213.1, 256.1)
SE	13.42	17.95	9.734	8.532	12.37	21.49	10.84
Age							
Estimate	**-0.426**	**-0.445**	**-0.460**	**-0.505**	**-0.458**	**-0.517**	**-0.512**
(95% CI)	(-0.527, -0.324)	(-0.536, -0.354)	(-0.51, -0.41)	(-0.547, -0.463)	(-0.543, -0.373)	(-0.656, -0.377)	(-0.654, -0.371)
SE	0.051	0.046	0.025	0.021	0.043	0.071	0.071
Sex (Male=1)							
Estimate	**-3.197**	**-4.196**	**-4.663**	**-5.849**	**-8.304**	**-6.990**	**-9.249**
(95% CI)	(-6.708, 0.315)	(-6.675, -1.716)	(-6.253, -3.073)	(-7.126, -4.572)	(-10.43, -6.175)	(-11.792, -2.188)	(-13.813, -4.684)
SE	1.770	1.250	0.801	0.644	1.073	2.420	2.301
Height							
Estimate	**-0.384**	**-0.271**	**-0.311**	**-0.367**	**-0.431**	**-0.372**	**-0.421**
(95% CI)	(-0.509, -0.259)	(-0.434, -0.108)	(-0.385, -0.236)	(-0.436, -0.299)	(-0.508, -0.355)	(-0.519, -0.225)	(-0.546, -0.297)
SE	0.063	0.082	0.037	0.035	0.039	0.074	0.063
BMI							
Estimate	**-0.268**	**-0.352**	**-0.470**	**-0.586**	**-0.673**	**-0.773**	**-0.795**
(95% CI)	(-0.422, -0.114)	(-0.500, -0.204)	(-0.547, -0.394)	(-0.655, -0.517)	(-0.781, -0.566)	(-1.055, -0.49)	(-1.019, -0.571)
SE	0.077	0.075	0.038	0.035	0.054	0.142	0.113
Temp							
Estimate	**-1.855**	**-3.049**	**-2.345**	**-2.301**	**-2.504**	**-2.308**	**-1.767**
(95% CI)	(-2.760, -0.950)	(-3.831, -2.266)	(-2.813, -1.878)	(-2.658, -1.945)	(-3.157, -1.850)	(-3.538, -1.079)	(-2.677, -0.858)
SE	0.456	0.394	0.236	0.180	0.329	0.620	0.458
Hand (ND=1)							
Estimate	**2.514**	**2.423**	**2.215**	**2.610**	**2.651**	**3.149**	**3.666**
(95% CI)	(1.368, 3.66)	(1.122, 3.723)	(1.509, 2.92)	(2.024, 3.196)	(1.756, 3.546)	(1.227, 5.071)	(1.753, 5.578)
SE	0.578	0.656	0.356	0.295	0.451	0.969	0.964

Table I9. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic ulnar sensory conduction velocity (Hands = 8,640) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept *Estimate* *(95% CI)* *SE*	**18.61** (14.47, 22.74) 2.083	**16.43** (12.43, 20.44) 2.018	**15.08** (10.84, 19.32) 2.137	**18.25** (13.66, 22.85) 2.314	**15.94** (12.14, 19.74) 1.915	**16.16** (12.04, 20.27) 2.075	**16.55** (12.25, 20.85) 2.166
Age *Estimate* *(95% CI)* *SE*	**-0.105** (-0.139, -0.072) 0.017	**-0.116** (-0.142, -0.089) 0.013	**-0.099** (-0.120, -0.078) 0.010	**-0.081** (-0.104, -0.059) 0.011	**-0.072** (-0.095, -0.049) 0.012	**-0.083** (-0.11, -0.057) 0.013	**-0.080** (-0.107, -0.054) 0.013
Sex (Male=1) *Estimate* *(95% CI)* *SE*	**-1.021** (-2.03, -0.012) 0.509	**-1.310** (-2.282, -0.338) 0.490	**-0.449** (-1.100, 0.201) 0.328	**-0.952** (-1.351, -0.553) 0.201	**-0.537** (-1.084, 0.009) 0.275	**-0.311** (-0.938, 0.316) 0.316	**-0.340** (-1.014, 0.333) 0.340
Height *Estimate* *(95% CI)* *SE*	**-0.031** (-0.072, 0.011) 0.021	**-0.042** (-0.081, -0.003) 0.020	**-0.062** (-0.088, -0.036) 0.013	**-0.067** (-0.084, -0.05) 0.008	**-0.080** (-0.101, -0.059) 0.011	**-0.078** (-0.102, -0.054) 0.012	**-0.086** (-0.111, -0.061) 0.013
BMI *Estimate* *(95% CI)* *SE*	**0.106** (0.054, 0.158) 0.026	**0.099** (0.052, 0.145) 0.023	**0.126** (0.092, 0.160) 0.017	**0.154** (0.124, 0.184) 0.015	**0.162** (0.139, 0.186) 0.012	**0.165** (0.123, 0.206) 0.021	**0.166** (0.130, 0.202) 0.018
Temp *Estimate* *(95% CI)* *SE*	**0.862** (0.643, 1.082) 0.111	**1.020** (0.822, 1.218) 0.100	**1.141** (1.012, 1.269) 0.065	**1.076** (0.939, 1.212) 0.069	**1.232** (1.115, 1.349) 0.059	**1.265** (1.116, 1.414) 0.075	**1.296** (1.131, 1.462) 0.084
Hand (ND=1) *Estimate* *(95% CI)* *SE*	**-0.076** (-0.360, 0.209) 0.143	**-0.127** (-0.34, 0.087) 0.108	**-0.065** (-0.188, 0.059) 0.062	**-0.049** (-0.144, 0.046) 0.048	**0.128** (0.009, 0.247) 0.06	**0.003** (-0.239, 0.245) 0.122	**-0.041** (-0.338, 0.257) 0.150

Table I10. Summary of parameter estimates from the linear quantile mixed models for 14 cm antidromic sensory MUD (Hands = 8,588) for a range of quantiles.

