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Carpal Tunnel Syndrome (CTS) represents the most common nerve compression syndrome. Osteopathic Manipulative Therapy (OMT) may be more efficacious in certain populations secondary to demographic variability in CTS etiology and OMT's greater efficacy in addressing certain causations.

A composite score derived from subjective and objective findings in a pilot study, was utilized to assess initial and change of disease severity after OMT in the study population and these subgroups: age, gender, ethnicity, BMI and chronicity.

Trends suggest more severe disease in older patients, women, and whites. OMT results in improvement in composite scores in younger subjects, females, whites, both non-obese and obese subjects and more chronic subjects.

OSTEOPATHIC MANIPULATIVE TREATMENT AND CARPAL TUNNEL SYNDROME: ANALYSIS OF PATHOGENESIS, MECHANISMS OF TREATMENT AND APPLICABILITY TO SPECIFIC AND GENERAL POPULATIONS

THESIS

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THESIS

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CHAPTER 1

INTRODUCTION

Carpal Tunnel Syndrome (CTS) involves compression of the median nerve at the wrist resulting in a cluster of symptoms. Some symptoms are subjective, such as pain in the palmar aspect of the wrist, decreased functionality in the effected hand, and numbness and tingling in the first through medial aspect of the fourth digit. These symptoms often occur at night and are relieved by shaking the hands. Other findings are objective, such as motor weakness and decreased strength in the effected hand. Because the complete CTS process includes all of the above components, an ideal assessment tool of disease severity should address both subjective and objective findings.

In the 1990s, CTS represented the most commonly reported nerve compression syndrome, resulting in over one billion dollars in direct medical costs, and more than 200,000 surgeries, annually.[1,2] These estimates include medical office visits and medical care, but fail to account for millions spent on ergonomic innovations to prevent, decrease, or alleviate this condition. However, certain demographic subsets of the general population may suffer from more severe disease and warrant more aggressive education to curb the trend in the population.

Furthermore, Osteopathic Manipulative Treatment (OMT) may provide a cost-effective adjunct to medical therapy to delay the progression of the disease and the necessity for surgical intervention. While ergonomic changes address external factors contributing to the disease process, they do not address anatomic pathology. Not only does OMT slow the progression of the disease, it potentially, or at least partially, reverses

the process. Given demographic variability in CTS etiology, and manual medicine's greater treatment-efficacy in addressing certain causal factors, OMT-directed treatment might achieve even greater efficacy in certain populations. This is significant from a public health standpoint because it directs education and research efforts towards demographic populations in which OMT will likely be most effective.

Purpose

The first aim of the present study was to utilize data from a pilot study, performed at the Osteopathic Research Center from September 2003 to November 2004 with a sample size of thirty-seven, to create a composite score which encompasses both objective and subjective clinically-assessed findings in CTS. Next, the composite score was used to assess disease severity variances in both demographic factors—age, gender and ethnicity and known CTS risk factors—obesity and time since onset of the disease. Finally, changes in the composite score after treatment in the OMT arm of the study was assessed to determine which groups, based upon the above demographic and risk factors, had a statistically significant change.

Literature Review

Epidemiology of Carpel Tunnel Syndrome

Although the true prevalence of CTS in the United States is unknown, it is estimated that forty million symptomatic individuals with symptoms do not seek professional help.[3] Findings of prevalence studies in Sweden, Italy, and the Netherlands, with larger data sets, corroborate those few done in the U.S.[4,5,6] These studies have found CTS prevalence to be between 0.53 and 16.3% .[7,8,9]

A large number of clinical studies have been conducted which consistently document the demographic characteristics of patients with CTS. CTS may be found in either gender, but it occurs most frequently in women. Examining various prevalence studies, the average female to male ratio was computed to be 3.6:1.[4,5,6,8,9,10] Rosenbaum et al found that nearly 70% of patients with CTS were female and 30% male. Although less frequent in men, CTS is typically more severe in males.[4] In both men and women, disease prevalence peaks between forty and sixty years of age, and is rare before twenty or after eighty years of age.[3] CTS has been found to be 1.8 times more likely to occur in White than in non-White populations. The cause of this racial difference is currently unknown but may include differences in education about the disease and its clinical signs, medical care access for evaluation and treatment and occupation-related reasons.[5,8]

Multiple potential risk factors for CTS have been identified, including female gender, obesity, age greater than thirty years, repetitive motor activity, and the presence of systemic diseases such as diabetes mellitus, rheumatoid arthritis and hypothyroidism. Furthermore, several demographic, physiologic, anatomic, social and occupational

categories have been identified as independent risk factors for CTS including: female gender, obesity (BMI >30), physical inactivity, small carpal tunnel dimensions, cigarette smoking, vibrations associated with job tasks, and age of 40 to 60 years.[11,12] While the literature identifies diabetes mellitus as a risk factor for CTS, further analysis is needed secondary to the relationship between obesity and diabetes mellitus.[10]

In a review of epidemiological studies of external risk factors associated with musculoskeletal problems, Malchaire et al. found occupational factors to include repetitiveness, physical workload, and number of working hours to be statistically significant in more than half of the studies.[13] Support for the relationship between CTS and repetitive work is the finding of a higher prevalence of CTS among workers using excessive wrist or hand motion and force, and an increased frequency of the disease in blue-collar compared to white-collar counterparts.[5]

In the secondary analysis of the CTS study performed at the national Osteopathic Research Center from September 2003 to November 2004 with a sample size of thirty-seven, the following risk factors were available for analysis: age, gender, ethnicity, obesity represented as BMI, and time since diagnosis of CTS. Time since onset of CTS, a surrogate for disease progression, permitted analysis of the quality of the composite score.

Etiologic Variables in the Addressed Risk Factors for Carpal Tunnel Syndrome

In theory, the available demographic and other risk factors should each play a role in the severity of the disease process. Since each factor has potential for varying etiologies, among different subgroups, one would expect different results in disease

severity; such as more advanced disease in older patients. Also, different degrees of change in CTS disease severity in response to OMT would also be expected. For example, decreased response to treatment from males is likely because the etiology in androgenous subjects tends to be primarily external forces, such as ergonomic or occupationally-induced pathology, as opposed to a greater role for physiologic changes in feminine counterparts.

Average disease severity should increase with age. Several plausible theories include: the onset of many CTS-associated conditions and diseases occur later in life, accumulation of multiple disease-forming conditions happens over time (including the accrual of repetitive trauma), and an increased likelihood for greater time since onset of the disease exists. In fact, reality probably involves an amalgam of all of the above conditions. Menopause, renal failure, rheumatoid arthritis, and hypothyroidism have greater prevalence in older populations, and a direct relationship between disease incidence and age.[1] In younger populations, there is more likely to be an anatomic anomaly which may lead to a decreased intra-compartmental space.[14] While increasing the intra-compartmental pressure to some degree, the body may be able to alter fluid balance enough to, at least partially, counteract this source of increased intra-carpal pressure, resulting in milder disease. Furthermore, several prominent conditions that cause CTS in younger patients, pregnancy and eclampsia, are temporary events that do not persist long enough to result in permanent fibrotic changes in the median nerve.[1]

Theoretically, one would expect the average disease severity to be greater in non-White populations than White populations, due to a greater number of anatomical variations and higher-prevalence chronic conditions, which alter fluid balance in non-White populations. The prevalence of palmaris longus, a muscle in the forearm, results in decreased space in the carpal tunnel. The presence of this tendon is a strong independent risk factor for CTS.[15] In addition, the presence of this tendon is more common in non-White populations, suggesting that anatomic variations may play a more significant role in CTS etiology in non-Whites.[16] Furthermore, many secondary conditions such as hypothyroidism and diabetes mellitus, which alter fluid mechanics, are also more common in non-White populations.[1] Finally, a greater percentage of blue collar jobs are performed by non-Whites than Whites—especially with the rise in non-White migrant workers.[5]

While it has been stated that females are more frequently diagnosed, yet males have more severe disease, this data must be qualified. Of the studies mentioned above, only those that measured nerve conduction were utilized to assess disease severity. Furthermore, epidemiological data found fewer men with mild disease and more men with severe or extreme disease than women.[4] This phenomena can be best explained by social-occupational etiologies. Males tend to perform more blue collar jobs that require excessive wrist flexion than females.[5] Several consequences of blue-collar jobs include: often low quality or lack of health insurance coverage, leading workers to seek medical care once the disease has progressed to a more advanced state, lower education requirements, a lack of education concerning ergonomics and symptoms of disease, and

greater physical strain upon the wrists than white-collar workers. If the converse is true and overall disease is more severe in women, then anatomical (i.e. smaller wrist dimensions) and physiologic (i.e. greater changes in fluid balance) etiologies would likely be more prominent.

Finally, BMI is the last risk factor addressed. While it is known to increase the risk for developing CTS in the first place, little is known about its effects upon disease severity. Intuitively, obesity should increase intra-carpal pressures in multiple ways. Adiposity in the carpal region increases the intra-carpal pressure mechanically. Increased adipose tissue surrounding the lymphatic drainage system impedes fluid from exiting the limb as efficiently leading to an alteration in fluid balance. Furthermore, adiposity is also associated with atherosclerosis which results in decreased blood flow to the small vessels that supply the median nerve itself.

Clinical Overview of Carpel Tunnel Syndrome

The most salient distinction, with regard to pathophysiology, diagnosis, and treatment of CTS, occurs between acute and chronic disease. Chronic compression significantly varies from acute neuropathy pertaining to "magnitude, duration, mechanism and consequences." [17] The acute form of the disease involves a brisk and persistent elevation in carpal canal interstitial pressure. This presents in numerous clinical settings that result in rapid swelling or carpal canal fluid accumulation such as supporative infections, hemorrhage or improperly immobilized, distal fracture.[17] First line

therapy still remains antibiotics, surgical decompression, repositioning the immobilized wrist and fracture reduction respectively.

Chronic CTS results from a gradual increase in carpal tunnel interstitial pressure. While this may initially be intermittent, it ultimately remains elevated as the disease progresses resulting in a crescendo of symptoms. Additionally, chronic CTS may be divided further into three subcategories: early, intermediate, and advanced disease.[18] In early disease, symptoms are generally intermittent, mild, and of relatively recent onset—less than one year.[17] There is neither motor impairment nor abnormal electrophysiological tests present in this stage of CTS.[18] Progression to intermediate CTS involves constant numbness and paresthesias, prolonged distal motor latency on nerve conduction studies (NCS), and minimal, if any, thenar atrophy. [17,18] In advanced disease, significant sensory changes exist, more pronounced abnormalities in NCS, as well as both thenar motor weakness and atrophy.[17] Physiologically, diminished nerve function is a result of vascular, metabolic and mechanical compression leading to increased interstitial pressure in the carpal canal. This results in deficiencies in impulse generation and transmission that ultimately leads to clinical symptoms.[17] While the end result is the same, the etiology of this increase in carpal pressure is quite varied.

Even though the vast majority of CTS cases are idiopathic, numerous other causes exist. Michelsen suggests four etiological categories based upon location of the pathologic insult with relation to the carpal tunnel: intrinsic factors, extrinsic factors, exertion/overuse conditions and neuropathic factors.[19] The latter category is not associated with elevated interstitial pressure; a genetic component exists in some cases.[20]

Although the above paradigm assists in creating inclusion and exclusion criteria, an alternative to the Michelsen model may best provide a framework for the role of OMT as a conservative therapy for CTS.

Kerwin classifies conditions based upon the pathologic source of the insult: anatomical, physiologic, or secondary to external forces.[17] While external forces, such as repetitive movements, may cause CTS, anatomic and physiologic changes exemplify the Osteopathic principle of somatic dysfunction. The Glossary of Osteopathic Terminology defines somatic dysfunction as "impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements."[21] The treatment approach to diminishing CTS-causing somatic dysfunction involves three models: Fluid, Musculoskeletal and Neurologic.

The Fluid Model emphasizes the physiologic movement of blood and lymph through the respective arterial, venous, and lymphatic pathways in order to optimize circulation, cellular metabolism, and fluid balance. This model emphasizes the necessity of proper vascular and lymphatic flow in order to optimize circulation, nutrient and waste product exchange, and fluid balance. The Musculoskeletal Model highlights the interrelation between biomechanical structure and function. A change in structure, such as a decrease in carpal canal space from a mal-aligned carpal bone, will increase the intra-carpal pressure and mechanically inhibit optimal nerve conduction. Also, function alterations, such as hormonal changes which alter systemic fluid balance, may ultimately result in median nerve fibrosis and other structural problems associated with chronic

CTS. Finally, the Neurologic Model stresses the role of somatic dysfunction in creating somatic and autonomic neurologic dysregulation. In this model, somatic nerve dysfunction may result from direct impingement of the median nerve itself or secondary to increased carpal pressure. If there is a relative increase in sympathetic tone, lymphatics in the upper extremity will constrict impeding fluid flow away from the canal, further contributing to CTS.[22-26] This increase in sympathetic tone may be secondary to pain or somatic dysfunction in the thoracic spine resulting in a somato-somatic reflex.

The use of OMT to treat CTS applies the Fluid, Musculoskeletal, and Neurologic models to create a treatment regimen aimed at increasing the volume of the carpal tunnel, removing impediments to and promoting venous and lymphatic drainage, facilitating somatic and autonomic neurologic function, and addressing myofascial restriction patterns. This is accomplished by treating somatic dysfunction in areas of the body beyond the wrist, including associated areas of the affected wrist, arm, shoulder, neck and upper back. OMT to the wrist is specifically designed to stretch the transverse carpal ligament thus enlarging the dimensions of the carpal tunnel. The enlarged carpal tunnel should reduce compressive forces on the median nerve to improve its function and reduce the symptoms of carpal tunnel syndrome. Ensuring proper carpal bone alignment also diminishes any component of osseous mass effect in the tunnel.

Treatment of the arm and shoulder aligns joints and reduces patterns of fascial tension such that impediments to central venous and lymphatic fluid return will be reduced, thus restoring flow and reduce edema in the carpal canal. Myofascial pain reduction improves functionality. Peripheral neural entrapment releases permit some

reversal of the pathologic process, although this depends on how far the disease has progressed. OMT to the neck and upper back aligns these musculoskeletal structures such that nerve root and brachial plexus impingements are alleviated and autonomic neural traffic is optimized.

All of these treatments are aimed at improving median nerve conduction, increasing carpal tunnel dimensions, reducing edema, and improving hand and arm function. This optimizes the patient's anatomic and physiologic conditions in order to alter the course of the disease process. At this point, it is warranted to examine previous studies involving various modalities of manual medicine and their role in treating CTS.

Manual Medicine and Carpel Tunnel Syndrome

While research on the use of manual medicine for CTS has been reported as efficacious in some literature, there are too few prospective, randomized, blinded, controlled clinical trials to provide adequate evidence to unequivocally verify this reported efficacy. The studies reported in the literature have used different designs, outcome measures, and interventions to evaluate manual medicine. Also, each study possesses methodologic variations that make creating generalized conclusions difficult. The following is a review of the available literature on manual medicine and its use as a therapy for CTS.

An extensive search of the literature was performed with Ovid MEDLINE and OSTMED® using keywords: osteopathic medicine, manual medicine, manipulation, OMT, and Chiropractic manipulation. In addition, other source material was identified in the references of the literature found in the electronic search. This literature search

revealed a total of eighteen articles, ten osteopathic and eight chiropractic publications, evaluating the efficacy of manual medicine treatments for CTS. Among these eighteen reports there were four abstracts (all osteopathic), seven case reports (three osteopathic and four chiropractic), and seven clinical trials (three osteopathic and four chiropractic).

The earliest identified literature that evaluates the use of manual medicine as a treatment for CTS is found in the chiropractic literature. These articles are single case reports only providing clinical insight and perhaps guidance in future research.[27-30] The largest portion of the literature on CTS and manual medicine is in a series of five osteopathic publications by Sucher et al. These articles include three case reports, two clinical trials, and one abstract. The three articles published as a collection of case reports documented the treatment of CTS with OMT in a total of ten subjects. These reports primarily describe OMT techniques at the wrist and also provide future research guidance.[31-33]

The first article Sucher presented as a clinical study consisted of four experimental groups utilized to compare both OMT and stretching to controls. This study lacked randomization, blinding, and a clear description of methodology resulting in limited external validity.[34] The second clinical study tested the earlier hypothesis that OMT could increase the dimensions of the carpal tunnel. This was accomplished by measuring changes in the diameter of the canal with varying weights and OMT applied to fresh cadaver upper extremities. Research occurred in two parts and was then published first as a full length article followed by an abstract. Even though the study demonstrated that one could stretch the transverse carpal ligament and maintain the new length,

multiple potential confounding variables, including cadaver limb type, weight used, and manipulation use, were not consistently held constant in this study. This makes the change in one cadaver limb difficult to compare to the rest of the limbs; thus, again, limiting full interpretation of results.[35,36]

In addition to Sucher, Ramey et al. evaluated the treatment of CTS with OMT on six subjects using NCS, MRI, pain and distress (PAD) scale, analog pain scale, and wrist range of motion. The results of this study were published in both abstract and full length article form. Complete interpretation of the results is guarded, in spite of the discovery of some benefit, by no control groups, no direct wrist OMT in the protocol, small sample size, and lack of statistical analysis of those patients that did not show improvement.[37,38] Of note, this is one of the few studies where both subjective and objective findings were incorporated in the protocol.

Another osteopathic study, which included a two month follow-up, was conducted by Strait and Huu et al. This study was reported in the literature as two abstracts, but was never published as full length articles. This study involved randomization of 23 subjects into OMT and control groups. While some improvement was shown, no statistical analysis was performed to determine if this result was statistically significant.[39,40]

The earliest chiropractic clinical study, which was published as two full length articles, was by Bonebrake et al. This two-group, single-blinded clinical trial consisted of an initial study (n=51) with a six month follow-up (n=22). While outcome measures were independently obtained, blinding did not occur since only the treatment groups were reassessed. Though statistical improvement was found in some outcome measures in

both the initial and follow-up study, interpretation is difficult secondary to a variable treatment protocol, poor control of patients during the intra-study time period, and the large number of measured outcomes (thirty-four), leading to a significantly increased risk for type I error.[41,42]

In addition to Bonebrake, Davis et al. conducted a chiropractic clinical trial which was published as a full length article. The protocol involved a two-group, randomized, single-blinded trial of nine weeks duration (n=70) with a one-month follow-up evaluation (n=67). The randomization scheme, which was conducted by computer, assigned subjects to two experimental groups: medical management and chiropractic. Analysis of the outcome measures revealed significant improvement in physical and mental distress, NCS, and vibrometry, but no differences were found between the two experimental groups. While the methodology used by Davis is the most sound of all the manual medicine literature discussed here, improvements in design could include either a treatment group to account for the placebo effect of physical touch or a more cost-effective case-crossover design with each candidate serving as their own matched control, more emphasis on objective testing instead of primarily subjective findings, extending the length of the follow-up period and removal of potentially confounding therapeutic-level of ultrasound therapy from the chiropractic group.[43]

Finally, Burke et al. conducted a chiropractic clinical trial published as a full article. In this trial, twenty-six patients with CTS were randomized and placed in treatment groups consisting of one of two chiropractic treatment modalities. This study found statistically significant change compared to control limb, but no difference between

the two treatment modalities. Limitations to this study include small sample size, emphasis on subjective results, and lack of a control group. This is especially relevant to patients with bilateral disease in which the self-described "less effected limb" is used as a control.[44]

Overall, even though the literature is minimal and most studies have some inconsistencies in design, the available published literature of clinical trials and clinical case reports provides some promising evidence towards the efficacy of manual medicine as a treatment for CTS.

