INVESTIGATING THE TRANSITION FROM CHRONIC LOW BACK OR NECK PAIN TO WIDESPREAD PAIN AND FIBROMYLGIA

By

Lindsay Lancaster Kindler, MSN, RN, CNS

A Dissertation

Presented to

Oregon Health & Science University

School of Nursing

In partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

April 14, 2009

APPROVED:

Kim Dupree Jones, PhD, FNP, RN, Dissertation Chair

Robert M. Bennett, MD, Committee Member

Nancy Perrin, PhD, Committee Member

Michael R. Bleich, PhD, RN, MPH, FAAN, Dean, School of Nursing

ACKNOWLEDGEMENTS

This dissertation research was supported by a National Institute of Nursing Research Institutional National Service Research Award (5 T32 NR007061-15), a National Institute of Nursing Research Individual National Service Research Award (1 F31 NR010301-01), the Oregon Health & Sciences University Dean's Award for Doctoral Dissertation, the Sigma Theta Tau Beta Psi Research Award, and a University Club Foundation Fellowship Award. The generous funding provided by these institutions enabled the participants of this study to be compensated for their time and energy and allowed me to express my appreciation to several individuals who assisted with testing a subset of these participants for fibromyalgia. This funding also allowed me to present my research twelve times at various regional, national, and international conferences. Equally as important, this financial support paid for necessary research materials and services such as printing and mailing study surveys and invitation letters. Without the support provided to me by these considerate institutions, this research would not have been possible. Lastly, the generous award from the University Club Foundation will help me move into the next phase of my research career; a post-doctoral fellowship at the University of Florida.

Although I alone will be receiving this doctoral degree, it should really include the names of the many individuals who made this journey possible. Throughout this program I have come to appreciate how fortunate I have been to have a committee whose primary interest is helping me succeed. Dr. Kim Dupree Jones has consistently been an incredible cheerleader whose faith in me has helped me believe in myself as well. Throughout my work with her, Kim has served as a role model to demonstrate that a woman can be a successful researcher while maintaining a family life and being a kind person to others. Dr. Robert Bennett's expansive knowledge of the field has piqued my

own interest in the biological mechanisms of chronic pain and fibromyalgia, pushing me to further my research in this area through a post-doctoral fellowship. Finally, I am grateful to Dr. Nancy Perrin for patiently sharing her statistical expertise, all the while never making me feel inept. Although Nancy's skills are requested on much higher level projects, she treated me as if my study were just as critical to the advancement of the University. I am grateful to my committee for providing me with the support, expertise, and encouragement necessary to successfully complete this study.

Throughout my time in the program I was fortunate enough to work clinically with an incredibly supportive and flexible team of coworkers at the Kaiser Permanente Pain Clinic. Their flexibility allowed me to continue the work that has been the impetus for my research interests and stay connected with the patients whose courage in the face of continuous pain moves us to find better treatments. The Pain Clinic has truly been a second family whose love and support kept me motivated to continue this journey. When I felt unsure of myself as a researcher, my coworkers reminded me that I was a valued clinician and had the ability to develop myself as a researcher as I had done with my clinical work. Their confidence in me has maintained my motivation throughout this journey.

Finally, words cannot express the gratitude I feel towards the people who truly deserve this degree, my parents and husband. The support given to me by my parents astonishes me every day. Their unconditional belief in my abilities has allowed me to accomplish things I never thought possible. When I have doubted myself (as can occur regularly in a doctoral program), a simple phone call to them renewed my self confidence as I gain a glimpse of myself through their eyes. They are my biggest, most loyal fans, which has been invaluable throughout my journey. Finally, my husband,

Travis, has met my seemingly unending journey in school with patience and understanding. He has endured the emotional ups and downs that come with waiting for grant approval, working with the IRB, patient recruitment, months of data entry, and preparation for conferences. He has kindly modified his expectations of a “normal” relationship as he has allowed me to focus on my own career development. And when I informed him of this thing called a post-doc, he put his own vision of our future on hold to support me in this endeavor. He has consistently demonstrated his love by allowing me to partake in the opportunities that advance my career, while placing his needs on the back burner.

I am forever indebted to the people who made this journey not only possible, but enjoyable. You have given me an invaluable gift that I will never forget.