Variable	2.5th Percentile	5th Percentile	25th Percentile	50th Percentile	75th Percentile	95th Percentile	97.5th Percentile
Intercept							
Estimate	**-0.277**	**-0.951**	**-0.579**	**-0.294**	**-0.641**	**-0.589**	**-0.066**
(95% CI)	(-1.392, 0.839)	(-2.052, 0.149)	(-1.425, 0.268)	(-0.733, 0.145)	(-1.232, -0.049)	(-1.252, 0.074)	(-0.904, 0.773)
SE	0.562	0.555	0.426	0.221	0.298	0.334	0.423
Age							
Estimate	**0.001**	**0.000**	**0.003**	**0.006**	**0.007**	**0.009**	**0.011**
(95% CI)	(-0.002, 0.004)	(-0.003, 0.004)	(0.001, 0.004)	(0.004, 0.007)	(0.004, 0.009)	(0.005, 0.013)	(0.007, 0.015)
SE	0.002	0.002	0.001	0.001	0.001	0.002	0.002
Sex (Male=1)							
Estimate	**0.000**	**-0.057**	**-0.009**	**-0.007**	**-0.007**	**0.027**	**0.034**
(95% CI)	(-0.174, 0.175)	(-0.165, 0.051)	(-0.046, 0.028)	(-0.039, 0.024)	(-0.066, 0.052)	(-0.126, 0.180)	(-0.251, 0.319)
SE	0.088	0.055	0.019	0.016	0.030	0.077	0.143
Height							
Estimate	**-0.002**	**0.000**	**-0.001**	**-0.001**	**0.000**	**-0.001**	**-0.003**
(95% CI)	(-0.012, 0.007)	(-0.006, 0.007)	(-0.004, 0.001)	(-0.003, 0.000)	(-0.002, 0.002)	(-0.006, 0.005)	(-0.012, 0.006)
SE	0.005	0.003	0.001	0.001	0.001	0.003	0.005
BMI							
Estimate	**0.008**	**0.006**	**0.011**	**0.012**	**0.015**	**0.014**	**0.018**
(95% CI)	(0.002, 0.014)	(0.001, 0.011)	(0.008, 0.013)	(0.009, 0.014)	(0.012, 0.019)	(0.008, 0.021)	(0.011, 0.025)
SE	0.003	0.003	0.001	0.001	0.002	0.003	0.003
Temp							
Estimate	**0.004**	**0.017**	**0.011**	**0.003**	**0.009**	**0.014**	**0.005**
(95% CI)	(-0.051, 0.06)	(-0.033, 0.067)	(-0.007, 0.029)	(-0.007, 0.013)	(-0.006, 0.023)	(-0.018, 0.045)	(-0.049, 0.058)
SE	0.028	0.025	0.009	0.005	0.007	0.016	0.027
Hand (ND=1)							
Estimate	**-0.019**	**-0.020**	**-0.031**	**-0.033**	**-0.034**	**-0.042**	**-0.048**
(95% CI)	(-0.046, 0.009)	(-0.043, 0.003)	(-0.042, -0.021)	(-0.043, -0.023)	(-0.047, -0.021)	(-0.069, -0.016)	(-0.078, -0.018)
SE	0.014	0.012	0.005	0.005	0.006	0.013	0.015