CHAPTER 2

METHODOLOGY

Specific Aims Statement

Most research involving disease severity utilizes only objective findings such as nerve conduction studies and perhaps may include evidence of muscle weakness or atrophy. Few address functional status, symptom severity or other methods of presenting subjective aspects of the disease. Even fewer address both categories. The first tenant of osteopathy is to treat the whole person. This involves accounting for all aspects of an illness: both subjective and objective. For this reason, composite scores were created using data from a randomized, controlled, single-blind pilot study on the effectiveness of OMT, which was completed at the national Osteopathic Research Center from September 2003 to November 2004 with a total sample size of thirty-seven, in order to give a better overall picture of the severity of the disease throughout multiple aspects of the patient's life. To accommodate this, all the composite scores included standardized objective findings, both motor and sensory latencies from nerve conduction studies, a net strength score, which accounts for grip, key pinch, tripod pinch, and tip pinch strengths, and standardized subjective findings—symptom severity scale and functional status scale. This score was used to address a more global picture when comparing dynamic changes in composite scores after treatment with OMT and static initial disease severities, with the addition of a unilateral or bilateral disease component, in the latter analysis. This holistic approach is a unique contribution to the field.

Furthermore, since the prevalence of CTS is not homogenous among the general population, the composite scores were utilized to determine if the same was true about disease severities in various demographic and actuary groups in the population with the disease. The demographic factors addressed were age, gender and ethnicity; the actuary group analyzed was obesity, a known risk factor for the development of CTS, and a final category, time since disease onset, was utilized as a proxy for progression of the disease. Due to small sample sizes, each group was broken into dichotomous subgroups in order to detect trends that exist with regards to disease severity. This last group represented progression of disease since the course of CTS is insidiously progressive. This allows for an adequate measure of the static sensitivity of the composite scores. It was postulated that different demographic factors may have different etiologic components that alter the degree of the severity of the disease.

Finally, since CTS is such a widespread disease, cost-effective therapies, such as OMT, need to be tested to see what their role is in evidence-based medicine. Again, the demographic factors addressed were age, gender and ethnicity, the actuary group analyzed was obesity, a known risk factor for the development of CTS, and a final category, time since disease onset was utilized as a proxy for progression of the disease. This allowed for the determining in which groups OMT was effective, and in which subgroups OMT was more effective. It was postulated that the different etiologic components in the groups may result in different outcomes in subgroups. Finally, the time since disease onset will be utilized to test the ability of the composite scores to detect dynamic change in disease severity in moderately severe CTS.

Study Sample and Design

This study involved secondary analysis of a small, single-blinded, randomized, controlled trial to determine the efficacy of OMT on CTS performed at the Osteopathic Research Center associated with the University of North Texas Health Science Center in Fort Worth, Texas from September 2003 to November 2004. This study had a total sample size of thirty-seven (nineteen subjects randomized to OMT group; eighteen to a sub-therapeutic ultrasound placebo group). Of these, fourteen subjects in the OMT group, and all eighteen in the ultrasound group, completed the trial. Exclusion criteria included: severe disease with muscle atrophy, pregnancy, previous wrist surgery, systemic disease (i.e., diabetes mellitus or thyroid disease in which peripheral neuropathies are common), and other secondary causes of CTS. Inclusion criteria included: age twenty-one to seventy, clinical diagnosis of CTS, and changes in nerve conduction studies (NCS) consistent with CTS. The data was de-identified, and the University of North Texas Health Science Center institutional review board approved the original trial.

Study design first involved synthesizing a composite score from collected data relevant to disease severity. These scores were used to determine if any severity-variation trends existed among either demographic factors or other CTS risk factors upon subject inclusion into the study. Finally, analysis among the same factors compared pre- and post-composite scores among the patients in the OMT arm that completed the study to determine if any particular group was more susceptible to the benefits to OMT.

Formulation of the Composite score

Illness includes the patient's perception of a disease. Therefore, a more realistic picture of the severity of a syndrome would include both objective and subjective findings. In order to create the most complete picture of CTS disease severity, it was necessary to combine the results from the nerve conduction studies (NCS), both motor (NCS_M) and sensory (NCS_S) differences, the symptom severity scale (SSS), the functional status scale (FSS), the average net strength score (NSS) and whether the disease was unilateral (1H) or bilateral (2H). This was done for values determined upon patient inclusion in the study and those found at the end of the research course. Since these data points involved different scales, they were standardized to a percentage of the largest value using equation (1).

$$\text{Equation (1): } X' = X/X_{max}$$

Where X is a value from the NCS, SSS, FSS, NSS, 1H/2H data set, X' is the standardized value of X and X_{max} is the maximum value of X found in both initial and final assessments in order to permit later comparison between the initial and final composite scores after treatment with OMT.

Furthermore, the NSS was calculated by using equation (1) to standardize grip strength (GS), key pinch (KP), tripod pinch (TrP) and tip pinch (TiP). For each patient the average of these values was utilized to create the total strength score (TSS). Since disease severity is muscle weakness, TSS was modified with equation (2) to calculate the

NSS. The average TSS was 0.53±0.06 at a 95% confidence interval (0.47, 0.59). The average NSS was 0.47±0.06 at a 95% confidence interval (0.41, 0.53).

Equation (2): NSS=1-TSS

In the standardized score, one is the most severe disease and zero is no disease. Since the disease course of CTS progresses from unilateral to bilateral disease, 1H will receive a value of 0.50 and 2H will receive a value of 1.00.

For each subject, the composite score (CS) was created by multiplying the average of NCS_M, NCS_S, SSS, FSS, NSS and 1H/2H by one-hundred using equation (3). The average CS value was 52.27±3.60 at a 95% confidence interval (48.66, 55.87).

Equation (3): $CS=100*((NCS_M+NCS_S+SSS+FSS+NSS+1H/2H)/6)$

However, since 1H/2H is a non-modifiable severity factor, this was excluded when calculating the pre- and post-OMT CS values. Therefore, and alternative CS without this component (CS*) was calculated with equation (4).

Equation (4): $CS^*=100*((NCS_M+NCS_S+SSS+FSS+NSS)/5)$

Because some data points were not obtained during the study, values were imputed by averaging the remaining available constituents. For the initial CS (CSi) components, fourteen NCS_S, one SSS and one FSS were imputed. For the final CS (CSf) components, seven NCS_S, one SSS and one FSS were imputed in this manner.

Finally, due to the small sample size, the CS values were also divided into quartiles using the Microsoft Excel 2007 quartile function to determine if trends were hidden by the paucity of data since a trend is more visible in discrete than continuous data when sample sizes are small. From these values, the midpoints between quartiles was determined using equation (5).

Equation (5): $Q_{n.5} = Q_n + (Q_{n+1} - Q_n)/2$

Where $Q_{n.5}$ equals the midpoint value between quartiles, Q_n equals the quartile, where n equals zero, one, two, three or four, and Q_{n+1} is the next quartile above Q_n. If the CS value was greater than $Q_{n.5}$, then it was rounded up to Q_{n+1}. This resulted in integer values ranging from 0.00 to 4.00 creating the final quartile CS value (CSq). For, CSi, this resulted in the following quartile values: Q_{min}=28.65, Q_1=44.89, Q_2=54.01, Q_3=60.05 and Q_{max}=74.21. The mid-quartile values used for rounding to the nearest quartile where $Q_{0.5}$=36.77, $Q_{1.5}$=49.45, $Q_{2.5}$=57.03 and $Q_{3.5}$=67.13. These rounded values represented each subjects' initial quartile composite score. In order to minimize error, this process was repeated at the end of calculating the difference in CS* values (ΔCS*). For, ΔCS*, this resulted in the following quartile values: Q_{min}= -31.77, Q_1= -11.09, Q_2= -3.00, Q_3=0.59 and Q_{max}=15.93. The mid-quartile values used for rounding to the nearest quartile where $Q_{0.5}$= -21.43, $Q_{1.5}$= -7.05, $Q_{2.5}$= -1.21 and $Q_{3.5}$= 8.26. Since, three values were negative, one was near zero, and one was positive. In order to retain any trends, quartiles were assigned the following integer values: negative three, negative two,

negative one, zero and one in order to maintain change in disease severity trends in the final analysis with ΔCSq*.

Analysis of Disease Severity upon Subject Inclusion into the Study

The demographic factors evaluated in this study included: age, gender and ethnicity. The associated-risk factors included obesity, measured as body mass index (BMI), and chronicity of disease (time since diagnosis). Initial Pearson tests were performed comparing these demographic factors to both CS and CSq values to assess any tendency towards linear trends.

For more detailed analysis, due to the small number of subjects, each continuous factor was divided into two groups in order to have the highest likelihood of detecting a trend. Age was divided into subjects forty years and younger and those older than forty years. This dichotomy was chosen because the odds of observing an anatomic variation is 3.2 times higher in the younger population.[14] Since CTS is nearly twice as frequent in white populations, ethnicity was divided into white and non-white populations.[5,8] Obesity, defined as a BMI of thirty or greater, is an independent risk factor for CTS.[10] Therefore, BMI was divided into subjects with a BMI less than thirty and those that are obese. Furthermore, for analysis purposes, BMI was rounded to the nearest whole integer in determining which subset was most appropriate for each subject. Early disease is associated with an onset of less than one year.[17] Also, since pathologic changes to the median nerve, in early disease, are more likely to be reversible than in more advanced cases, this was a logical choice to divide disease chronicity. However, since there was

such a large percentage of patients on the border of this age range, nearly eighteen percent, and since the two subgroups were so close in age relative to the time-course of the disease process, half of the patients at the one year point since diagnosis, were randomly placed in the older group and half were placed in the younger group. Finally, gender was already a dichotomy of male and female.

For each subset, Microsoft Excel 2007 was used to determine the average CSi and CSq values, to create a 95% confidence interval for CSi and CSq, and to perform a two-tailed, heteroscedastic Student's t-test with an $\alpha=0.05$ to look for statistical significance. CS values were used instead of CS* values because this is a static measurement in which 1H/2H appropriately assisted in measuring the desired outcome-initial disease severity.

Analysis of Change in Disease Severity after OMT

The same demographic and CTS-risk factor dichotomies used in analysis of initial disease severity were again utilized in addressing changes in disease severity. For age, the two subgroups were less than or equal to forty years old and greater than forty years old. The gender dichotomy included male and female. Ethnicity was divided into White and non-White. BMI was separated into obese (BMI greater than or equal to thirty) and BMI less than thirty. The last group, chronicity of disease, was broken into disease onset less than one year and disease onset greater or equal to one year. Furthermore, change in overall disease severity was also determined.

Since OMT cannot change whether or not one or two hands were affect by carpal tunnel syndrome, and the ultimate measure is a dynamic change in disease severity after OMT, CS* values will be utilized instead of CS values. Therefore, in determining the change in CS scores, equation (6) was utilized.

Equation (6): $\Delta CS^* = CSf^* - CSi^*$

Where ΔCS^* is the change in CS*, and CSf* and CSi* are the final and initial CS values. All of these were values that did not include whether or not disease was unilateral or bilateral in the calculation. The mean CSi* was 43.09±4.22 at a 95% confidence interval (38.87, 47.31) and the mean CSf* was 37.81±5.43 at a 95% confidence interval (32.38, 43.24). For the quartile change in CS calculation (ΔCSq^*), quartile determination of ΔCS^* occurred using the Microsoft Excel 2007 quartile function, equation (5) was used to determine mid-quartile points used for rounding, and values were assigned integers that maintained the integrity of the direction of change calculated in ΔCS^* by using integers negative three, negative two, negative one, zero, and one as previously described.

Because these calculations only included OMT subjects that completed the study, the maximum total sample size was fourteen. Each demographic factor had varying sample sizes based upon which data was collected. For age, the total sample size was fourteen with five subjects forty years old or younger, and nine subjects older than forty years old. For gender, total sample size was fourteen with five males and nine females. For ethnicity, total sample size was thirteen with twelve Whites and one non-White. For

BMI, total sample size was thirteen with six obese individuals and seven individuals with a BMI less than thirty. For chronicity of disease, total sample size was thirteen with five individuals presenting with a diagnosis up to or equal to one year ago and eight individuals diagnosed more than one year ago.

For the overall OMT group and each demographic factor, Microsoft Excel 2007 was utilized to determine the average ΔCS* and ΔCSq* and the 95% confidence intervals for each subset population. Values in which the confidence interval was entirely negative suggested a statistically significant decrease in disease severity after treatment with OMT.

CHAPTER 3

RESULTS

This project is a secondary analysis of depersonalized data of an Institutional Review Board- approved randomized, controlled trial on the role of OMT in the treatment of CTS that occurred from September 2003 to November 2004 at the University of North Texas Health Science Center in the national Osteopathic Research Center. The initial sample size of this trial was thirty-seven, with nineteen subjects randomized into the OMT group and eighteen into the placebo-ultrasound group. Due to the attrition of five subjects in the OMT group and clerical error resulting in the loss of data for one subject in the placebo group, the final sample size of the OMT group was fourteen, and that of the placebo group was seventeen, with a total final sample size of thirty-one. Exclusion criteria included: severe disease with muscle atrophy, pregnancy, previous wrist surgery, systemic disease (i.e., diabetes mellitus or thyroid disease in which peripheral neuropathies are common), and other secondary causes of CTS. Inclusion criteria included: age twenty-one to seventy, clinical diagnosis of CTS, and changes in nerve conduction studies (NCS) consistent with CTS.

Analysis of Disease Severity upon Subject Inclusion into the Study

Upon inclusion into this study, some demographic and CTS-associated risk factor data was obtained. The demographic factors evaluated in this study included: age, gender and ethnicity. The associated-risk factors included obesity, measured as body mass index (BMI), and chronicity of disease (time since diagnosis).

In the study population, the average age was 44.16 ± 4.16 years old at a 95% confidence interval (39.98, 48.30) with a range of twenty-two to sixty-five years old. The population was thirty percent male and seventy percent female; eighty-nine percent White and eleven percent non-White. The average BMI was 29.41 ± 2.39 at a 95% confidence interval (27.02, 31.80) with a minimum BMI of 16.95 and a maximum BMI of 47.83. Finally, the average time since onset of disease was 3.18 ± 1.49 years at a 95% confidence interval (1.69, 4.66) with the most recent onset being 0.08 years ago, and the longest time since diagnosis being eighteen years.

Initial Pearson tests were performed comparing these demographic factors to both CSi and CSq values to assess any tendency towards linear trends. The variables include age in years, gender, where one equals male and two equals female, ethnicity where one equals White and two equals non-White, BMI and time since diagnosis in years. For CSi, Pearson correlations were as follows: age was 0.30, gender was 0.25, ethnicity was -0.13, BMI was 0.40 and time since disease onset was 0.09. For CSq, Pearson correlations were as follows: age was 0.38, gender was 0.27, ethnicity was -0.15, BMI was 0.40 and time since disease onset was 0.20. This data is summarized in Table 1.

Pearson correlations may be positive (i.e. increasing independent variables are associated with increasing dependent variables) or negative (i.e. increasing independent variables are associated with decreasing dependent variables) and range from a complete negative correlation (-1.00) to a complete positive correlation (1.00). Furthermore, the degree of correlation gives a relative sense of the strength of the correlation. Values ranging from -0.1 to 0.1 have indeterminate correlation.

Using the initial composite score, CSi, the following conclusions are drawn: age has a small positive correlation, gender has an indeterminate correlation; ethnicity has a small negative correlation (i.e. disease severity is greater in Whites); BMI has a medium positive correlation; and time since diagnosis has an indeterminate correlation. Using the initial quartile composite score, CSq, the following correlations are suggested: age has a medium positive correlation, gender has a medium positive correlation (i.e. disease severity is greater in females), ethnicity has a small negative correlation (i.e. disease severity is greater in Whites), BMI has a medium positive correlation, and time since diagnosis has a small, positive correlation.

While this is encouraging, more detailed analysis required dichotomizing all continuous variables to analyze trends in disease severity further, due to the small number of subjects. Each continuous factor was divided into two groups in order to have the highest likelihood of detecting a trend. Age was divided into subjects forty years and younger and those older than forty years. Ethnicity was divided into White and non-White populations. BMI was divided into subjects with a BMI less than thirty and those

greater than thirty. Early disease is associated with an onset of one year or less; therefore, disease chronicity was divided into early and advanced disease at this point. Finally, gender was already a dichotomy of male and female.

The initial sub-group analyzed was age. In this analysis, the total sample size for age was thirty-six, those less than or equal to forty years old was eleven, and those greater than forty years old was twenty-five. This data may be found in Table 2. In the younger group, the average age was 28.09 ± 2.79 years old at a 95% confidence interval (25.30, 30.88). In the older group, the average age was 51.20 ± 2.96 years old at a 95% confidence interval (48.24, 54.16). The analysis of the correlation between age and initial composite score and initial quartile composite score resulted in the average CSi and CSq values for the dichotomous age categories presented in Figure 1 and Figure 2, respectively and described below.

For CSi, the average CS value for age less than or equal to forty years was 47.77 ± 7.52 at a 95% confidence interval (40.25, 55.29). The average CSi value for age greater than forty years old was 53.76 ± 3.97 at a 95% confidence interval (49.79, 57.73). A two-tailed, heteroscedastic (two-sample with unequal variance) Student's t-test resulted in a p-value of 0.19, which was not significant at the 0.5 level.