ABSTRACT

Objectives: Emerging evidence suggests that chronic low back pain, chronic neck pain, widespread pain (WSP), and fibromyalgia (FM) share a common underlying mechanism, namely central sensitization. Research demonstrates that a majority of individuals with WSP and FM and some people with chronic low back or neck pain (termed chronic regional spinal pain, CRSP) exhibit altered pain processing which is characteristic of the neuroplastic changes of central sensitization. Perhaps due to this shared pathophysiology, recent studies have demonstrated that a subset of individuals with chronic low back or neck pain develop WSP and/or FM over time. Less clear are the specific risk factors that predispose a person with chronic low back or neck pain to the development of these widespread pain disorders. The purpose of this study was to determine the frequency with which patients with chronic low back or neck pain develop WSP or FM and to determine the risk factors which place a person at risk for this transition. Knowing the predictive factors for the development of WSP and FM in patients with CRSP is critical in that numerous studies have demonstrated that WSP and FM are associated with more severe clinical outcomes as compared to CRSP. Identifying a group of patients with CRSP who are at a higher risk of developing WSP or FM would provide an opportunity for the nursing and medical community to intervene in this downward trajectory.

Methods: 2,256 patients previously seen by a multidisciplinary pain clinic in 2001 or 2002 for evaluation and treatment of a chronic low back or neck pain disorder were invited to participate in this study in 2007. The researchers used data collected on two questionnaires, one completed by the patients in 2001 or 2002 and one sent to them by the study team in 2007. Predictive factors investigated in this study fell broadly into three categories; features thought to influence the development of central sensitization, risk

factors known to precede WSP and FM, and clinical features that frequently co-occur with WSP and FM. Both questionnaires included a body drawing, allowing the study team to determine which participants, who had CRSP in 2001 or 2002, had developed WSP by 2007. Those participants who had developed WSP by 2007 were invited to undergo an examination to evaluate the presence of a FM diagnosis. The 2001/2002 questionnaire was used to determine participant status on proposed risk factors prior to their development of WSP or FM.

Results: Out of the 512 participants who had presented with CRSP in 2001/2002, 114 (22.3%) had developed WSP by 2007. Risk factors present in 2001/2002 that were associated with the development of WSP included moderate or severe pain intensity, female gender, history of abuse, family history of WSP, severe interference with general activity, morbid obesity, having one or more central sensitivity syndromes, and using more pain management strategies. Out of the 23.6% of subjects with WSP who were willing to report to the study site for an examination, 22 (75.9%) were diagnosed with FM. These 22 participants were added to the 18 participants who had been diagnosed with FM by their health plan provider between 2003 and 2007 for a total of 40 study participants who had presented with chronic low back or neck pain in 2001/2002 and developed FM by 2007. Risk factors present in 2001/2002 that were associated with a transition to FM included moderate or severe pain intensity, female gender, history of abuse, having a sibling with WSP, having one or more central sensitivity syndromes, and using more pain management strategies. Risk factors from 2001/2002 that did not significantly predict the development of WSP or FM in these participants with CRSP included depression, age, pain duration, number of back or neck surgeries, number of medication classes used to treat pain, tobacco pack year history, or receipt of disability benefits.

Conclusions: This study demonstrated that nearly a quarter of patients with CRSP developed WSP over a six-year period. Interestingly, 75.9% if those participants who were willing to be examined also had FM. Several risk factors were shown to be predictive of the development of WSP and FM which allows practitioners to identify a group of patients with CRSP who are at increased risk for progression to a worsening clinical condition. Information gained from this study can guide the management of this group of high risk patients in an attempt to mitigate this progression. The identification of clinical features that are characteristic of this high risk group could also inform future studies that investigate individual differences in pain processing and prospective investigations into the development of other central sensitivity syndromes. Overall, this study has advanced the understanding of the relationship between CRSP, WSP, and FM in several ways.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Chronic pain is a prevalent, costly, and medically challenging problem, prompting Congress to name the years 2000 to 2010 the Decade of Pain Control Research. Chronic low back and neck pain, sometimes referred to as chronic regional spinal pain (CRSP), are prevalent chronic pain disorders, which affect approximately 13.6% of the population (Webb, et al., 2003). Symptom severity in these disorders is rarely explained by objective radiological findings alone, as there is often a mismatch between anatomic abnormalities and symptoms (Clauw, et al., 1999; Giesecke, et al., 2004). Emerging evidence suggests that central sensitization, an increase in the excitability of spinal and supraspinal neurons, may play an important role in the pathophysiology in some patients with CRSP (Flor, Braun, Elbert, & Birbaumer, 1997; Giesecke, et al., 2004; Lidbeck, 2002; Wilder-Smith, Tassonyi, & Arendt-Nielsen, 2002).