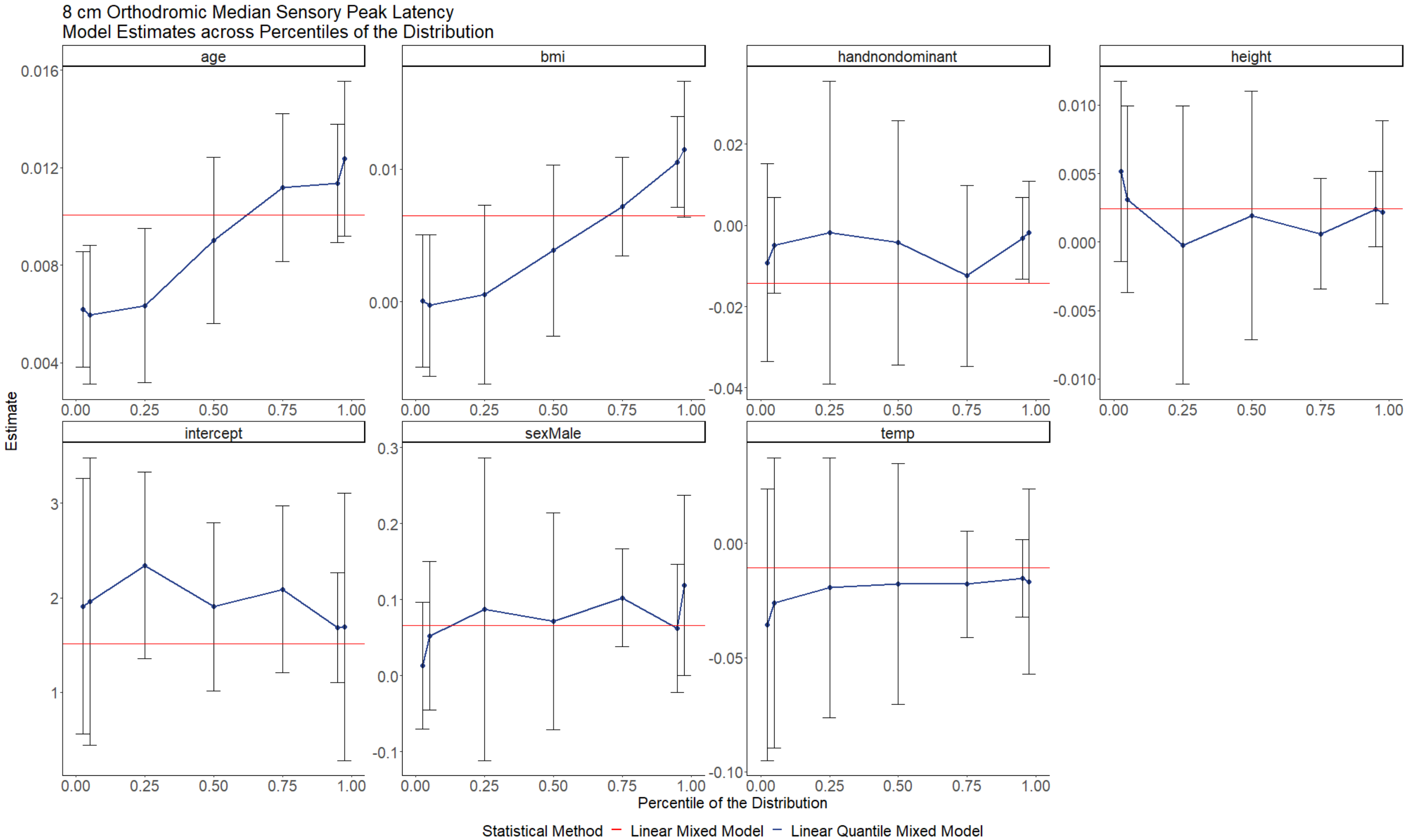


Figure I1. Plot of the range of quantiles versus the model coefficients for 8 cm orthodromic median sensory peak latency. The blue line represents the LQMM model (quantile regression), and the red line represents equivalent linear mixed effects model.

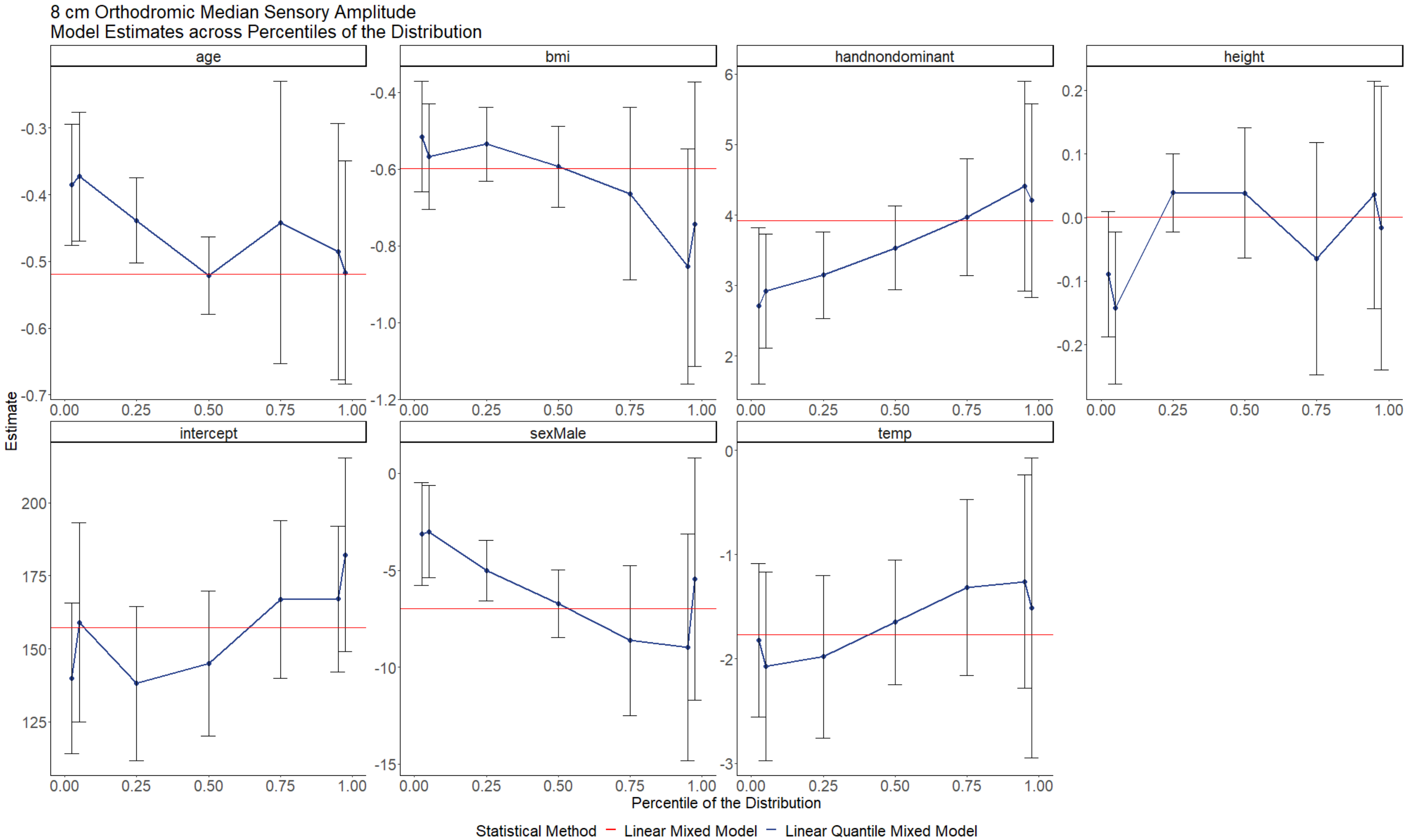


Figure I2. Plot of the range of quantiles versus the model coefficients for 8 cm orthodromic median sensory amplitude. The blue line represents the LQMM model (quantile regression), and the red line represents equivalent linear mixed effects model.