For CSq, the average CS value for age less than or equal to forty years was 1.36 ± 0.66 at a 95% confidence interval (0.70, 2.03). The average CSq value for age greater than forty years old was 2.12 ± 0.41 at a 95% confidence interval (1.71, 2.53). A two-

tailed, heteroscedastic Student's t-test resulted in a p-value of 0.07, which was not significant at the 0.5 level.

The next sub-group analyzed was gender. In this analysis, the total sample size was thirty-seven with eleven males and twenty-six females. The results are summarized in Table 2. The analysis of the correlation between gender and initial composite score and initial quartile composite score resulted in the average CSi and CSq values for both genders presented in Figure 3 and Figure 4, respectively.

For CSi, the average CS value for males was 48.03 ± 6.54 at a 95% confidence interval (41.49, 54.57). The average CSi value for females was 54.06 ± 4.21 at a 95% confidence interval (49.85, 58.27). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.15 which was not significant at the 0.5 level.

For CSq, the average CS value for males was 1.45 ± 0.61 at a 95% confidence interval (0.84, 2.07). The average CSq value for females was 2.12 ± 0.43 at a 95% confidence interval (1.69, 2.54). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.10 which was not significant at the 0.5 level.

The sub-group of ethnicity included a total sample size of thirty-five with thirty-one Whites and four non-Whites. The results are presented in Table 2. The analysis of the correlation between ethnicity and initial composite score and initial quartile composite score resulted in the average CSi and CSq values for the dichotomous ethnicity categories presented in Figure 5 and Figure 6, respectively.

For CSi, the average CS value for Whites was 53.09 ± 3.46 at a 95% confidence interval (49.63, 56.56). The average CSi value for non-Whites was 48.75 ± 15.67 at a 95% confidence interval (33.40, 64.11). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.62, which was not significant at the 0.5 level.

For CSq, the average CS value for Whites was 2.00 ± 0.37 at a 95% confidence interval (1.63, 2.37). The average CSq value for non-Whites was 1.50 ± 1.27 at a 95% confidence interval (0.23, 2.77). A two-tailed, heteroscedastic Student's t-test calculated in a p-value 0.50 was not significant at the 0.5 level.

In the analysis of body mass index (BMI), total sample size was thirty-five, with seventeen obese individuals with a BMI greater than or equal to thirty, and eighteen subjects with a BMI less than thirty. Data is again summarized in Table 2. In the non-obese group, the average BMI was 24.22 ± 1.59 at a 95% confidence interval (22.63, 25.81). In the obese group, the average BMI was 34.91 ± 2.83 at a 95% confidence interval (32.08, 37.73). The analysis of the correlation between BMI and initial composite score and initial quartile composite score resulted in the average CSi and CSq values for the dichotomous BMI categories presented in Figure 7 and Figure 8, respectively.

For CSi, the average CS value for non-obese subjects was 49.54 ± 5.07 at a 95% confidence interval (44.47, 54.61). The average CSi value for obese subjects was 54.34 ± 5.45 at a 95% confidence interval (48.89, 59.79). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.22 was not significant at the 0.5 level.

For CSq, the average CS value for non-obese subjects was 1.67 ± 0.48 at a 95% confidence interval (1.19, 2.14). The average CSq value for obese subjects was 2.12 ± 0.58 at a 95% confidence interval (1.54, 2.70). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.25 was not significant at the 0.5 level.

Finally, for the analysis of time since disease onset, total sample size was thirty-four with fifteen subjects diagnosed one or less years ago, and nineteen subjects diagnosed one or more years ago. The data for this subgroup is also presented in Table 2. As a reminder, for the six subjects diagnosed exactly one year ago, half were randomly assigned to the younger group, and half to the older group, since it is uncertain which side of the dichotomy they fall. In the more recently diagnosed group, the average time since onset was 0.50 ± 0.17 years ago at a 95% confidence interval (0.33, 0.67). In the more chronic group, the average time since onset was 5.29 ± 2.25 years ago at a 95% confidence interval (3.04, 7.54). The analysis of the correlation between time since onset and initial composite score and initial quartile composite score resulted in the average CSi and CSq values for the dichotomous chronicity categories presented in Figure 9 and Figure 10 , respectively.

For CSi, the average CS value for recently diagnosed subjects was 50.32 ± 5.33 at a 95% confidence interval (44.99, 55.64). The average CSi value for the more chronic subjects was 53.67 ± 4.69 at a 95% confidence interval (48.98, 58.36). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.36 was not significant at the 0.5 level.

For CSq, the average CS value for more recently diagnosed subjects was 1.67 ± 0.49 at a 95% confidence interval (1.17, 2.16). The average CSq value for the more chronic subjects was 2.11 ± 0.52 at a 95% confidence interval (1.59, 2.62). A two-tailed, heteroscedastic Student's t-test calculated a p-value of 0.24 was not significant at the 0.5 level.

Analysis of Change in Disease Severity after OMT

OMT has long been used by osteopathic physicians to treat CTS. Little research has been done to determine its efficacy in general and in specific populations. The purpose of this section is to evaluate whether or not any specific statistical change occurred in the composite score ΔCS* or the quartile composite score ΔCSq* in the OMT group as a whole, then in specific demographic and CTS-risk factor subgroups. Again the groups were: age, gender, ethnicity, BMI and time since disease onset. Also, they will be dichotomized in a similar fashion to the initial disease severity research. Age was divided into subjects forty years and younger and those older than forty years. Ethnicity was divided into white and non-white populations. BMI was divided into subjects with a BMI less than thirty and those that are obese. Early disease is associated with an onset of less than one year and included three random subjects, exactly at one year, for reasons stated previously. Finally, gender was dichotomized into male and female.

In general, the subjects in the OMT group had an average age of 42.00 ± 7.19 years old at a 95 % confidence interval (34.81, 49.19). The oldest patient was sixty and the youngest was twenty-two years old. The population was thirty-six percent male and

sixty-four percent female and ninety-two percent White and eight percent non-White. The average BMI was 29.29 ± 2.60 at a 95% confidence interval (26.61, 31.98). The lowest BMI was 22.89 and the highest was 40.77. Finally, the average time since onset of disease was 2.72 ± 1.56 years. The most recent onset was 0.17 years ago and the most distant onset was ten years ago.

Overall, the average change in composite score, ΔCS*, was a decrease by 4.88 ± 6.00 at a 95% confidence interval (-10.88, 1.12). Since this interval includes zero, it cannot be determined that this value was statistically significant. However, the average change in quartile composite score, ΔCSq*, was -0.93 ± 0.63 at a 95% confidence interval (-1.56, -0.30). Since zero was not included in this interval, this value was indeed statistically significant. In other words, the sample size was too small for this trend to be identified in ΔCS*.

For the analysis of change in composite scores versus subject age, total sample size was fourteen, with five subjects younger than forty and nine subjects forty or older. These results are presented in Table 3. In the younger group, the average age was 25.80 ± 4.70 years old at a 95% confidence interval (21.10, 30.50). In the older group, the average age was 51.00 ± 3.95 years old at a 95% confidence interval (47.05, 54.95). The analysis of the correlation between age and change in composite score and change in quartile composite score resulted in the average ΔCS* and ΔCSq* values for the dichotomous age categories presented in Figure 11 and Figure 12, respectively.

For younger patients, the average change in composite score, ΔCS*, was -7.79 ± 12.91 at a 95% confidence interval (-20.70, 14.73). Since zero is included in this confidence interval, it was not significant at the 0.5 level. However, the average change in quartile composite score, ΔCSq* was -1.33 ± 1.14 at a 95% confidence interval (-2.48, -0.19). This is statistically significant suggesting that the young OMT patients had a decrease in the disease severity over the course of the study.

For older patients, the average change in composite score, ΔCS*, was -3.89 ± 6.49 at a 95% confidence interval (-10.39, 2.60). Since zero is included in this confidence interval, it was not significant at the 0.5 level. Also, the average change in quartile composite score, ΔCSq* was -0.78 ± 0.79 at a 95% confidence interval (-1.56, 0.01). While not statistically significant, there is a clear trend towards significance. This suggests that in older OMT patients, disease severity may decrease over the course of treatment.

For the analysis of change in composite scores versus gender, total sample size was fourteen with five male subjects and nine female subjects. Results are in Table 3. The analysis of the correlation between age and change in composite score and change in quartile composite score using produced the average ΔCS* and ΔCSq* values for both genders presented in Figure 13 and Figure 14, respectively.

For males, the average change in composite score, ΔCS*, was -4.46 ± 8.68 at a 95% confidence interval (-12.95, 4.42). Since zero is included in this confidence interval, it was not significant at the 0.5 level. Also, the average change in quartile composite

score, ΔCSq* was -0.80 ± 0.96 at a 95% confidence interval (-1.76, 0.16). Since zero is again included, it is uncertain whether or not this is statistically significant. The trend suggests that male OMT patients may have decrease in the disease severity over a treatment course.

For females, the average change in composite score, ΔCS*, was -5.85 ± 8.35 at a 95% confidence interval (-14.20, 2.50). Since zero is included in this confidence interval, it was not significant at the 0.5 level. However, the average change in quartile composite score, ΔCSq* was -1.00 ± 0.86 at a 95% confidence interval (-1.86, -0.14). This is statistically significant suggesting that in female OMT subjects, disease severity decreased over the course of treatment.

For the analysis of change in composite scores versus ethnicity, total sample size was thirteen with twelve White subjects, and one non-White subject. Results are summarized in Table 3. The analysis of the correlation between ethnicity and change in composite score and change in quartile composite score yielded the average ΔCS* and ΔCSq* values for the dichotomous ethnicity categories presented in Figure 15 and Figure 16, respectively.

For Whites, the average change in composite score, ΔCS*, was -5.79 ± 6.97 at a 95% confidence interval (-12.76, 1.18). Since zero is included in this confidence interval, it was not significant at the 0.5 level. However, the average change in quartile composite score, ΔCSq* was -1.00 ± 0.72 at a 95% confidence interval (-1.72, -0.28). This is

statistically significant suggesting that White OMT patients had a decrease in disease severity over the course of the study.

For non-Whites, the average change in composite score, ΔCS*, was -5.12. Confidence intervals could not be determined since the sample size is only one. The average change in quartile composite score, ΔCSq* was -1.00. Again, confidence intervals could not be determined. A larger sample size is necessary to determine statistically whether or not non-White OMT subjects may have a decrease in disease severity over the course of treatment.

In the analysis of change in composite scores versus BMI, total sample size was thirteen with seven non-obese subjects and six obese subjects. Results are presented in Table 3. The average BMI of the non-obese subjects was 25.84 ± 1.72 at a 95% confidence interval (24.12, 27.56). The average BMI of the obese subjects was 33.32 ± 3.20 at a 95% confidence interval (30.13, 36.52). The analysis of the correlation between obesity and change in composite score and change in quartile composite score resulted in the average ΔCS* and ΔCSq* values for dichotomous BMI values presented in Figure 17 and Figure 18, respectively.

For non-obese subjects, the average change in composite score, ΔCS*, was -8.88 ± 8.46 at a 95% confidence interval (-17.33, -0.42). This is a statistically significant change. Furthermore, the average change in quartile composite score, ΔCSq* was -1.29 ± 0.93 at a 95% confidence interval (-2.21, -0.36) which is also statistically significant

corroborating the ΔCS* results. Therefore, the non-obese OMT patients had a statistically significant decrease in the disease severity over the course of the study.

For obese patients, the average change in composite score, ΔCS*, was -4.63 ± 6.99 at a 95% confidence interval (-11.62, 2.36). Since zero is included in this confidence interval, it was not significant at the 0.5 level. However, the average change in quartile composite score, ΔCSq* was -0.83 ± 0.79 at a 95% confidence interval (-1.62, -0.05). This is statistically significant suggesting that in the obese OMT subjects, disease severity decreased over the course of the study.

Finally, in the analysis of change in composite scores versus time since onset of the disease, the total sample size was thirteen, with four subjects diagnosed with CTS less than one year ago, and nine subjects diagnose at least one year ago. Results again are in Table 3. The average time since onset in the more recently diagnosed subjects was 0.46 ± 0.20 years at a 95% confidence interval (0.26, 0.66). The time since disease onset in the more chronic subjects was 3.72 ± 1.93 at a 95% confidence interval (1.80, 5.65). The analysis of the correlation between disease chronicity and change in composite score and change in quartile composite score produced the average ΔCS* and ΔCSq* values for dichotomous time since disease onset values presented in Figure 19 and Figure 20, respectively.

For the more recently diagnosed subjects, the average change in composite score, ΔCS*, was -5.08 ± 18.06 at a 95% confidence interval (-23.14, 12.98). Since zero is included in this confidence interval, it was not significant at the 0.5 level. Also, the

average change in quartile composite score, ΔCSq* was -1.00 ± 1.61 at a 95% confidence interval (-2.61, 0.61). Again it cannot be determine if this change was significant. Therefore, a larger sample size is necessary to determine if more recently diagnosed OMT patients have a statistically significant decrease in disease severity over the course of treatment.

For the more chronic patients, the average change in composite score, ΔCS*, was -6.03 ± 4.35 at a 95% confidence interval (-10.38, -1.68). This is a statistically significant change. Furthermore, the average change in quartile composite score, ΔCSq* was -1.00 ± 0.66 at a 95% confidence interval (-1.65, -0.35). This is statistically significant suggesting corroborating the results of ΔCS*. In other words, in more chronic OMT subjects, disease severity decreased over the course of the study.

CHAPTER 4

DISCUSSION

Creation of a Composite Score of Disease Severity

Most research involving disease severity utilizes only objective findings such as nerve conduction studies and perhaps may include evidence of muscle weakness or atrophy. Few address functional status, symptom severity or other subjective measures of the disease. Even fewer, especially osteopathic studies involving OMT, include both subjective and objective measures of disease severity. The first tenant of osteopathy is to treat the whole person. This involves accounting for all aspects of an illness: both subjective and objective. For this reason, the composite scores were created to give a better overall picture of the severity of the disease throughout multiple aspects of the patient's life. To accommodate this, all the composite scores included standardized objective findings, NCS_M' , NCS_S' , NSS and standardized subjective findings—SSS' and FSS'. Static severity scores included 1H/2H while dynamic findings utilized to address changes in disease severity did not. This was secondary to OMT not changing whether a subject had 1H or 2H disease and the small sample size which would limit the ability to detect a change. Conceptually, if the sample sizes were large enough, 1H/2H was included in all calculations.

For the CSi, the average score was 52.27 ± 3.60 at a 95% confidence interval (48.66, 55.87). This is suggestive of moderate disease severity since the scores range from zero (no disease) to one-hundred (extreme disease). The minimum score was 28.65

and the maximum score was 74.21. This corresponds to the middle forty-five percent of the disease range—those with moderate disease. In other words, the CSi is a good representation of the expected degree of severity for which the randomized controlled trial was designed to study. For the average change in composite score without 1H/2H, ΔCS*, the average change was a decrease in disease severity by 5.28 ± 6.00 at a 95% confidence interval (-11.29, 0.72) which is not quite significant. However, this is likely due to small sample size.

In order to have a better chance of detecting a change that exists but is masked by small sample size, the continuous ΔCS* and CSi needed to be broken into larger, more discrete increments. Each value was rounded to the nearest whole integer. Values were rounded up at the inter-quartile midpoints. The new quartile composite scores, even when not statistically significant, made it possible to determine if an output was at least approaching significance.

Analysis of Disease Severity upon Subject Inclusion into the Study

Initial analysis began with calculation of Pearson scores comparing demographic and risk factors to both composite scores and quartile composite scores. First, in comparison to CSi, there was a small correlation with gender (disease was more severe in females) and ethnicity (i.e. disease was more severe in Whites), a medium correlation with BMI and age, and an indeterminate correlation with time since disease onset. The associations became more apparent when the comparison was with the quartile composite score. This is likely secondary to the small, overall sample size. Compared to CSq, there

was a small correlation with ethnicity (disease was more severe in Whites) and time since disease onset and medium correlations between gender (disease was more severe in females), age and BMI. This gives credence to the concept that disease course is variable among these factors and is suggestive that they play a role in determining the severity of the CTS disease process.

More detailed examination of each factor individually may help to illuminate those precise roles. Furthermore, due to the small number of subjects, each continuous factor was divided into two groups in order to have the highest likelihood of detecting a trend. Age was divided into subjects forty years and younger and those older than forty years. This dichotomy was chosen because the odds of observing an anatomic variation is 3.2 times higher in the younger population.[12] Since CTS is nearly twice as frequent in white populations, ethnicity was divided into white and non-white populations.[5,8] Obesity, defined as a BMI of thirty or greater, is an independent risk factor for CTS.[10] Therefore, BMI was divided into subjects with a BMI less than thirty and those that were greater than thirty. Early disease is associated with an onset of less than one year.[17] However, since six of the thirty-four subjects were diagnosed approximately one year before inclusion in the trial, it was uncertain as to which subgroup these individuals belonged. Therefore, three subjects in this category were randomly assigned to the more recent and more chronic groups, respectively. This was done in order to minimize recall bias. Finally, gender was already a dichotomy of male and female. With the dichotomies in place, each factor was addressed individually.

The first demographic category analyzed was age. In this analysis, the total sample size for age was thirty-six, those less than or equal to forty years old was eleven, and those greater than forty years old was twenty-five. The average age in the younger group, age less than forty years, was 28.09 ± 2.79 years old at a 95% confidence interval (25.30, 30.88). In the older group, age greater than or equal to forty years, the average age was 51.20 ± 2.96 years old at a 95% confidence interval (48.24, 54.16). There was clearly no overlap in the groups. For both CSi and CSq, while statistically significance could not be determined; there was clearly a trend in the direction of statistical significance that is likely masked by the small sample size. This is especially true in the younger population. Based upon average disease severity, this would suggest higher composite scores in older patients.

These results suggest that older patients are more likely have more severe disease than the other age groups. Since many secondary diseases were included in the exclusion criteria, these are less likely to play prominent roles in the disease etiology in the subjects included in this study; however, natural physiologic events such as menopause, which alter fluid balance, were not excluded from the study. Furthermore, natural decrease in carpal tunnel size due to arthritic changes, and decrease in lymphatic flow resulting in increased intra-compartmental pressure, may also play a significant role in the development of CTS. As expected, upon performing a Pearson's test, there is a medium positive correlation value between age and time since disease onset (0.35). Therefore, while there is some association between these two variables, neither completely accounts for the other. In conclusion, there is a trend for more severe disease in older patients that

is possibly due to, among others causes, natural anatomic and physiologic changes, accumulation of one or more diseases or conditions which physiologically create conditions favorable for the development of CTS, accumulation of repetitive trauma over a greater period of time, and greater time from disease onset for the disease to progress.