Central sensitization in CRSP

Persistent pain is often associated with changes in the central processing of pain at the spinal and supraspinal levels (Flor, 2003; Katz & Rothenberg, 2005; Mendell, 1966). It is well known that ongoing nociceptive stimulation of unmyelinated type C peripheral nerves, as may occur in CRSP, can induce a frequency dependent increase in the excitability of second order spinal cord neurons (Marchand, 2008). This phenomenon is typically referred to as temporal summation or "windup" (Eide, 2000; Mendell & Wall, 1965; Woolf & Thompson, 1991). Second order spinal neurons include nociceptive neurons (responding only to nociceptive input) and wide dynamic range neurons (responding to both nociceptive and non-nociceptive input). Following sensitization, wide dynamic range neurons (WDRN) respond as intensely to non-nociceptive stimuli as they did to nociceptive stimuli prior to sensitization (Almeida, Roizenblatt, & Tufik, 2004; Bennett, 1999). This results in regional sensitization, with the clinical findings of focal hyperalgesia and sometimes allodynia at the neck or back (Urban & Gebhart, 1999;

Zusman, 2002). In some cases, persistent WDRN sensitization leads to an expansion of receptive fields, with the clinical finding of widespread hyperalgesia/allodynia (Coderre, Katz, Vaccarino, & Melzack, 1993; Staud, 2007; Urban & Gebhart, 1999). Based on these experimental underpinnings, the development of widespread pain from an initial focus of segmental pain, such as CRSP, can be envisaged in terms of disordered neurophysiology (Bennett, 1999).

Ongoing pain, as occurs in CRSP, also causes a sensitization of peripheral tissues as a result of the antidromic release of potassium ions, substance P, bradykinin and prostaglandins (Dadabhoy, et al., 2008; Graven-Nielsen & Arendt-Nielsen, 2002). Substance P also plays a role in the occurrence of widespread central sensitization by lowering the threshold of synaptic excitability, which allows the sensitization of second order spinal neurons (Curatolo, 2004). Substance P can also migrate within the spinal cord and sensitize dorsal horn neurons at a distance from the initial locus of the stimulus. This can result in an expansion of receptive fields into adjacent, uninjured tissue. This is the mechanism whereby focal segmental sensitization in the low back or neck can develop into widespread central sensitization, the characteristic neurophysiological aberration found in fibromyalgia (FM) (Lidbeck, 2002; Urban & Gebhart, 1999). There are several reports that suggest that CRSP disorders are uniquely predisposed to FM and widespread pain (WSP) transition, due to the potential development of central sensitization (Buskila, 1997; Giesecke, et al., 2004; Huppe, Brockow, & Raspe, 2004; O'Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2006; Scott, Jull, & Sterling, 2005). This hypothesis proposes that longstanding bombardment of spinal cord neurons by A-beta and C-fibers as a result of ongoing spinal pain gives rise to the neuroplastic changes characteristic of central sensitization and FM (Meeus, Nijs, Meeus, & Nijs, 2007; Nielsen & Henriksson, 2007). This hypothesis has been substantiated by evidence of central sensitization in patients with CRSP including

generalized hyperalgesia, decreased pain thresholds and brain imaging evidence of altered pain sensitivity (Laursen, Bajaj, Olesen, Delmar, & Arendt-Nielsen, 2005; O'Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2007; Staud, 2007).