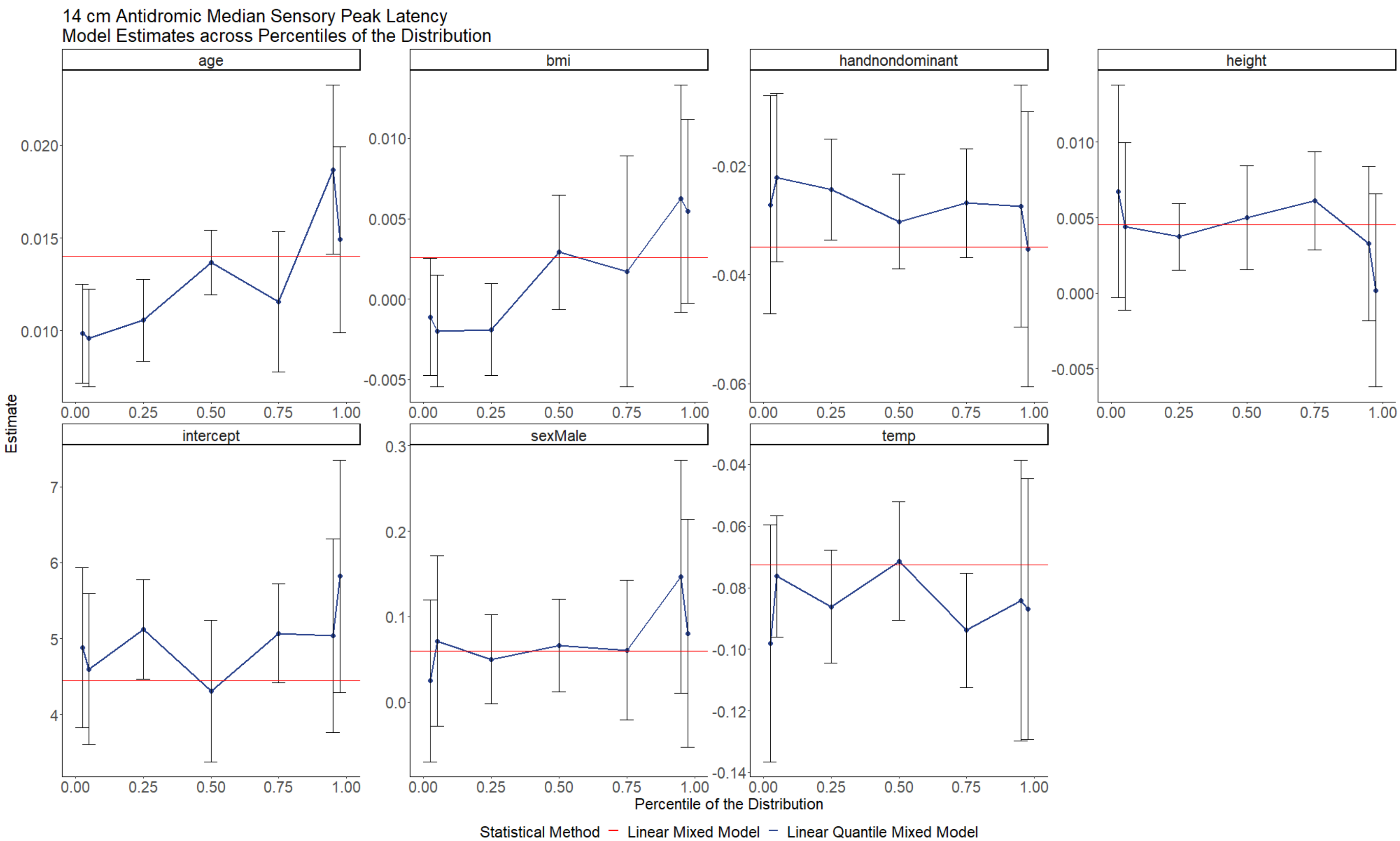


Figure I3. Plot of the range of quantiles versus the model coefficients for 14 cm antidromic median sensory peak latency. The blue line represents the LQMM model (quantile regression), and the red line represents equivalent linear mixed effects model.