The next demographic category addressed was gender. In this analysis, the total sample size was thirty-seven with eleven males and twenty-six females. For both CSi and CSq values, while no significant difference was detected, there was a definite trend in that direction. The lack of statistical significance may be due to small sample size as a whole and especially in the male subgroup. If this trend continues, then in patients with moderately severe disease, there is a tendency for greater disease severity in females. This must be qualified as greater disease severity in the spectrum of patients with moderate disease using a score which accounts for both objective and subjective findings of CTS. This may help clarify the difference between these results and those found in previous studies that suggested a greater disease severity in men. In those studies, only nerve conduction studies were utilized to assess disease severity. Furthermore, epidemiological data found fewer men with mild disease and more men with severe or extreme disease than women.[4] While the results of previous studies are best explained with a socio-occupational model, these results are more likely due to anatomical (smaller wrist dimensions in females) and physiological (increased fluid imbalance secondary to conditions such as hormonal changes) etiological models. Since occupational data was never obtained, it is uncertain what percentage of these subjects worked in blue collar jobs, a known risk factor, as opposed to white collar positions.

The most likely explanation for the greater disease severity in women with moderate disease lies in the greater prevalence of etiologic factors.[1] While external forces and repetitive trauma may result in more extreme disease in men, physiologic changes in women are far more frequent and could easily increase the intra-carpal pressure to a strong enough degree to cause more severe moderate CTS than in males.

The final demographic category was ethnicity. The sub-group of ethnicity included a total sample size of thirty-five, with thirty-one Whites and four non-Whites. Both the average CSi and CSq were higher in White subjects than the non-White counterparts. For both composite scores, statistical significance was indeterminate. However, there was a slight trend towards statistical significance. These results are likely due to extremely small sample sizes—especially in the non-White population. From these results we cannot conclude the degree of disease severity between the two groups. Of note, there was a small association between ethnicity and BMI with a Pearson's correlation factor of 0.17 that suggested Whites were more obese than non-Whites in this study. Since, in the general population, the opposite tends to be true, this could be a significant confounding factor which may have skewed the results even with a larger non-White sample size because obesity is a known independent risk factor for CTS.

Another possible explanation involves the recruitment of subjects in a university setting. It is possible that the non-White subjects were employed in more physically active occupations than the White counter-parts. Since physical inactivity is a known risk

factor for CTS this is plausible. However, since occupations of the subjects are unknown, this cannot be verified.

The first associated independent risk-factor for CTS examined was obesity (BMI ≥30). While obesity is a known risk factor for the development of carpal tunnel syndrome, little has been done to determine its role in the severity of disease. On a small scale, this was addressed in this project. In this analysis, total sample size was thirty-five, with seventeen obese individuals with a BMI greater than or equal to thirty, and eighteen subjects with a BMI less than thirty. In the non-obese group, the average BMI was 24.22 ± 1.59 at a 95% confidence interval (22.63, 25.81). In the obese group, the average BMI was 34.91 ± 2.83 at a 95% confidence interval (32.08, 37.73). These are independent groups since there is no overlap at a 95% confidence interval. While both the average CSi and CSq were higher in the obese population, neither value was statistically significant, nor was there a trend towards significance. There are several explanations. First, the small sample size resulted in large confidence intervals which were the likely source of indeterminate significance. Next, while obesity clearly plays a role in the initiation of the disease, it may have a smaller impact on the propagation of pathologic processes. Third, an unidentified confounding variable may be the primary risk factor for which obesity is merely a surrogate. For example, one may assume that the underlying etiologic factor is physical inactivity. This can cause CTS physiologically via fluid stasis since lymphatic return is primarily mobilized by muscular contracture. Inactivity can also result in CTS anatomically by shortening myofascial structures leading to a smaller intra-carpal space. While physical inactivity is common among obese individuals, this is

not an exclusive association, and may be present in non-obese individuals with sedentary lifestyles or minimally active occupations. Of these explanations, any of them could be the solution, and further testing is necessary.

The other disease severity risk-factor addressed was time since onset of CTS. In this analysis, total sample size was thirty-four with thirteen subjects diagnosed less than one year ago, and twenty-one subjects with CTS for one or more years. In the more recently diagnosed group, the average time since onset was 0.50 ± 0.17 years ago at a 95% confidence interval (0.33, 0.67). In the more chronic group, the average time since onset was 5.29 ± 2.25 years ago at a 95% confidence interval (3.04, 7.54). While statistical significance was indeterminate, there was a clear trend to suggest that disease severity was proportionate to time since onset. Beyond the small sample sizes, the lack of statistical significance may also lie in that while these are distinct groups, the timeframes since disease onset are still relatively close to each other in comparison to the insidious nature of the course of CTS. Since more severe disease over time is the nature of the CTS disease course, this is an encouraging indication that the composite score may be a valid measure of overall disease severity. What is unknown from this is the incremental extent to which the score can detect changes in disease severity. If the composite scores can detect disease severity changes at a statistically significant level, then they will have value in both static and dynamic evaluation of the overall disease severity in CTS.

Analysis of Change in Composite Score after OMT

When analyzing the change in both composite score and quartile composite score of the OMT group as a whole, while ΔCS* did not quite show statistical significance, ΔCSq* did. Therefore, as a whole, the sample population of patients in the OMT group had a decrease in disease severity over the course of the study. With an average initial quartile composite score of 1.93 ± 0.48 at a 95% confidence interval (1.45, 2.41) and a ΔCSq* of -0.93 ± 0.63 at a 95% confidence interval (-1.56, -0.30), at a 95% confidence interval, there was a reduction of disease severity ranging from twelve to one-hundred percent. This is likely a direct result of decreasing somatic dysfunction by improving function of skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements. The function of skeletal, arthroidial and myofascial structures mechanically increase or decrease the intra-carpal pressures. The associated vascular, lymphatic and neural elements directly play a role in the histopathology of the disease process. Vascular elements provide nutrients and eliminate waste. Lymphatic elements eliminate edema which can alter impulse transmission ability. Finally, poor health of the median nerve is the nature of the disease process itself. The next question to be addressed involves the utility of OMT in different demographic and actuarial subgroups.

With regards to the effect of OMT on disease severity based upon patient age, the total sample size was fourteen, with five subjects younger than forty and nine subjects forty or older. In the younger group, the average age was 25.80 ± 4.70 years old at a 95%

confidence interval (21.10, 30.50). In the older group, the average age was 51.00 ± 3.95 years old at a 95% confidence interval (47.05, 54.95). These are clearly independent groups. In both groups, ΔCS* was indeterminately significant; however, ΔCSq* was statistically significant for younger patients, and nearly so for the older group. The overall change was larger in the younger group, reflecting the likelihood of more reversible change in subjects with less of an accumulation of CTS-inducing stressors. Furthermore, since disease in younger populations is more likely due to anatomical anomalies decreasing the intra-carpal space, stretching of the flexor retinaculum in order to enlarge this area can counteract the mechanical effect of these variations. It was also encouraging to see changes in the older population, even if they are somewhat limited by some irreversible damage over time. Since the scores were lower in the younger patients and they still had a greater change, this is evidence for identifying and utilizing OMT to treat patients as soon as possible. A key feature here will be patient education with regards to symptoms of CTS.

The effect of OMT on disease severity, as it pertains to each gender, was also encouraging. The total sample size was fourteen, with five male subjects and nine female subjects. Again, while gender had a statistically significant, ΔCS*, the trend was towards a decrease in disease severity. For males, this was shown by a nearly significant average change in quartile composite score; for females, ΔCSq* was statistically significant. The decrease in composite score was greater in females suggests several things. First, the etiology of CTS in females likely represents the anatomic and physiologic dysfunctions addressed by OMT. CTS etiology in males, while partially of anatomic and physiologic

origin, may possess either a socio-occupational component, such as poor work ergonomics, or be less reversible by addressing somatic dysfunction. However, in this sample population, there was a small correlation between female gender and more time since disease onset (Pearson correlation of 0.14), thus nullifying the possibility of the males having more advanced disease. In other words, since males, in general, have a more recent time of disease onset in this study sample; it is unlikely that they also have more progressive disease. This is affirmed by the overall greater disease severity in females in this project. Therefore, while beneficial in treating CTS in both genders, the nature of the therapy is especially beneficial towards the etiologies common in disease found in female patients.

The relative impact of OMT on both the White and the non-White subjects appears positive. The total sample size was thirteen, with twelve White subjects and one non-White subject. Unfortunately, due to a sample size of one for the non-White population, no statistical inferences may be made, in spite of data to suggest that CTS may decrease overall disease severity in this subgroup. With regards to White populations, ΔCS* was nearly significant, and ΔCSq* was statistically significant. There was slightly more improvement in White populations but nothing can be inferred due to the paucity of data from both groups. At this point, we now know that OMT decreases disease severity in White populations but further research needs to be done to determine outcomes in non-White subjects. This will require significantly greater sample sizes to do so.

The last factor tested, with regards to the effect of OMT on disease severity, was obesity, which was measured as BMI. The total sample size was thirteen with seven, non-obese subjects, and six obese subjects. The average BMI of the non-obese subjects was 25.84 ± 1.72 at a 95% confidence interval (24.12, 27.56). The average BMI of the obese subjects was 33.32 ± 3.20 at a 95% confidence interval (30.13, 36.52). While there was a trend towards a statistically significant ΔCS* in the obese population, it was statistically significant for the non-obese subjects. Furthermore, ΔCSq* was statistically significant for both groups. This means that obesity is not an exclusion factor when physicians select CTS patients who are likely to benefit from OMT. However, the average ΔCS* of non-obese subjects was nearly twice that of the obese counterparts. The contrast was nearly as strong with ΔCSq* as well. This suggests that while some change may occur in obese patients, the negative effects adiposity has on the carpal tunnel itself, mechanically, the impaired lymphatic drainage and poorer circulation secondary to concomitant systemic atherosclerosis, negate some of the beneficial power of OMT in CTS. Practically, this means that in order for an obese patient with CTS to receive the maximum benefit from OMT, a concerted effort must be put forth to lose weight.

Finally, analysis of the effect of OMT as it pertains to time since onset versus change in severity scores is two-fold. It addresses whether OMT is still effective in chronic patients as well as determines if the composite scores can detect dynamic fluctuations in overall disease severity. In this group, the total sample size was thirteen with four subjects diagnosed with CTS less than one year ago, and nine subjects diagnose at least one year ago. The average time since onset in the more recently diagnosed

subjects was 0.46 ± 0.20 years at a 95% confidence interval (0.26, 0.66). The time since disease onset in the more chronic subjects was 3.72 ± 1.93 at a 95% confidence interval (1.80, 5.65). Since the time increment between these two groups is relatively small with regards to the total length of the CTS disease course, this gives a good approximation of the composite score's ability to detect small changes. It is exciting to see that in the more chronic patients, both ΔCS* and ΔCSq* are statistically significant. This may in part be due to the relative early nature of the chronicity in this particular sample population.

Furthermore, the more recently diagnosed patients do not have statistical significance in either average change in composite score; however, this is largely due to the extremely small sample size. Since the trend is towards significance, this group to likely will benefit from OMT, although further studies with larger populations are necessary to statistically verify this assertion. With regards to the utility of the composite scores for detecting changes in overall disease severity in moderate CTS, at this point, they are most useful in more advanced disease. To some degree, this may be explained by more pronounced changes as disease progresses in NCS, changes in the net strength score, and symptoms affecting daily life more severely. However, it is possible that further research will find that the same sensitivity exists in earlier disease as well.

Limitations

The most obvious limitation to this analysis is small sample size. While trends were detected, few resulted in confirmed statistical significance. Due to the attrition of five subjects in the OMT arm of the study, the sample size diminished even further than

the original nineteen in the OMT group. Next, missing data, required for the creation of composite scores, resulted imputation which may, or may not represent the true value for that subject. Furthermore, additional information, such as occupation, smoking status, and other known risk factors would have allowed for a more thorough examination of the factors contributing to CTS. Finally, the lack of a control group may lead to artificial decrease in disease severity due to regression towards the mean.

Future Considerations

Future research on this specific topic should include far more substantial sample sizes, equal sizes in the subgroups, and additional actuary data such as subject occupation, smoking status, and socio-economic factors. With a sufficiently large sample size, one could also analyze each subgroup in a randomized controlled trial compared to a placebo, such as the ultrasound used in the original study, to determine what the benefit of OMT is beyond a mere "healing touch." Additional projects may include the role of obesity in the progression of CTS, the role of OMT in treating recently-diagnosed CTS subjects, disease severity in non-White populations, and cost-benefit analysis of OMT for CTS.

CHAPTER 5

CONCLUSION

Composite scores showed encouraging trends towards effectively measuring accurate overall disease severity in moderately severe cases of CTS. The correlation with time since onset suggests that the composite scores can accurately reflect progressive severity of CTS in static analysis. Furthermore, changes in composite scores were also effective in evaluating dynamic changes in CTS disease severity. Currently, possibly due to small sample size, these scores have only been shown to be sensitive in detecting changes in more chronic patients; however, there is a trend suggesting that the ΔCS* may also prove useful in more recently diagnosed patients.

In summary, while not statistically significant, there were trends to suggest more severe disease exists in older patients, women, and Whites. Furthermore, no conclusions may be drawn with regards to the tendency for more obese individuals to have more severe disease. These results may be accounted for by differences in disease etiologies. Finally, further testing must occur with larger sample sizes, in order to determine if these trends are valid. Therefore, future public health campaigns to educate the public about CTS, should address that not only is disease more common in older White females, but it is also more severe.

In conclusion, it has been found that OMT results in statistically significant improvement in average composite scores in patients forty years or younger, females, Whites, non-obese and obese subjects, and the more chronic subjects. Furthermore,

trends were found towards significance in all other sub-groups with the exception of non-Whites because of a severely limited sample size. The differences in these sub-groups may be secondary to independent multi-factorial etiologic factors. Comparing the two groups for overall effectiveness of OMT, the average decrease in composite scores was greater in younger patients, females, non-obese subjects, and those with more chronic disease. Further testing with larger sample sizes and paired placebo counterparts will assist in determining the validity of these decreases in disease severity in patients, after treatment with OMT, is indeed a reality. Finally, since the non-obese subject decrease in severity score was nearly twice that of obese counterparts, it is essential for osteopathic physicians educating patients about OMT effectiveness to emphasize the role of weight loss in the treatment plan.

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APPENDIX: TABLES AND FIGURES

Table 1: Pearson Correlations for Demographic and CTS Risk Factors

Demographic & CTS Risk Factors	**Pearson CSi**	**Pearson CSq**
Age (years)	0.22	0.39
Gender(1=m,2=f)	0.04	0.34
Ethnicity (1=c, 2=nc)	-0.19	-0.13
BMI	0.38	0.42
Time since diagnosis (yrs)	-0.01	0.21

Table 2: Initial Composite Scores Summary

Category	**Dichotomy**	**Sample Size**	**Csi**		**CSq**	
			average	*95% CI*	*average*	*95% CI*
Age	≤40 years old	11	47.77	(40.25, 55.29)	1.36	(0.70, 2.03)
n=36	>40 years old	25	53.76	(49.79, 57.73)	2.12	(1.71, 2.53)
Gender	Male	11	48.03	(41.49, 54.57)	1.45	(0.84, 2.07)
n=37	Female	26	54.06	(49.85, 58.27)	2.12	(1.69, 2.54)
Ethnicity	White	32	53.09	(49.63, 56.56)	2.00	(1.63, 2.37)
n=36	non-White	4	48.75	(33.40, 64.11)	1.50	(0.23, 2.77)
BMI	BMI <30	18	49.54	(44.47, 54.61)	1.67	(1.19, 2.14)
n=35	Obese	17	54.34	(48.89, 59.79)	2.12	(1.54, 2.70)
Time since onset	<1 year*	15	50.32	(44.99, 55.64)	1.67	(1.17, 2.16)
n=34	>1 year*	19	53.67	(48.98, 58.36)	2.11	(1.36, 2,47)

* The six subjects who were diagnosed 1 year ago were randomly divided equally among the two subgroups

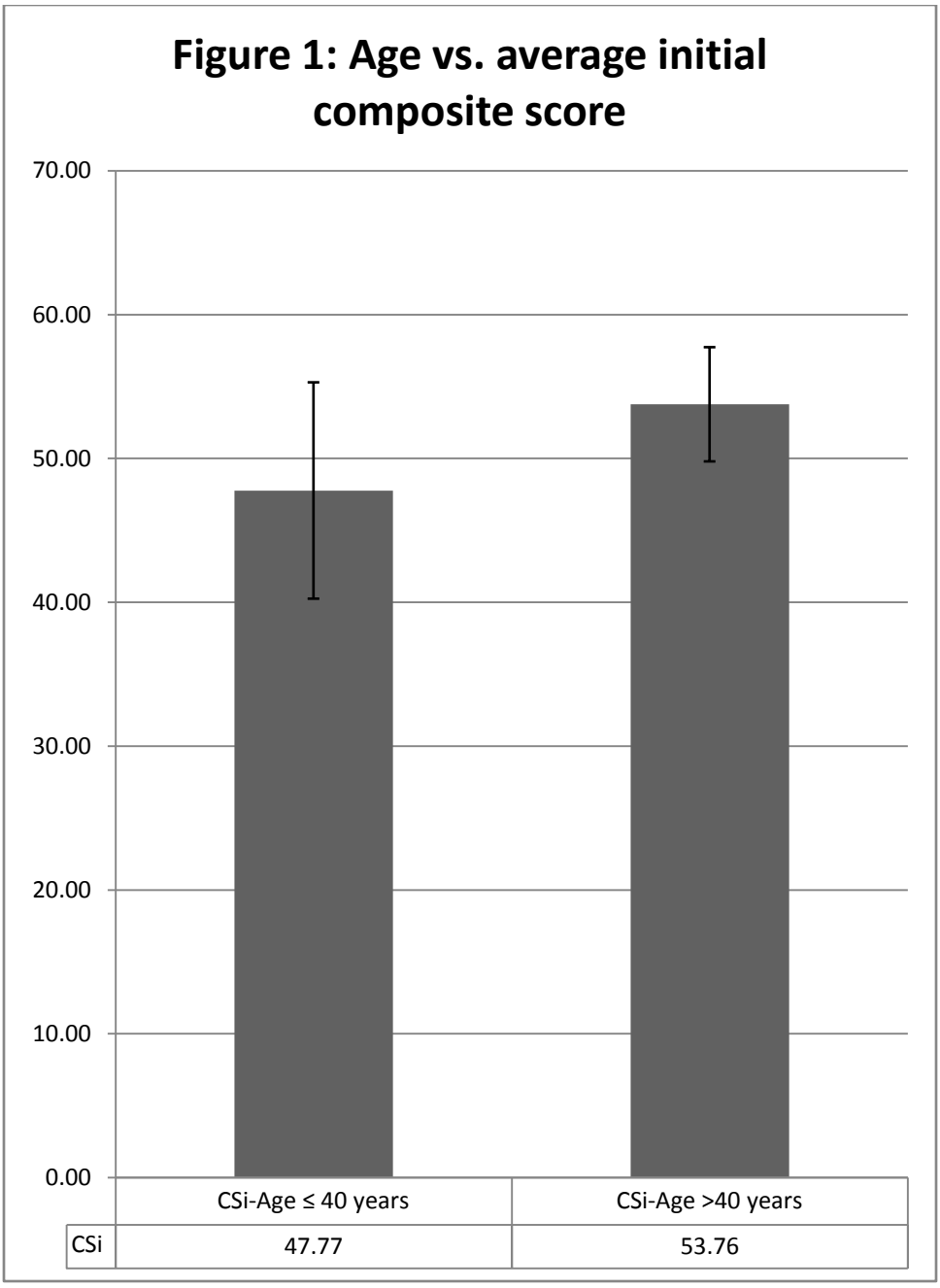


Figure 1: Age vs. average initial composite score
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
CSi-Age ≤ 40 years
CSi-Age >40 years
CSi
47.77
53.76