Central sensitization in WSP and FM

FM is a chronic widespread pain state characterized by self-report of WSP for at least three months with the presence of specific muscle tendon junction tenderness on physical exam (Wolfe, et al., 1990). WSP is defined as having pain in three out of four body quadrants and pain in the axial spine. The four body quadrants are designated as the upper body, lower body, right side of the body and left side of the body. It has become a generally accepted paradigm that central sensitization may be one underlying mechanism of abnormal pain processing in FM (Perrot, et al., 2008). Persuasive experimental evidence, such as findings of increased touch sensitivity (Price & Staud, 2005); decreased pain thresholds (Cook, et al., 2004; Desmeules, et al., 2003; Price & Staud, 2005); increased levels of excitatory amino acids, neuropeptides, and neurotransmitters (Dadabhoy, et al., 2008; Staud & Domingo, 2001); decreased analgesic neurotransmitters (Julien, Goffaux, Arsenault, & Marchand, 2005);alterations in the descending nociceptive modulating system (Staud, 2007); changes in cortical blood flow (Burgmer, et al., 2009; Cook, et al., 2004; Gracely, Petzke, Wolf, & Clauw, 2002; Mountz, Bradley, & Alarcon, 1998; Staud & Domingo, 2001); and abnormal summation and resolution of pain (Arendt-Nielsen & Graven-Nielsen, 2003; Staud, Price, Robinson, Mauderli, & Vierck, 2004), suggests that central sensitization may represent one pathophysiological mechanism underlying this syndrome (Bennett, 2005; Staud, 2002).

Predictive factors

Despite the demonstration of a shared pathophysiology between WSP, FM and CRSP, there have been relatively few studies on the clinical factors that might drive the

transition from CRSP to WSP or FM. This gap is significant, as patients with WSP and FM have a higher rate of disability and decreased quality of life as compared to patients with CRSP, representing a worsening clinical picture (Bergman, 2005; Burckhardt, Clark, & Bennett, 1993; Henriksson, 1995; Peolsson, et al., 2007; White, Speechley, Harth, & Ostbye, 1999). Determination of potential predictive factors could help clinicians identify a high-risk group of chronic spinal pain patients and potentially lead to interventions that might mitigate this transition to fibromyalgia. Risk factors examined in this study included variables from three categories; those proposed to contribute to the development of central sensitization, factors thought to place a person at risk for developing WSP or FM, and clinical features known to accompany FM.

The purpose of this study was to identify the clinical characteristics of patients with CRSP that predict their transition to WSP or FM. This study was innovative in that it was the first, to our knowledge, that specifically followed the transition of CRSP to WSP or FM. This study was timely as there is no uniformly agreed upon treatment algorithm for WSP or FM, often leading to less than ideal clinical outcomes. The identification of clinical features within CRSP patients that predict the transition to WSP and FM has the potential to shift the management paradigm of CRSP by identifying a higher risk group that needs to be managed more aggressively. This study was feasible in scope, as it utilized Kaiser Permanente's (KP) large, well-maintained clinical database for the generation of data to test the following hypotheses.

Specific aims

The specific aims of this proposed study are to:

Aim 1: Describe the rate of transition to WSP in a cohort of adults originally presenting with CRSP.

Hypothesis 1: It was hypothesized that approximately fifteen percent of individuals with CRSP in 2001 or 2002 would have transitioned to WSP by 2007.

Aim 2: Identify risk factors that predispose individuals with CRSP to a transition to WSP.

Hypothesis 2: Based on a review of the relevant literature, it was hypothesized that risk factors would include the baseline presentation of the following variables: increased duration and intensity of pain, presence of greater than four symptoms of depression (from DSM-IV), tobacco usage, female gender, older age, positive family history for chronic pain, history of childhood or spousal abuse, high body mass index (BMI >30), low levels of physical activity, positive disability status, more than two spinal surgeries, presence of pain in other locations, and a diagnosis of irritable bowel syndrome, migraines, or osteoarthritis.

Aim 3: Identify risk factors that predispose individuals with CRSP to a transition to FM using a case control design.

Hypothesis 3: It was hypothesized that risk factors associated with a transition to FM would be similar to those proposed for the development of WSP (Aim 2).

Significance to nursing

Understanding and attempting to modify disease progression have always been of significant interest to the nursing profession. Nurses are in a unique position to assist patients in altering the course of disease progression through patient education and assistance with changes in behaviors and activities. A major goal of the nursing profession is the modification of disease progression in order to prevent declines in health status and functional ability. This study presents an opportunity to inform this goal in regards to patients with CRSP.