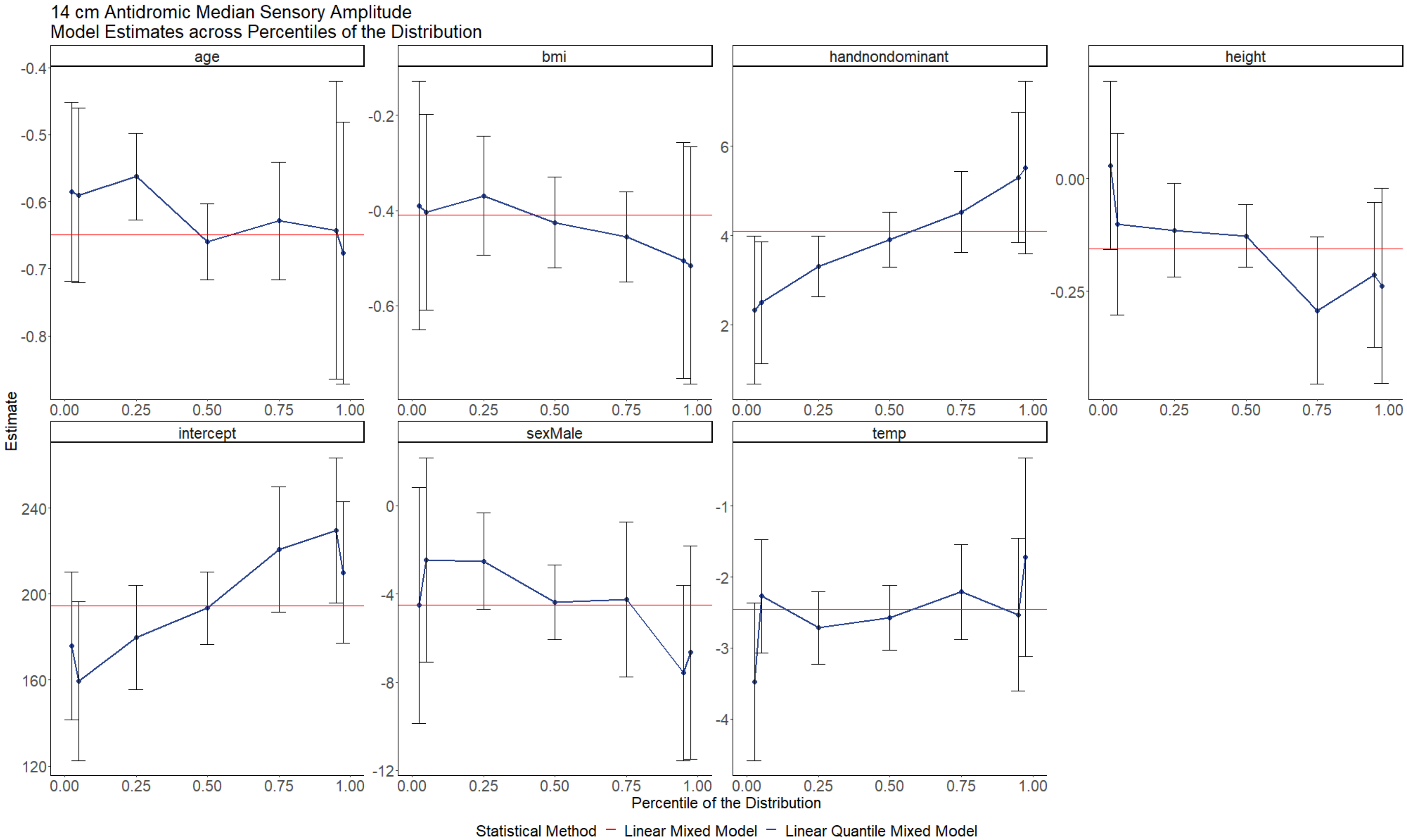


Figure I4. Plot of the range of quantiles versus the model coefficients for 14 cm antidromic median sensory amplitude. The blue line represents the LQMM model (quantile regression), and the red line represents equivalent linear mixed effects model.