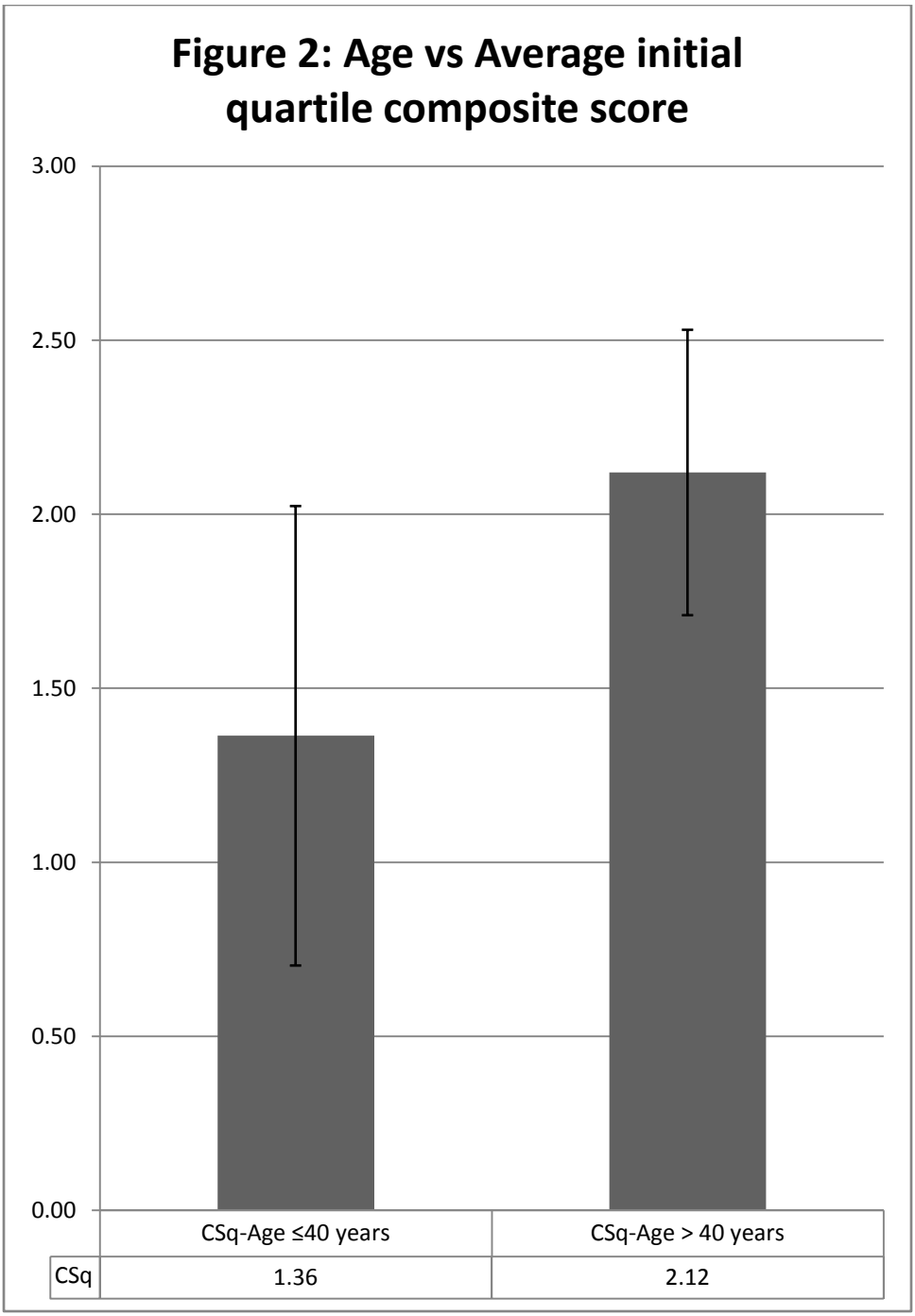


Figure 2: Age vs Average initial quartile composite score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
CSq-Age ≤40 years
CSq-Age > 40 years
CSq
1.36
2.12

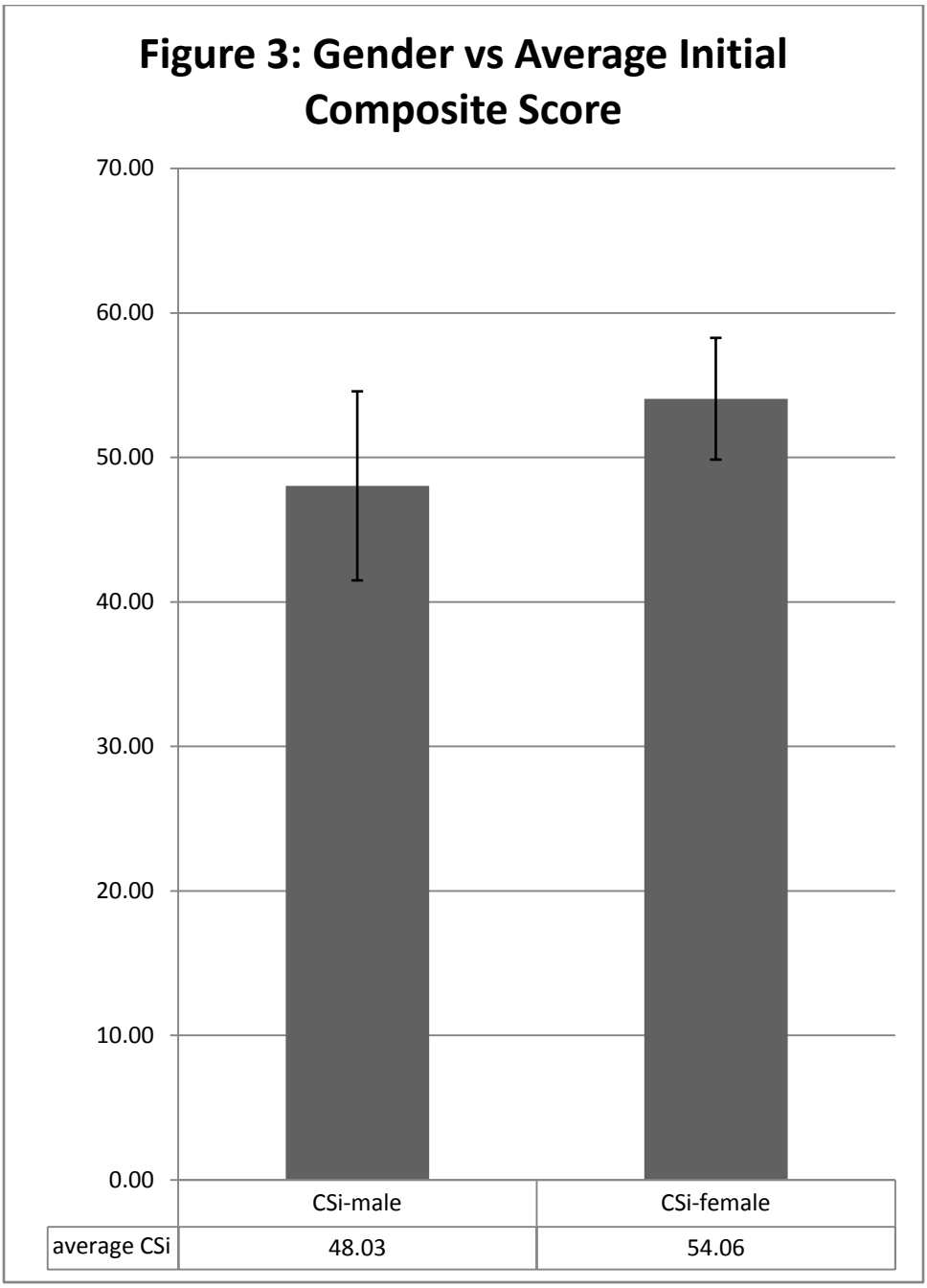


Figure 3: Gender vs Average Initial Composite Score
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
CSi-male
CSi-female
average CSi
48.03
54.06

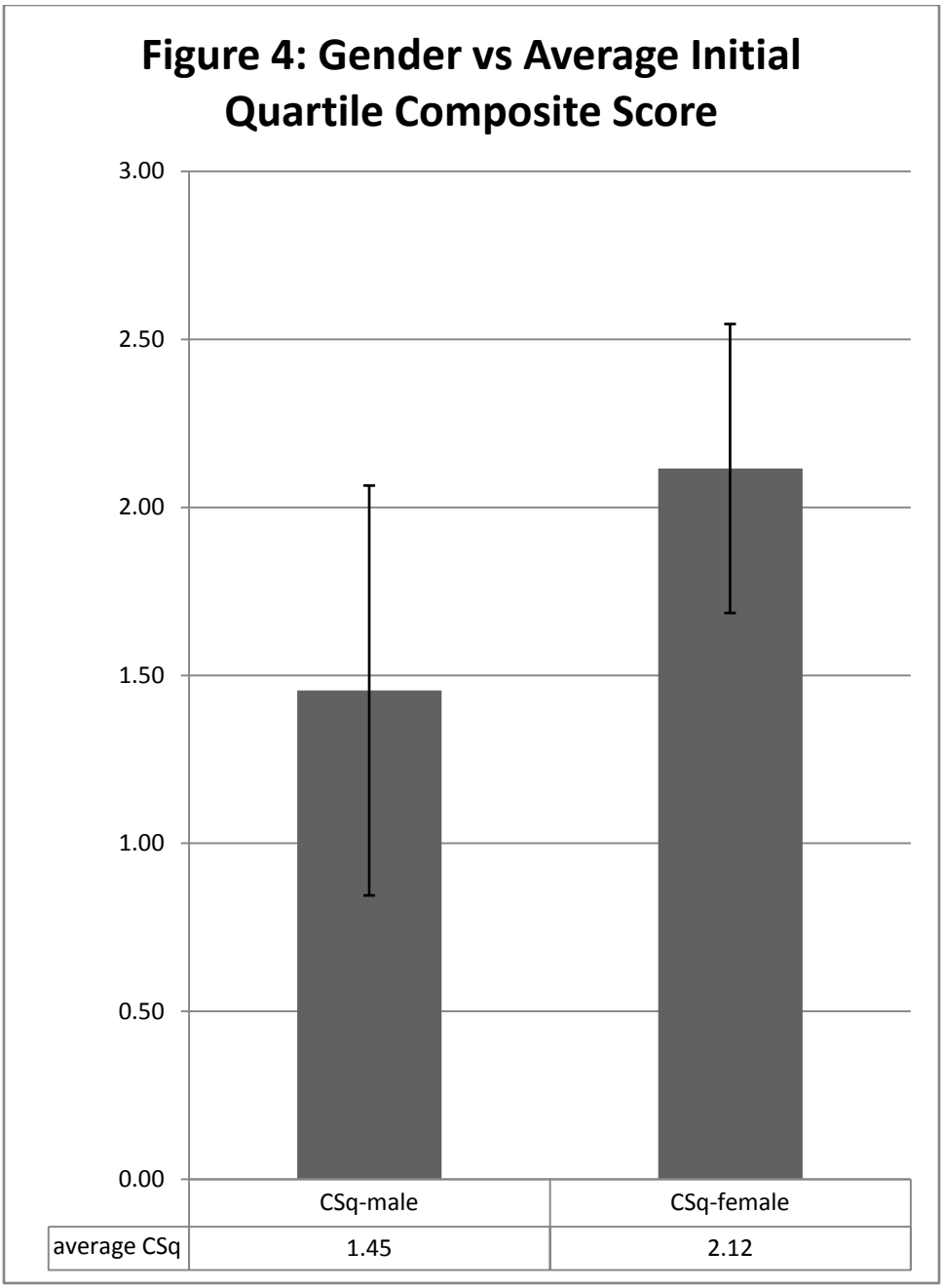


Figure 4: Gender vs Average Initial Quartile Composite Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
CSq-male
CSq-female
average CSq
1.45
2.12

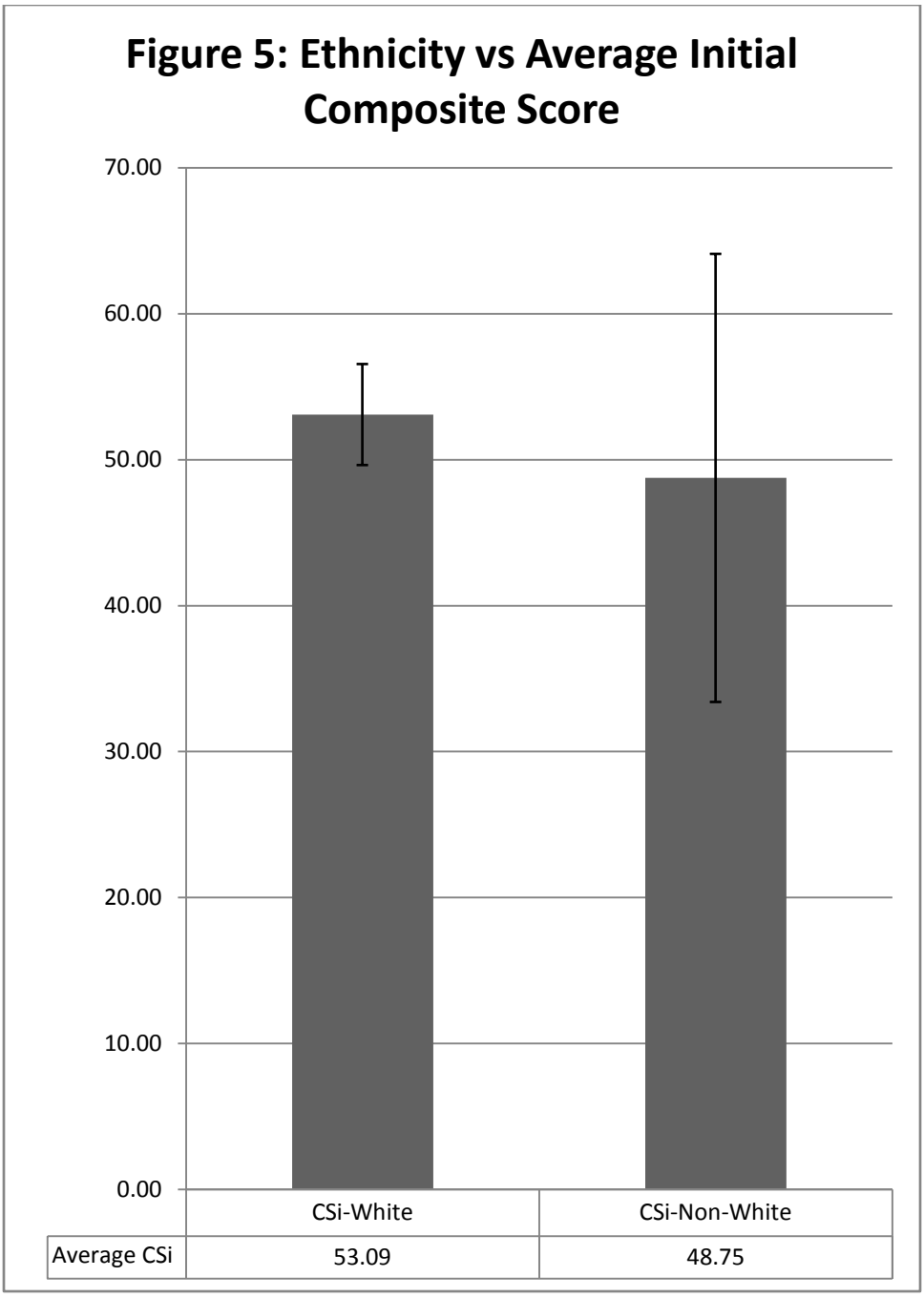


Figure 5: Ethnicity vs Average Initial Composite Score
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
CSi-White
CSi-Non-White
Average CSi
53.09
48.75

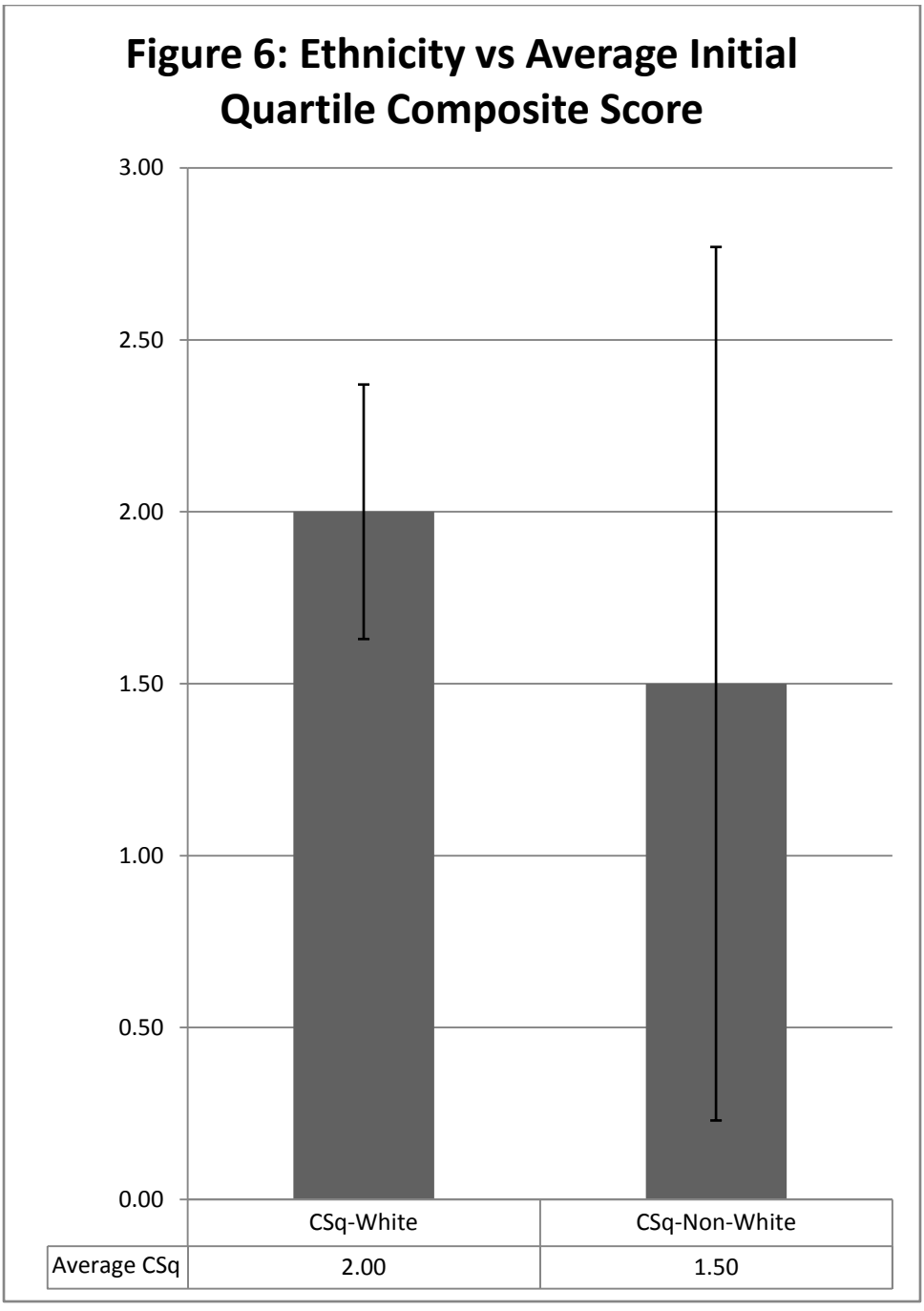


Figure 6: Ethnicity vs Average Initial Quartile Composite Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
CSq-White
CSq-Non-White
Average CSq
2.00
1.50

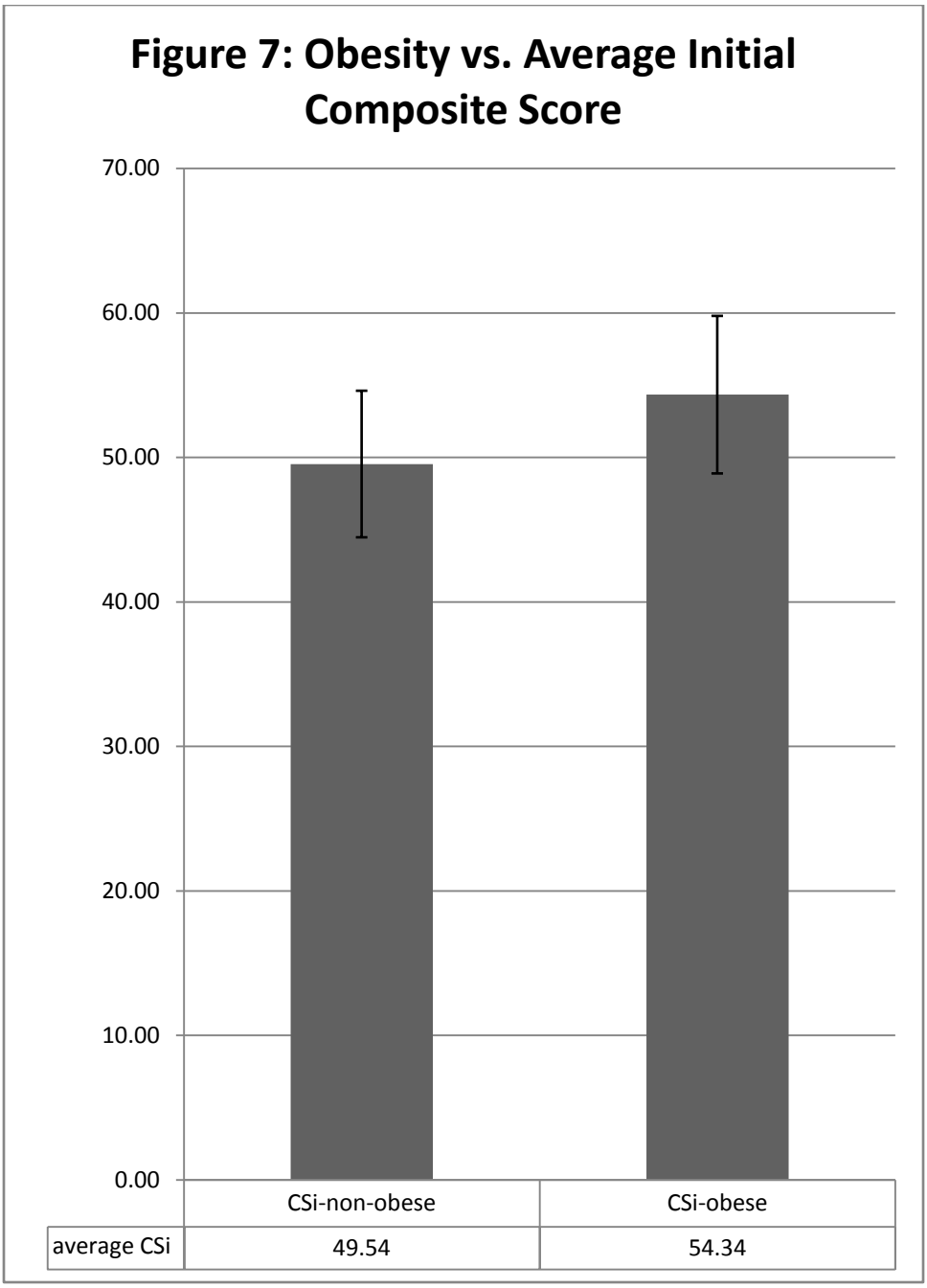


Figure 7: Obesity vs. Average Initial Composite Score
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
CSi-non-obese
CSi-obese
average CSi
49.54
54.34

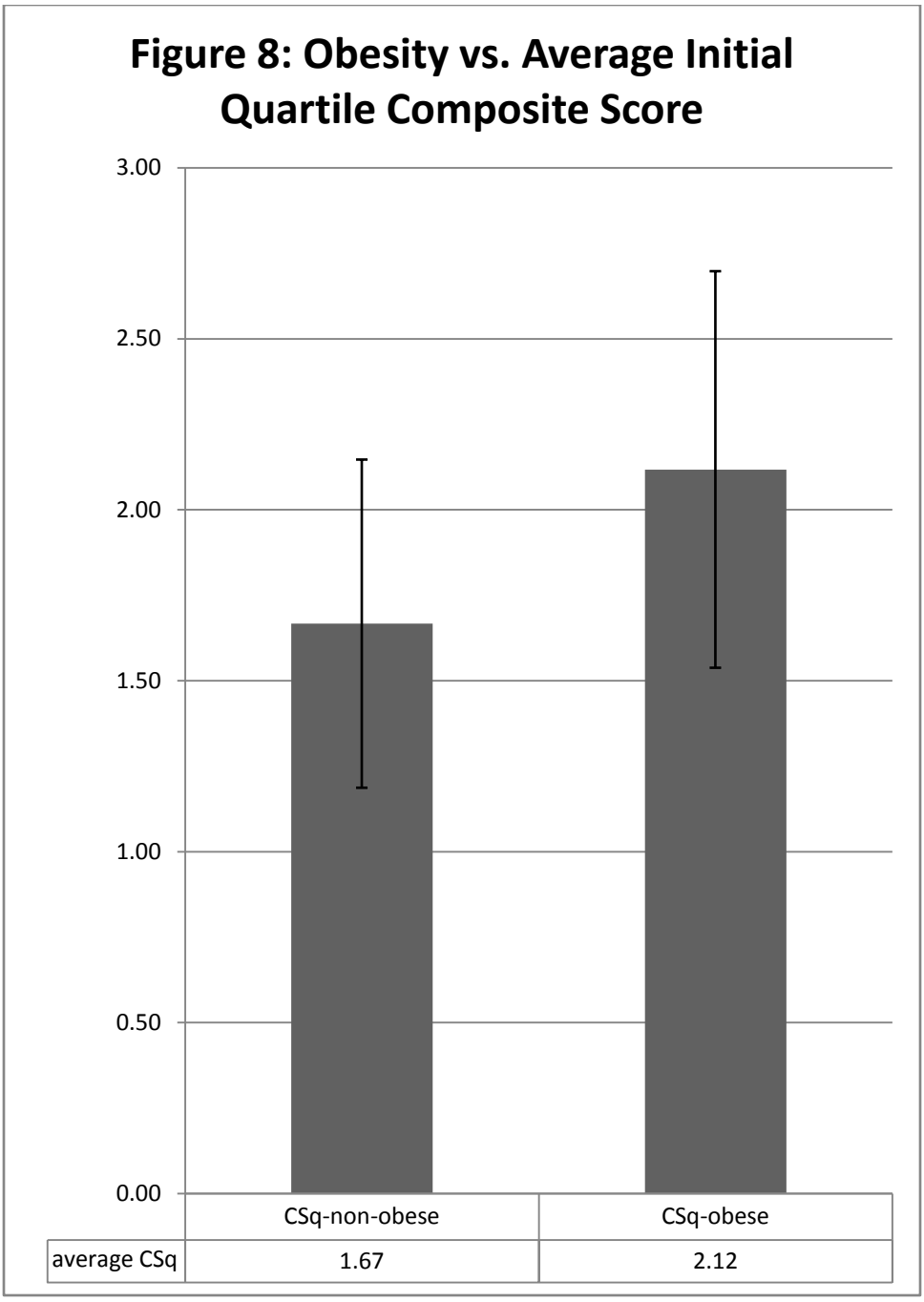


Figure 8: Obesity vs. Average Initial Quartile Composite Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
CSq-non-obese
CSq-obese
average CSq
1.67
2.12

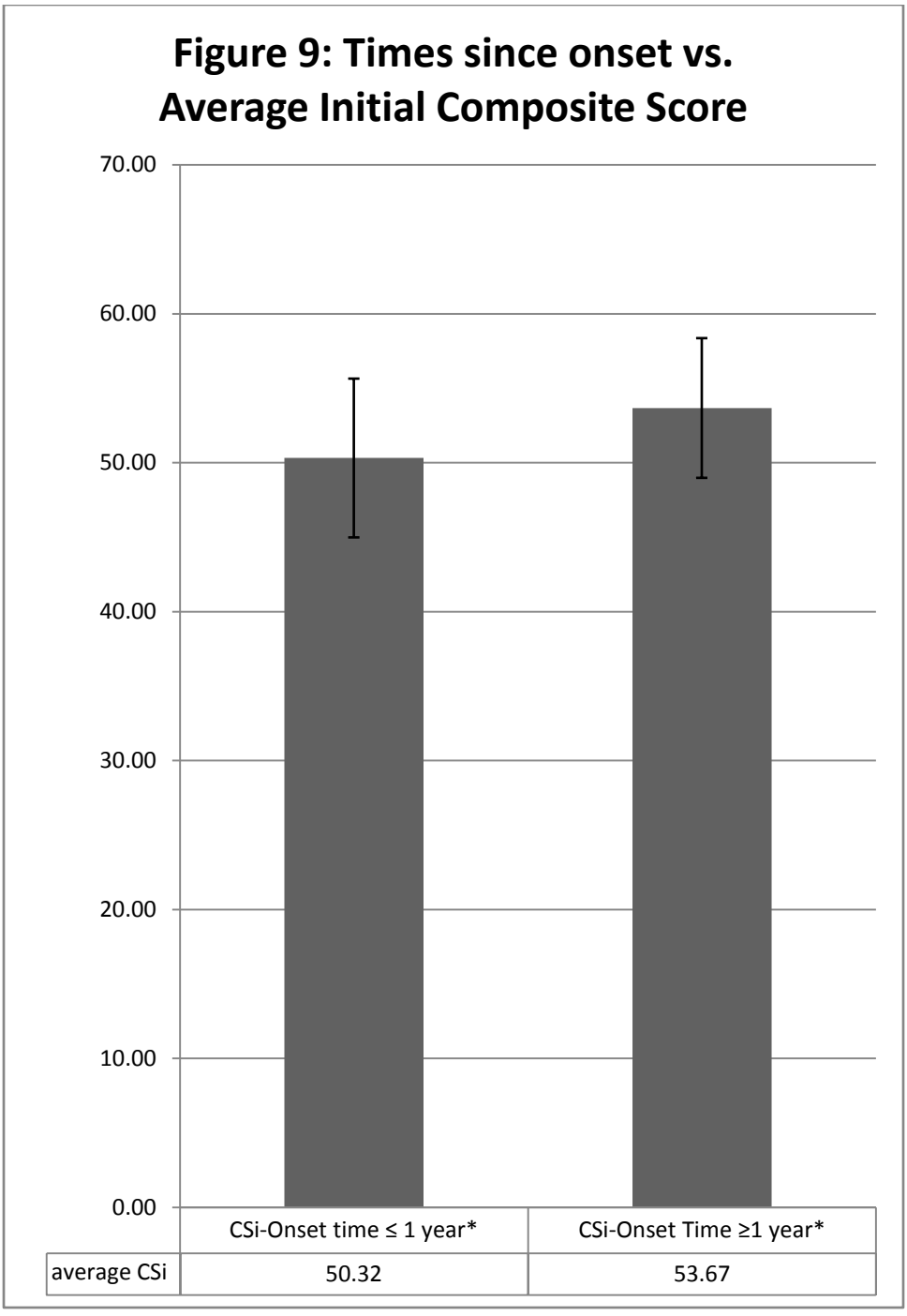
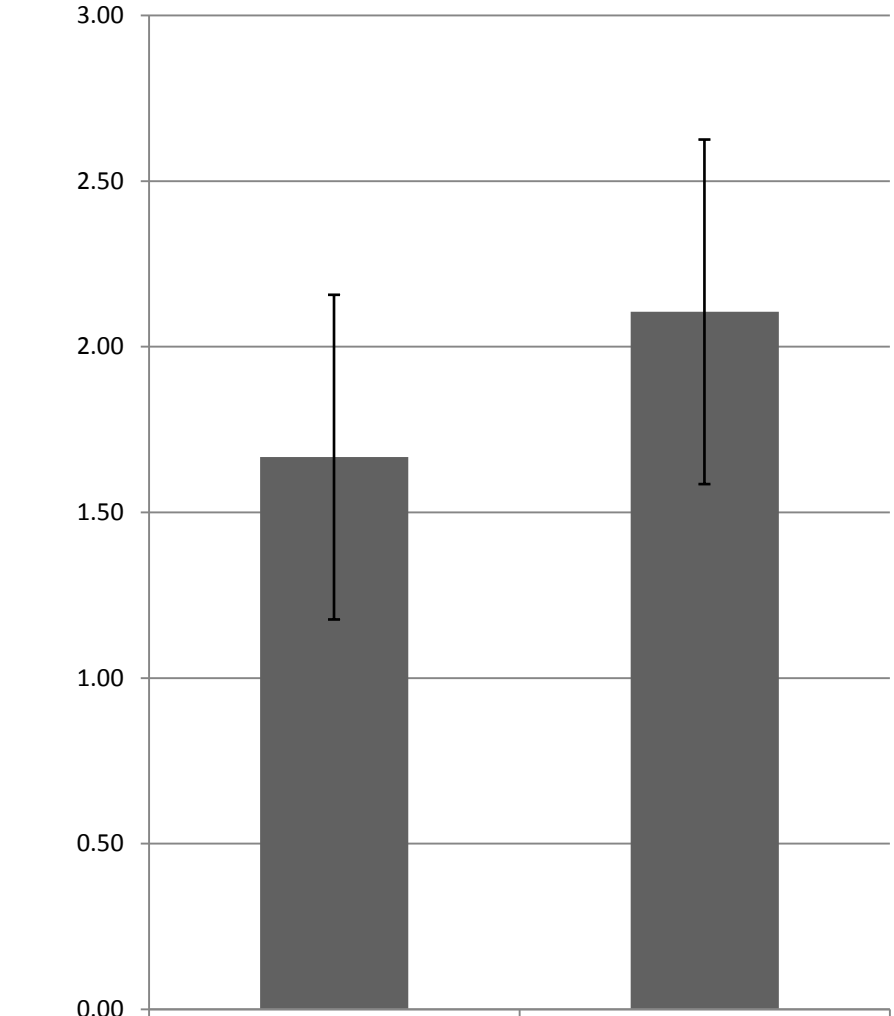


Figure 9: Times since onset vs. Average Initial Composite Score
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
CSi-Onset time ≤ 1 year*
CSi-Onset Time ≥1 year*
average CSi
50.32
53.67

Figure 10: Time since Disease Onset vs Average Initial Quartile Composite Score



	CSq-Onset Time ≤1 year*	CSq-Onset Time ≥ 1 year*
average CSq	1.67	2.11

Table 3: Average change of Composite Scores with OMT Summary

Category	**Dichotomy**	**Sample Size**	**ΔCS***		**ΔCSq***	
			average	*95% CI*	*average*	*95% CI*
Age	≤40 years old	5	-7.79	(-20.70, 5.12)	-1.33	**(-2.48, -0.19)**
n=14	>40 years old	9	-3.89	(-10.39, 2.60)	-0.78	(-1.56, 0.01)
Gender	Male	6	-4.26	(-12.95, 4.42)	-0.80	(-1.76, 0.16)
n=14	Female	9	-5.85	(-14.20, 2.50)	-1.00	**(-1.86, -0.14)**
Ethnicity	White	12	-5.79	(-12.76, 1.18)	-1.00	**(-1.72, -0.28)**
n=13	non-White	1	-5.12	**	-1.00	**
BMI	BMI <30	7	-8.88	**(-17.33, -0.42)**	-1.29	**(-2.21, -0.36)**
n=13	Obese	6	-4.63	(-11.62, 2.36)	-0.83	**(-1.62, -0.05)**
Time since onset	<1 year*	4	-5.08	(-23.14, 12.98)	-1.00	(-2.61, 0.61)
n=13	>1 year*	9	-6.03	**(-10.38, -1.68)**	-1.00	**(-1.65, -0.35)**