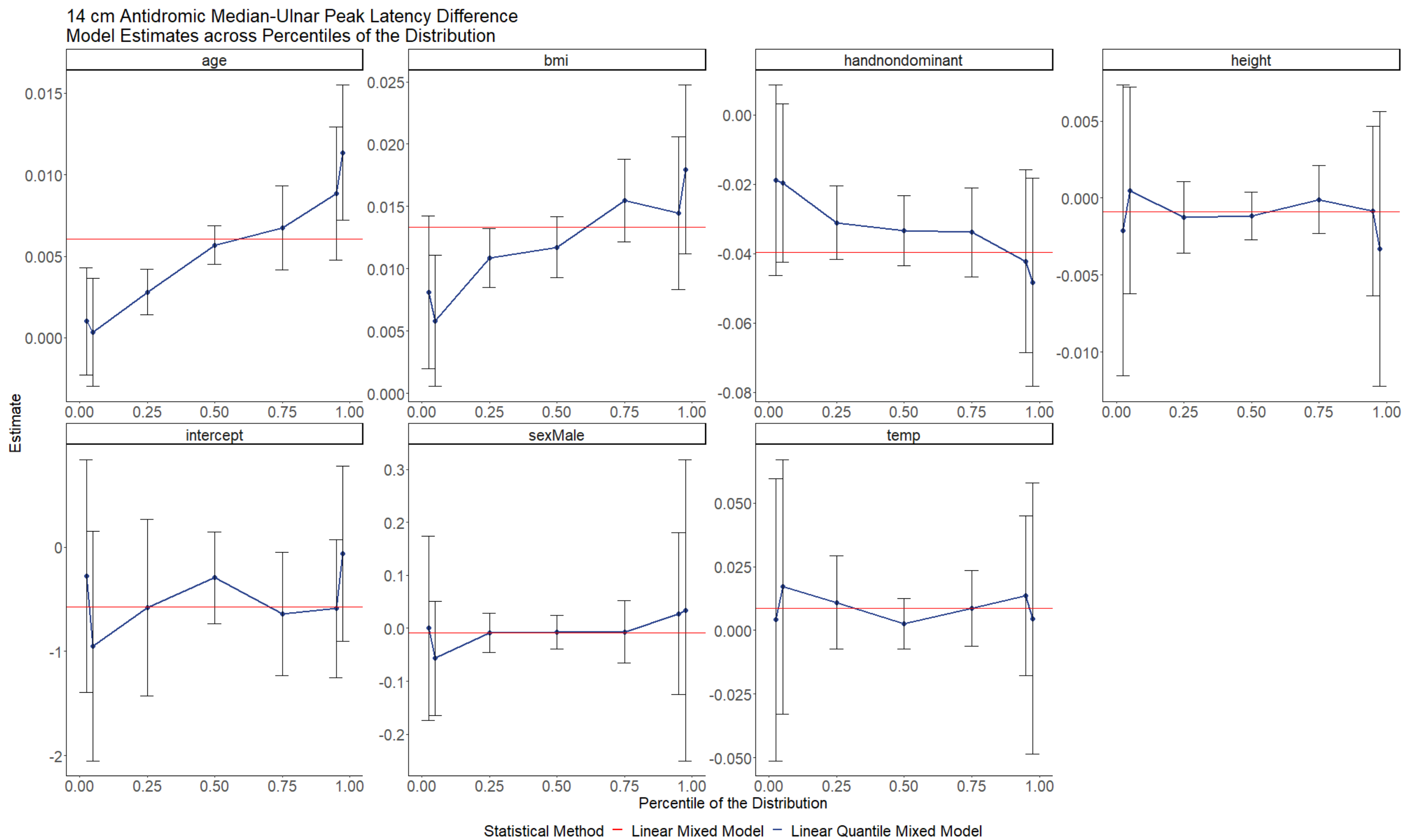


Figure I5. Plot of the range of quantiles versus the model coefficients for 14 cm antidromic difference between the median and ulnar sensory peak latency (MUD). The blue line represents the LQMM model (quantile regression), and the red line represents equivalent linear mixed effects model

Appendix J: Summary of the linear quantile mixed models for nerve conduction outcomes for those with and without comorbidities.

Table J1. Summary of the linear quantile mixed models for the median sensory nerve 5th and 95th Percentiles for the 8 cm orthodromic nerve conduction outcomes with and without comorbidities.

	8 cm Orthodromic Without Comorbidities (Median)			8 cm Orthodromic With Comorbidities (Median)		
Variable	**Peak Latency (95th Percentile)** Hands = 19,215 N = 9,649	**Amplitude (5th Percentile)** Hands = 19,156 N = 9,639	**Conduction Velocity (5th Percentile)** Hands = 19,215 N = 9,649	**Peak Latency (95th Percentile)** Hands = 23,970 N = 12,163	**Amplitude (5th Percentile)** Hands = 24,062 N = 12,144	**Conduction Velocity (5th Percentile)** Hands = 23,970 N = 12,163
Intercept						
Estimate	**1.684*****	**159.0*****	**40.32*****	**1.857*****	**146.0*****	**42.93*****
(95% CI)	(1.103, 2.264)	(124.9, 193.2)	(34.22, 46.43)	(1.581, 2.133)	(123.7, 168.3)	(38.63, 47.23)
SE	0.293	17.202	3.075	0.139	11.24	2.167
Age						
Estimate	**0.011*****	**-0.373*****	**-0.178*****	**0.012*****	**-0.429*****	**-0.176*****
(95% CI)	(0.009, 0.014)	(-0.469, -0.277)	(-0.208, -0.148)	(0.010, 0.014)	(-0.500, -0.358)	(-0.201, -0.15)
SE	0.001	0.048	0.015	0.001	0.036	0.013
Sex (Male=1)						
Estimate	0.062	**-3.005***	-0.881	**0.103*****	**-4.118*****	**-1.662*****
(95% CI)	(-0.022, 0.147)	(-5.39, -0.62)	(-1.806, 0.045)	(0.043, 0.164)	(-5.917, -2.32)	(-2.5, -0.823)
SE	0.043	1.202	0.466	0.030	0.906	0.423
Height						
Estimate	0.002	**-0.143***	**-0.045***	**0.002***	**-0.066**	0.000
(95% CI)	(0, 0.005)	(-0.262, -0.023)	(-0.084, -0.005)	(0.0002, 0.004)	(-0.137, 0.005)	(-0.027, 0.027)
SE	0.001	0.06	0.02	0.001	0.036	0.014
BMI						
Estimate	**0.011*****	**-0.567*****	**-0.106*****	**0.011*****	**-0.423*****	**-0.188*****
(95% CI)	(0.007, 0.014)	(-0.705, -0.429)	(-0.146, -0.065)	(0.008, 0.014)	(-0.531, -0.315)	(-0.234, -0.143)
SE	0.002	0.069	0.020	0.002	0.054	0.023
Temp	-0.015	**-2.071*****	**0.364*****	**-0.022****	**-2.13*****	0.141
Estimate	(-0.032, 0.002)	(-2.976, -1.165)	(0.173, 0.555)	(-0.036, -0.008)	(-2.741, -1.519)	(-0.025, 0.307)