* Of the six subjects who were diagnosed 1 year ago were randomly divided equally among the two subgroups, only one was in the OMT arm of the study

**Cannot determine due to sample size of one

NOTE: Those in Bold are statistically significant

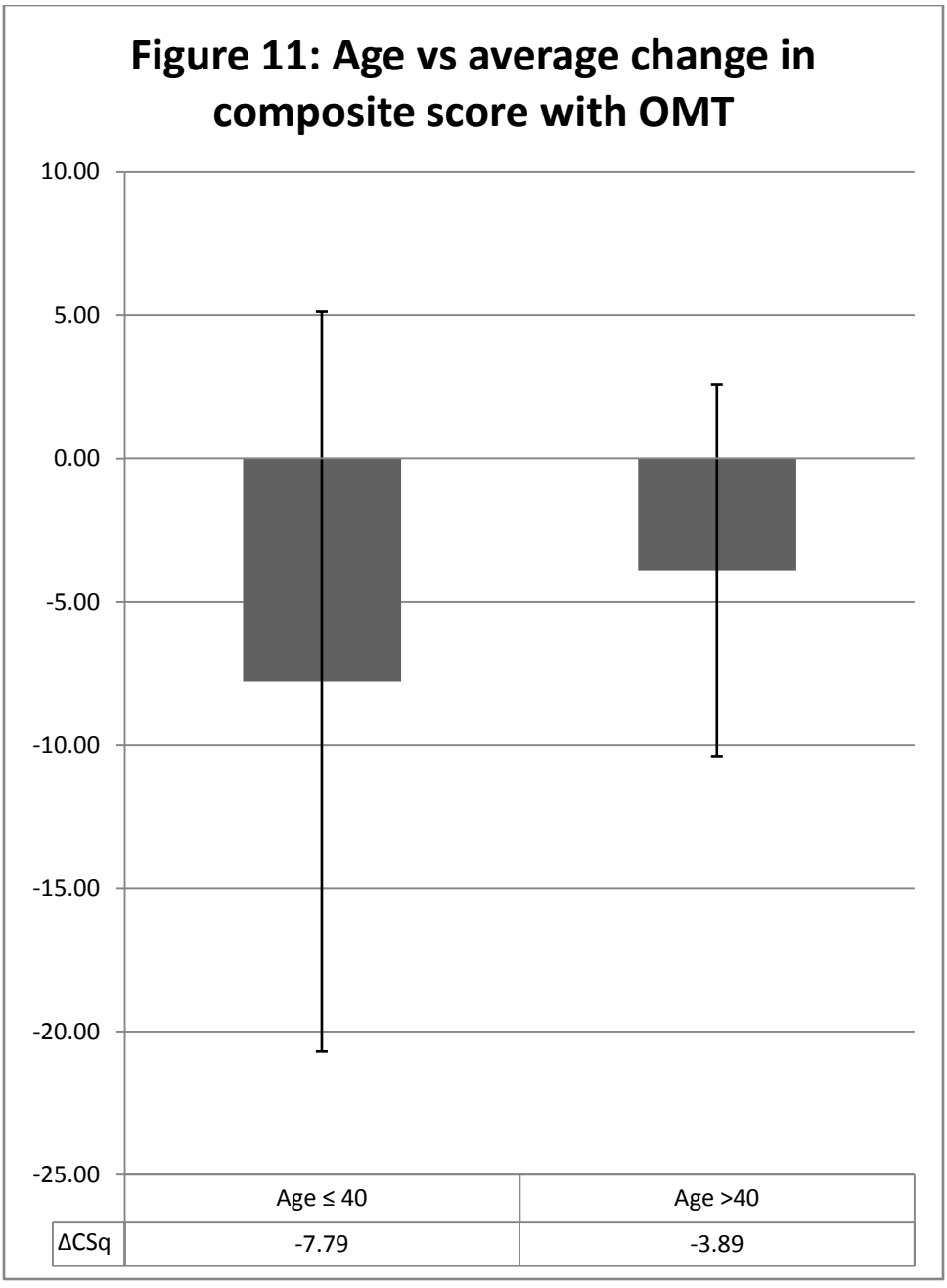
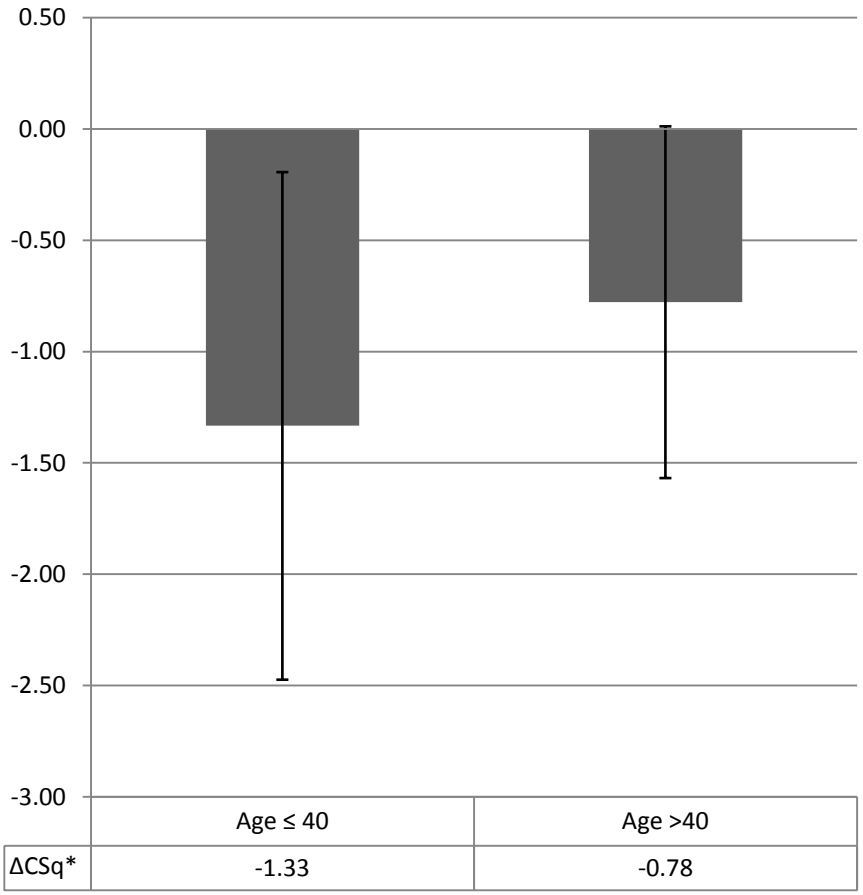


Figure 11: Age vs average change in composite score with OMT
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
Age ≤ 40
Age >40
ΔCSq
-7.79
-3.89

Figure 12: Age vs average change in quartile composite score with OMT



	Age ≤ 40	Age >40
ΔCSq*	-1.33	-0.78

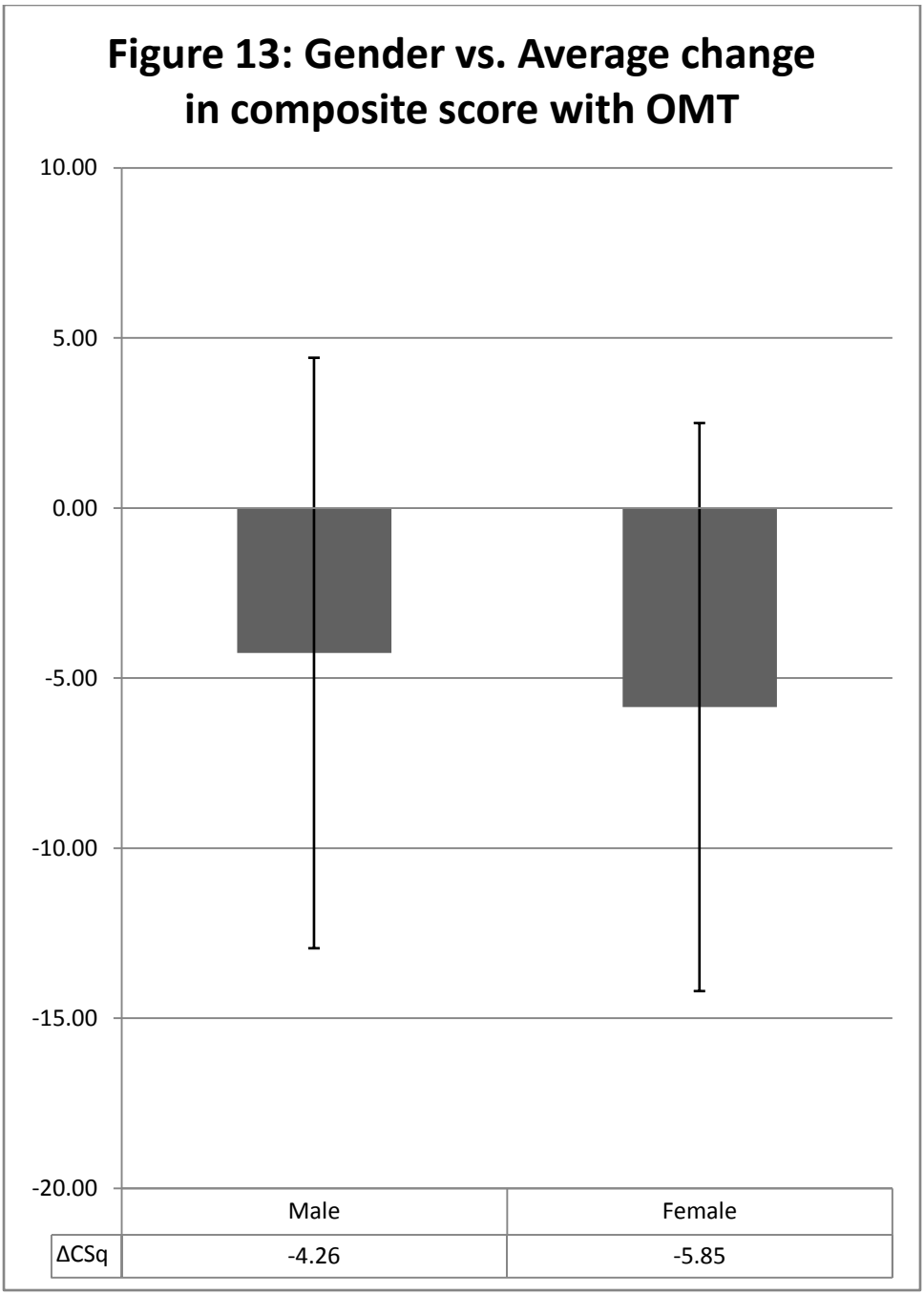
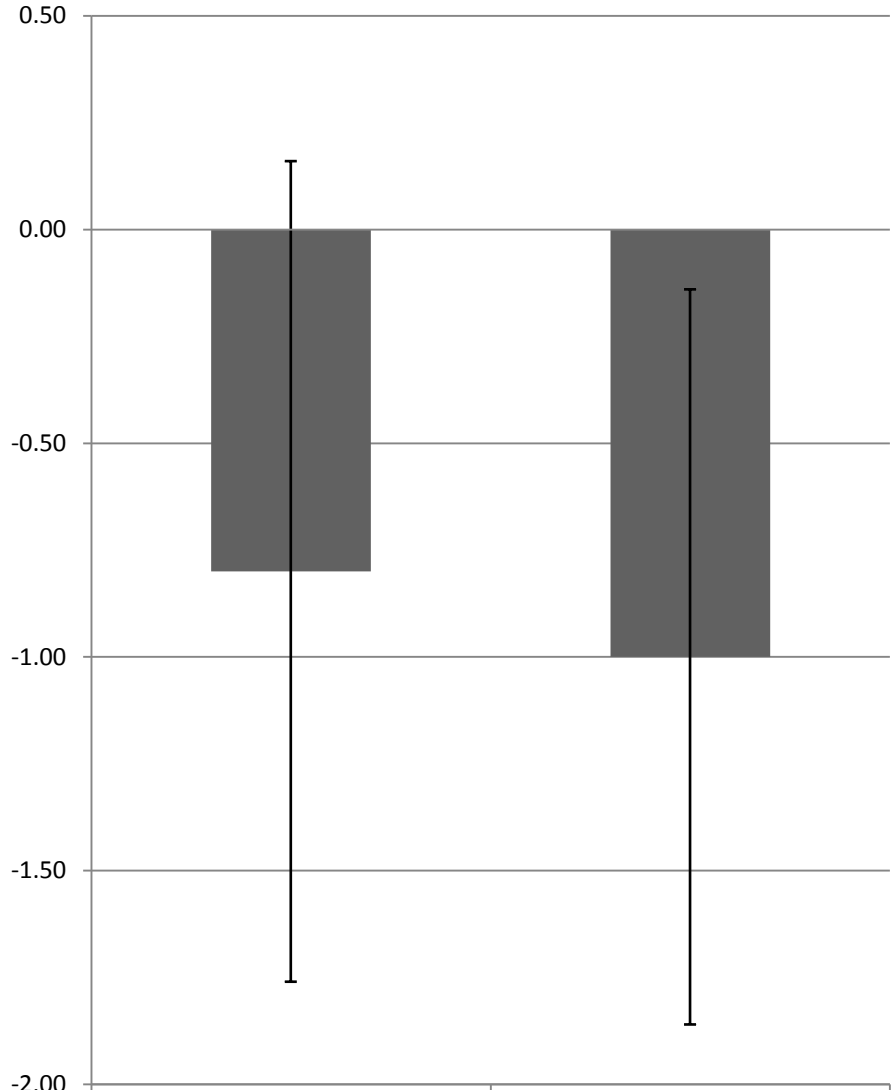
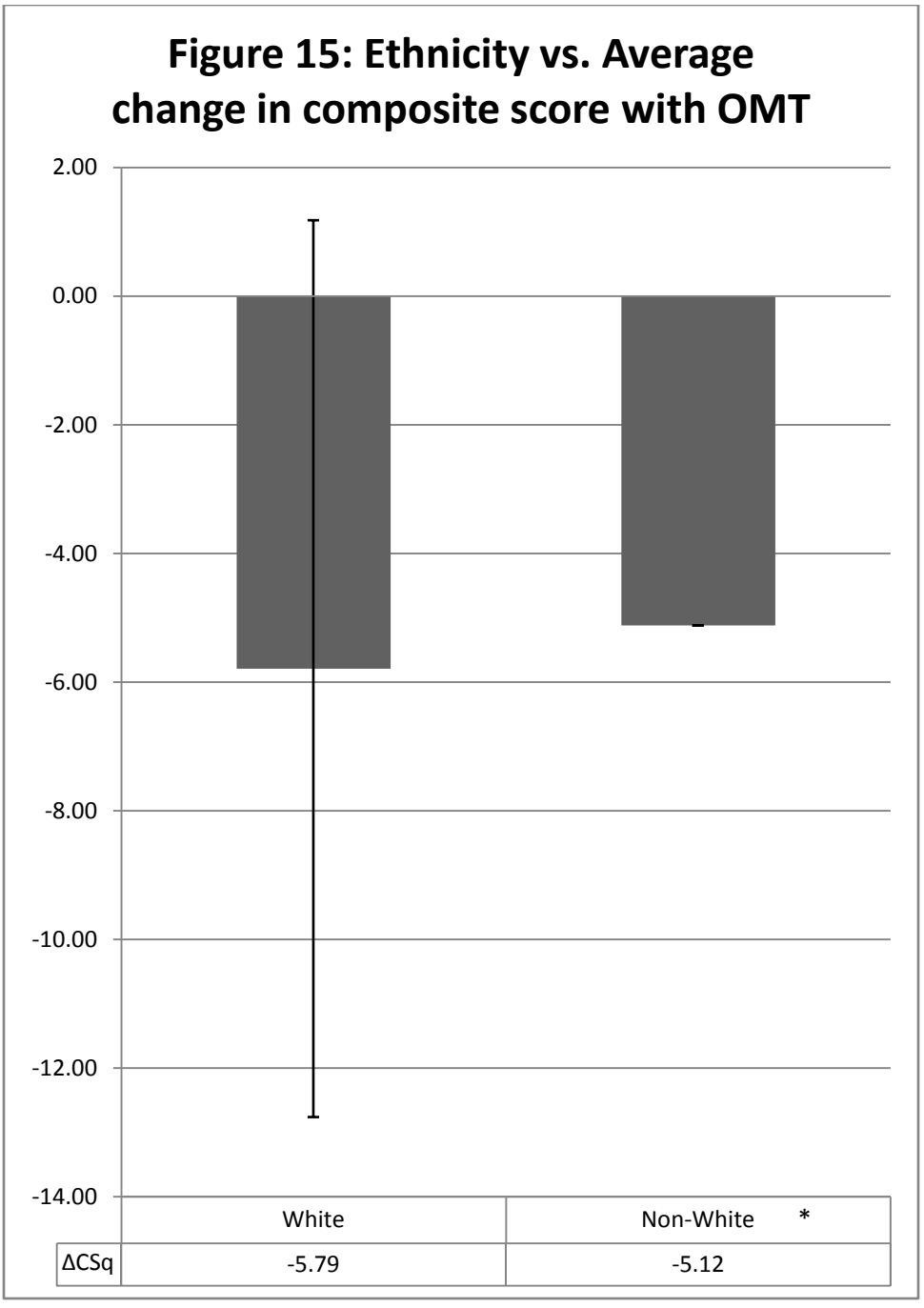


Figure 13: Gender vs. Average change in composite score with OMT
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
Male
Female
ΔCSq
-4.26
-5.85

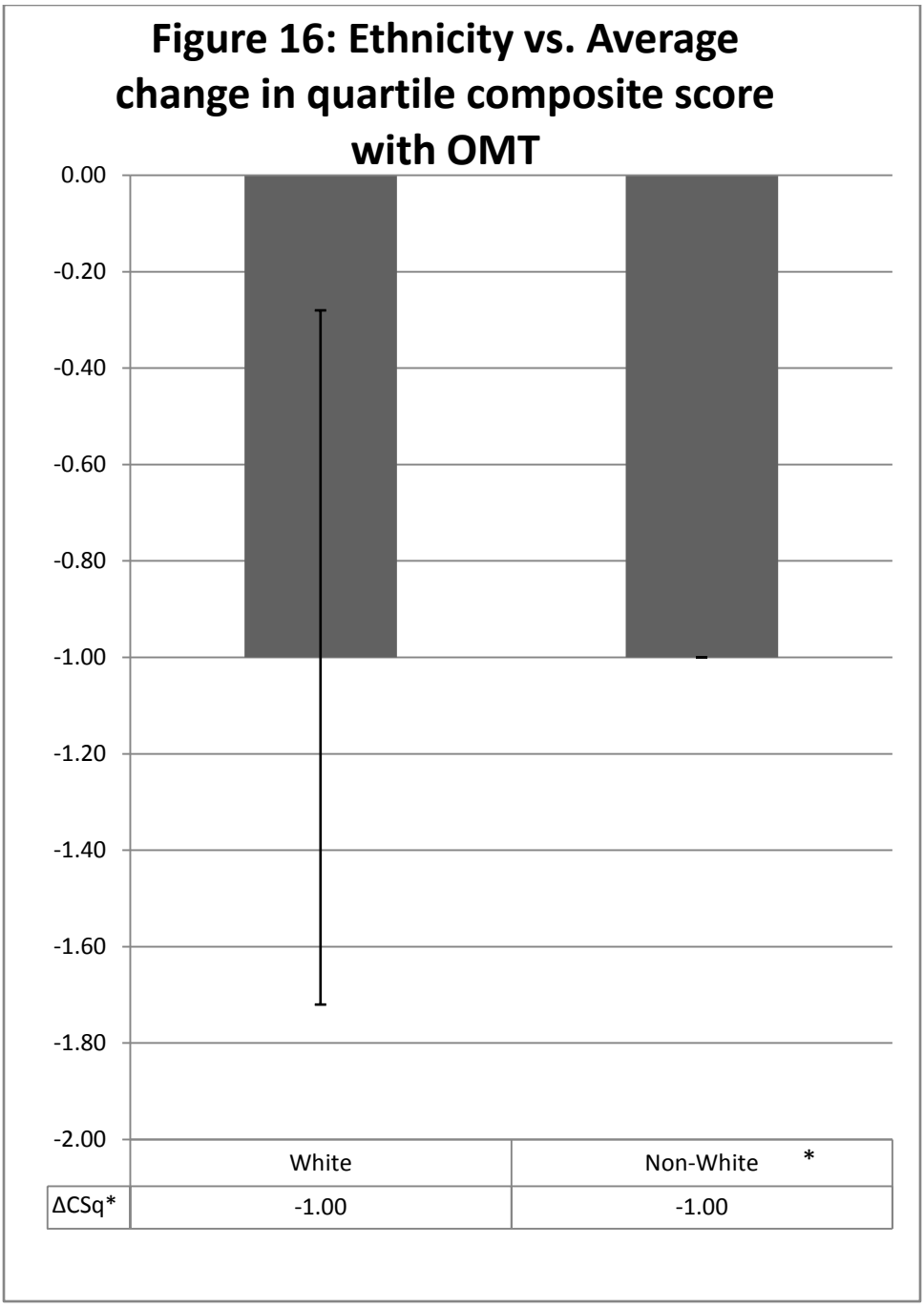
Figure 14: Gender vs. Average change in quartile composite score with OMT



	Male	Female
ΔCSq*	-0.80	-1.00

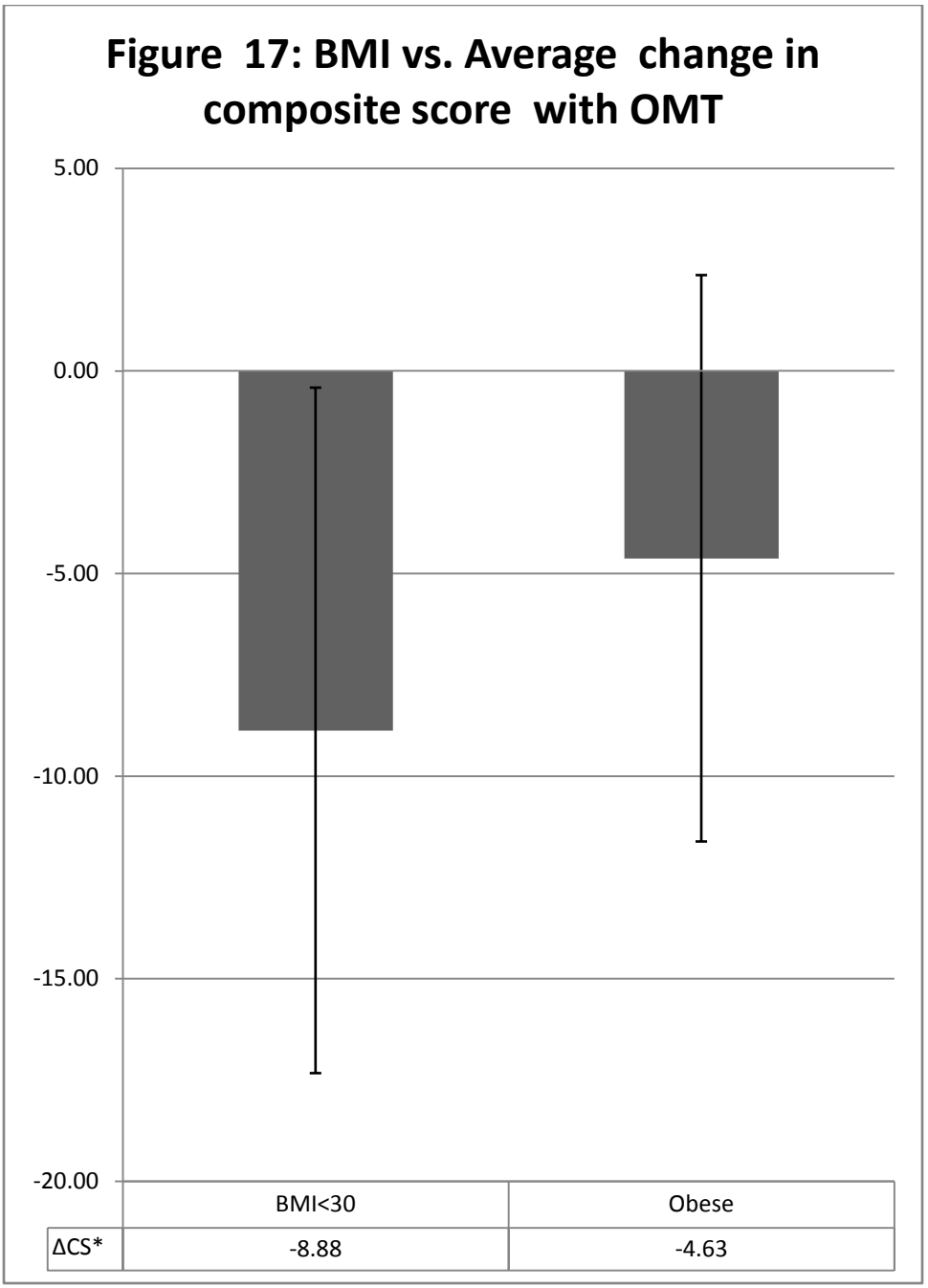


*Error Bar for non-white subgroup could not be calculated due to sample size of one



*Error Bar for non-white subgroup could not be calculated due to sample size of one

Figure 17: BMI vs. Average change in composite score with OMT



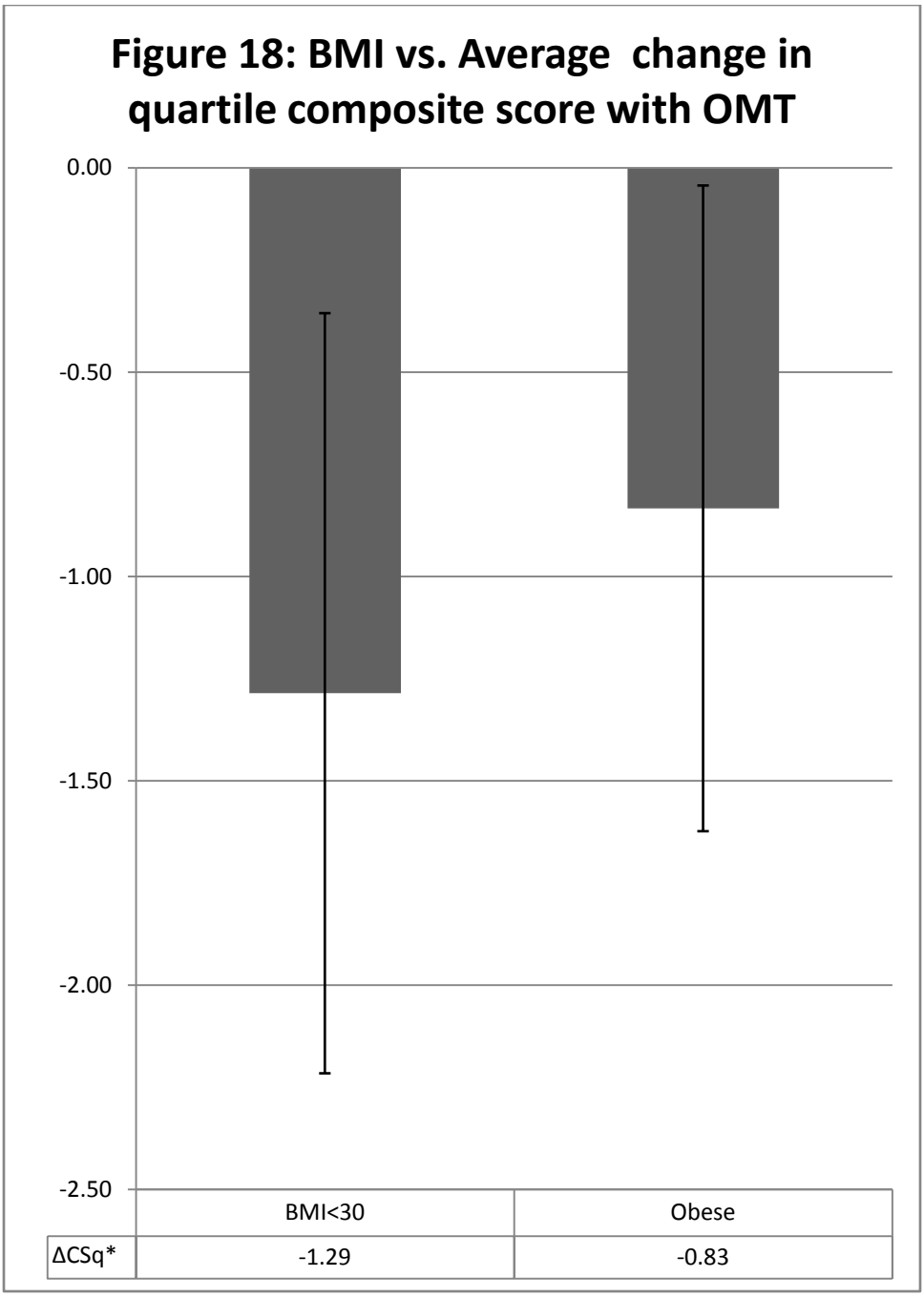


Figure 18: BMI vs. Average change in quartile composite score with OMT
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
BMI<30
Obese
ΔCSq*
-1.29
-0.83

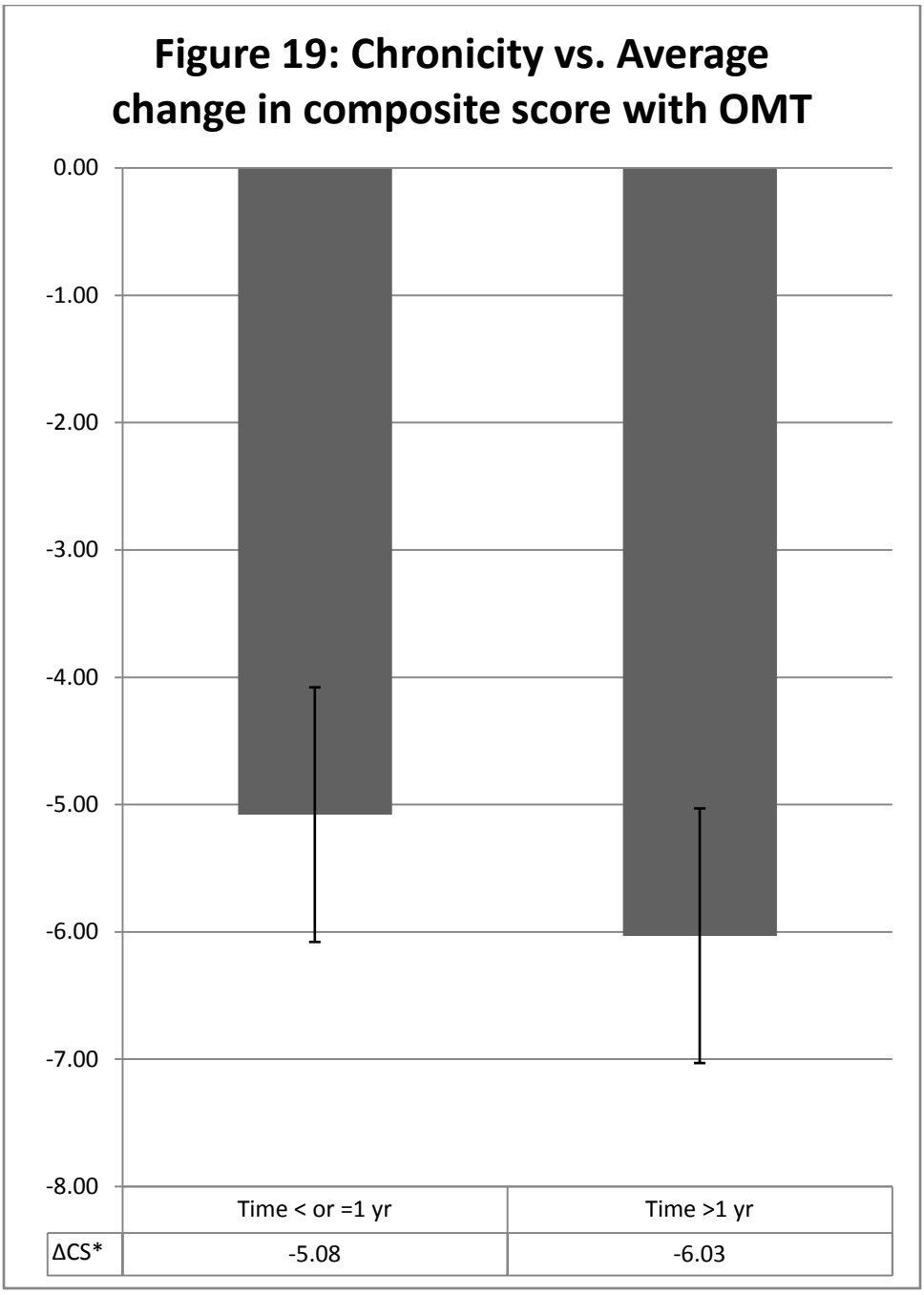
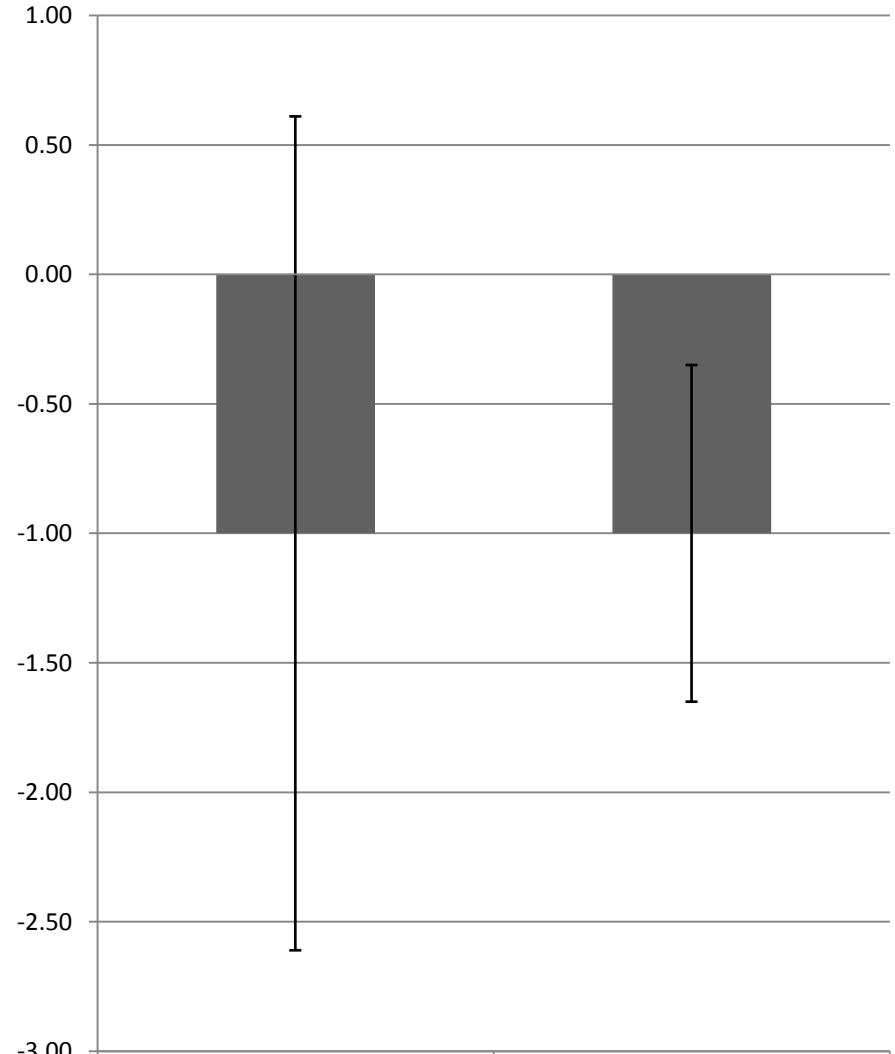


Figure 19: Chronicity vs. Average change in composite score with OMT
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
-8.00
Time < or =1 yr
Time >1 yr
ΔCS*
-5.08
-6.03

Figure 20: Chronicity vs. Average change in quartile composite score with OMT



	Time < or =1 yr	Time >1 yr
ΔCSq*	-1.00	-1.00