Variable	8 cm Orthodromic Without Comorbidities (Median) Peak Latency (95th Percentile) Hands = 19,215 N = 9,649	Amplitude (5th Percentile) Hands = 19,156 N = 9,639	Conduction Velocity (5th Percentile) Hands = 19,215 N = 9,649	8 cm Orthodromic With Comorbidities (Median) Peak Latency (95th Percentile) Hands = 23,970 N = 12,163	Amplitude (5th Percentile) Hands = 24,062 N = 12,144	Conduction Velocity (5th Percentile) Hands = 23,970 N = 12,163
(95% CI)	0.009	0.456	0.096	0.007	0.308	0.084
SE						
Hand (ND=1)						
Estimate	-0.003	**2.921*** **	0.157	-0.003	**2.976*** **	0.103
(95% CI)	(-0.013, 0.007)	(2.114, 3.728)	(-0.024, 0.338)	(-0.012, 0.007)	(2.23, 3.722)	(-0.061, 0.266)
SE	0.005	0.407	0.091	0.005	0.376	0.082
Diabetes = 1						
Estimate				**0.31*** **	**-7.44** **	**-1.811***
(95% CI)				(0.143, 0.477)	(-12.839, -2.041)	(-3.54, -0.081)
SE	-	-	-	0.084	2.721	0.871
Thyroid = 1						
Estimate				0.129	-4.387	0.664
(95% CI)				(-0.069, 0.326)	(-11.67, 2.896)	(-1.049, 2.376)
SE	-	-	-	0.100	3.671	0.863
Hand/Wrist Fracture = 1						
Estimate				0.007	-0.745	0.475
(95% CI)				(-0.018, 0.031)	(-2.697, 1.207)	(-0.307, 1.256)
SE	-	-	-	0.012	0.984	0.394
CTS = 1						
Estimate				**0.281***	**-7.623** **	-1.408
(95% CI)				(0.014, 0.549)	(-12.482, -2.763)	(-3.326, 0.51)
SE	-	-	-	0.135	2.449	0.967
CTS Surgery = 1				-0.078	6.620	0.920
Estimate				(-0.36, 0.203)	(-0.053, 13.294)	(-1.785, 3.624)
(95% CI)	-	-	-	0.142	3.363	1.363

Variable	8 cm Orthodromic Without Comorbidities (Median)			8 cm Orthodromic With Comorbidities (Median)		
	Peak Latency (95th Percentile) Hands = 19,215 N = 9,649	**Amplitude (5th Percentile)** Hands = 19,156 N = 9,639	**Conduction Velocity (5th Percentile)** Hands = 19,215 N = 9,649	**Peak Latency (95th Percentile)** Hands = 23,970 N = 12,163	**Amplitude (5th Percentile)** Hands = 24,062 N = 12,144	**Conduction Velocity (5th Percentile)** Hands = 23,970 N = 12,163
SE						
Hand/Wrist Surgery = 1						
Estimate				-0.011	-0.004	0.301
(95% CI)				(-0.078, 0.056)	(-2.666, 2.659)	(-0.491, 1.093)
SE	-	-	-	0.034	1.342	0.399
Symptomatic = 1						
Estimate				**0.28****	-3.54	**-4.13*****
(95% CI)				(0.074, 0.485)	(-9.451, 2.371)	(-6.003, -2.257)
SE	-	-	-	0.103	2.979	0.944

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table J2. Summary of the linear quantile mixed models for the median sensory nerve 5th and 95th Percentiles for the 14 cm antidromic nerve conduction outcomes with and without comorbidities.

	14 cm Antidromic Without Comorbidities (Median)			**14 cm Antidromic With Comorbidities (Median)**		
Variable	**Peak Latency (95th Percentile)** Hands = 8,640 N = 4,335	**Amplitude (5th Percentile)** Hands = 8,564 N = 4,323	**Conduction Velocity (5th Percentile)** Hands = 8,640 N = 4,335	**Peak Latency (95th Percentile)** Hands = 9,306 N = 4,684	**Amplitude (5th Percentile)** Hands = 9,218 N = 4,669	**Conduction Velocity (5th Percentile)** Hands = 9,306 N = 4,684
Intercept						
Estimate	**5.038*****	**159.4*****	**30.20*****	**5.451*****	**184.9*****	**23.21*****
(95% CI)	(3.76, 6.317)	(122.5, 196.3)	(24.36, 36.04)	(4.703, 6.199)	(153.0, 216.8)	(17.74, 28.69)
SE	0.644	18.602	2.945	0.377	16.103	2.759
Age						
Estimate	**0.019*****	**-0.590*****	**-0.159*****	**0.016*****	**-0.592*****	**-0.184*****
(95% CI)	(0.014, 0.023)	(-0.721, -0.46)	(-0.191, -0.126)	(0.012, 0.02)	(-0.7, -0.484)	(-0.211, -0.157)
SE	0.002	0.066	0.017	0.002	0.055	0.014
Sex (Male=1)						
Estimate	**0.147***	-2.459	-0.543	0.037	-1.796	**-1.133***
(95% CI)	(0.01, 0.283)	(-7.096, 2.178)	(-1.76, 0.674)	(-0.078, 0.153)	(-5.535, 1.942)	(-2.246, -0.021)
SE	0.069	2.337	0.613	0.058	1.884	0.561
Height						
Estimate	0.003	-0.101	-0.028	0.004	-0.113	-0.011
(95% CI)	(-0.002, 0.008)	(-0.302, 0.101)	(-0.066, 0.011)	(0.000, 0.008)	(-0.259, 0.034)	(-0.047, 0.024)
SE	0.003	0.102	0.019	0.002	0.074	0.018
BMI						
Estimate	0.006	**-0.404*****	-0.052	0.006	**-0.297***	**-0.058***
(95% CI)	(-0.001, 0.013)	(-0.61, -0.198)	(-0.108, 0.003)	(0.000, 0.012)	(-0.576, -0.018)	(-0.109, -0.006)
SE	0.004	0.104	0.028	0.003	0.141	0.026
Temp	**-0.084*****	**-2.269*****	**0.620*****	**-0.096*****	**-3.106*****	**0.777*****
Estimate	(-0.13, -0.039)	(-3.067, -1.47)	(0.416, 0.824)	(-0.116, -0.076)	(-3.96, -2.253)	(0.587, 0.966)

Variable	14 cm Antidromic Without Comorbidities (Median)			14 cm Antidromic With Comorbidities (Median)		
	Peak Latency (95th Percentile) Hands = 8,640 N = 4,335	**Amplitude (5th Percentile)** Hands = 8,564 N = 4,323	**Conduction Velocity (5th Percentile)** Hands = 8,640 N = 4,335	**Peak Latency (95th Percentile)** Hands = 9,306 N = 4,684	**Amplitude (5th Percentile)** Hands = 9,218 N = 4,669	**Conduction Velocity (5th Percentile)** Hands = 9,306 N = 4,684
(95% CI)						
SE	0.023	0.402	0.103	0.010	0.43	0.096
Hand (ND=1)						
Estimate	**-0.027***	**2.505*****	0.302	**-0.026****	**2.873*****	0.175
(95% CI)	(-0.05, -0.005)	(1.138, 3.871)	(0.049, 0.555)	(-0.045, -0.007)	(1.283, 4.462)	(-0.087, 0.437)
SE	0.011	0.689	0.128	0.009	0.801	0.132
CTS = 1						
Estimate	-	-	-	**0.856****	-13.77	-3.381
(95% CI)				(0.252, 1.46)	(-30.721, 3.182)	(-7.641, 0.879)
SE				0.304	8.543	2.147
CTS Surgery = 1						
Estimate	-	-	-	**-0.873***	14.863	**7.284****
(95% CI)				(-1.587, -0.16)	(-5.057, 34.783)	(2.025, 12.543)
SE				0.36	10.039	2.65
Symptomatic = 1						
Estimate	-	-	-	**0.677****	**-6.977*****	**-3.495****
(95% CI)				(0.226, 1.129)	(-13.823, -0.131)	(-5.852, -1.138)
SE				0.227	3.45	1.188

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table J3. Summary of the linear quantile mixed models for the 95th Percentile of the Median-Ulnar Difference for the 14 cm antidromic nerve conduction outcomes with and without comorbidities.

	Without Comorbid Conditions	**With Comorbid Conditions**
Variable	**Median-Ulnar Difference (95th Percentile)** Hands = 8,588 N = 4,333	**Median-Ulnar Difference (95th Percentile)** Hands = 9,239 N = 4,679
Intercept		
Estimate	-0.589	-0.427
(95% CI)	(-1.252, 0.074)	(-0.929, 0.075)
SE	0.334	0.253
Age		
Estimate	**0.009*****	**0.010*****
(95% CI)	(0.005, 0.013)	(0.007, 0.013)
SE	0.002	0.001
Sex (Male = 1)		
Estimate	0.027	0.035
(95% CI)	(-0.126, 0.18)	(-0.053, 0.123)
SE	0.077	0.044
Height		
Estimate	-0.001	-0.003
(95% CI)	(-0.006, 0.005)	(-0.007, 0.000)
SE	0.003	0.002
BMI		
Estimate	**0.014*****	**0.020*****
(95% CI)	(0.008, 0.021)	(0.015, 0.026)
SE	0.003	0.003
Temp		
Estimate	0.014	0.015
(95% CI)	(-0.018, 0.045)	(-0.007, 0.038)
SE	0.016	0.011
Hand (ND =1)		
Estimate	**-0.042****	-0.027
(95% CI)	(-0.069, -0.016)	(-0.054, 0.001)
SE	0.013	0.014
CTS = 1		
Estimate	-	**0.588***
(95% CI)		(0.109, 1.067)
SE		0.242
CTS Surgery = 1		
Estimate	-	-0.324
(95% CI)		(-0.977, 0.33)
SE		0.329
Symptomatic = 1		
Estimate	-	0.344
(95% CI)		(-0.069, 0.756)
SE		0.208

* p < 0.05, ** p < 0.01, *** p < 0.001

Appendix K: Sensitivity analysis

Table K1. Sensitivity and Specificity of symptoms reported during a post-offer pre-placement job screening (97.5th Percentile values).

Technique	Reference	Hand	Confusion Matrix: Symptoms	Reference 0	Reference 1	Sensitivity	Specificity
8 cm Orthodromic	Quantile Regression, 97.5th Percentile Median Sensory Peak Latency, and Ulnar Sensory Peak Latency < 2.3 ms	Dominant	0	9746	1638	2.3%	99.7%
			1	34	39		
		Nondominant	0	9988	1397	2.1%	99.7%
			1	26	30		
14 cm Antidromic	Quantile Regression, 97.5th Percentile Median & Ulnar Sensory Peak Latency	Dominant	0	4080	541	4.6%	99.5%
			1	21	26		
		Nondominant	0	4161	552	2.3%	99.7%
			1	14	13		
	Quantile Regression, 97.5th Percentile MUD	Dominant	0	3790	819	3.5%	99.6%
			1	16	30		
		Nondominant	0	3860	845	1.9 %	99.7%
			1	11	16		

Table K2. Sensitivity and Specificity of symptoms reported during a post-offer pre-placement job screening (75th Percentile values).

Technique	Reference	Hand	Symptoms	Reference 0	Reference 1	Sensitivity	Specificity
8 cm Orthodromic	Quantile Regression, 75th Percentile Median Sensory Peak Latency, and Ulnar Sensory Peak Latency < 2.3 ms	Dominant	0	8900	1986	2.1%	99.7%
			1	30	43		
		Nondominant	0	8941	1796	1.8%	99.8%
			1	20	32		
14 cm Antidromic	Quantile Regression, 75th Percentile Median & Ulnar Sensory Peak Latency	Dominant	0	3896	724	3.3%	99.4%
			1	22	25		
		Nondominant	0	4048	665	2.3%	99.7%
			1	11	16		
	Quantile Regression, 75th Percentile MUD	Dominant	0	3328	1277	2.1%	99.5%
			1	16	28		
		Nondominant	0	3400	1301	1.4 %	99.7%
			1	9	18		