Understanding factors involved in the progression of CRSP to WSP and FM, disorders accompanied by significant physical and psychological decline, presents an

opportunity for the modification of the clinical trajectory in high-risk patients with CRSP. Identification of predictive factors for the development of WSP and FM in CRSP patients informs future nursing research regarding more aggressive attempts to modify the progression of these disorders. Preventing progression from CRSP to FM represents an important nursing goal, in that the medical and nursing communities have better defined treatment strategies for managing CRSP as compared to FM. This nursing research study offers an opportunity to inform the nursing profession in regards to the disease progression of CRSP and risk factors that predispose these individuals to worsening outcomes. The study also produces unique knowledge that can provide the foundation for a follow up study to test aggressive therapies aimed at modifying the identified risk factors leading to transition to WSP and FM. This information could inform a randomized control trial where individuals with CRSP are randomly chosen to receive routine care or modified care aimed at modifying risk factors known to influence the development of WSP and FM. Customizing care strategies based on known risk factors could include targeting smoking cessation, weight management, depression control, medication management aimed at neuropathic pain, and aggressive control of comorbid conditions. This method would not only test the utility of a modified treatment regimen but would provide information into the causality of certain risk factors in the development of these widespread pain disorders.

CHAPTER 2: REVIEW OF THE LITERATURE

Epidemiology and Definition

This study investigated patients with one or more of four groups of diagnoses. For the purposes of this study, CRSP is defined as chronic low back or neck pain; WSP is defined as a patient who experiences pain in three out of four body quadrants and pain in the axial skeleton. Finally, FM is defined as having a history of WSP along with pain in at least eleven out of eighteen specified tender points on digital palpation.

Chronic low back pain

Chronic low back pain is one of the most common chronic regional pain disorders. One group of researchers used the 1988 National Health Interview Survey to determine the frequency of chronic conditions in the United States. They discovered that the most frequent cause of chronic disability was musculoskeletal impairment and that back and spine conditions represented the most frequently reported subgroup within the musculoskeletal disorders at 51.7% (Andersson, 1999). The study also reported that lumbar symptoms of the low back were 2.86 time more likely to result in a chronic condition. A survey completed in the United Kingdom (Webb, et al., 2003) found that out of 4,515 adult survey responders, 11.3% had chronic back pain that had lasted five years or longer. Based on the Oswestry Low Back Pain Disability questionnaire, the Modified Health Assessment Questionnaire, and an ordinal pain intensity scale, 5% qualified as having intense, disabling, chronic back pain.

A workgroup within the National Institute of Arthritis and Musculoskeletal and Skin Diseases came together to provide a national data source on the prevalence and impact of rheumatic disorders (Lawrence, et al., 1998). The authors noted that, in order to obtain the prevalence on back and neck pain, they pulled data from multiple sources, as a comprehensive data source on these disorders does not exist. Through their compilation of several reports, they concluded that five to ten percent of patients with

back pain had chronic symptoms lasting longer than three to six months. Chronic low back pain also represents the most frequently seen chronically painful diagnosis seen in the Kaiser Permanente Northwest (KPNW) Pain Clinic.

This prevalent pain disorder also represents a significant cost to society in terms of health care expenditure and days missed from work. Andersson (1999) estimated that back and spine impairments accounted for over 185 million missed workdays including 83 million days in which the affected individual was confined to bed. One study estimated that the total health care expenditure for patients with back pain approximated $91 billion (Luo, Peittrobon, Sun, Liu, & Hey, 2003). While this estimate includes acute and chronic back pain, studies of back pain expenditures estimate that a small percentage of chronic back pain patients incur a majority of these expenditures (Luo, et al., 2003). One study performed in the Netherlands estimated that total costs associated with chronic low back pain, including medical and productivity costs, equaled approximately 5,068 pounds per patient per year (Boonen, et al., 2005). Chronic low back pain represents one of the most frequent and costly chronic pain disorders in the United States and could characterize a large group of individuals at risk for further disease progression. The course of this chronically painful disorder needs further investigation as transition to FM likely represents increased cost associated with disability and dysfunction.

Chronic neck pain

Although the prevalence of chronic neck pain in the population has been less extensively researched (Webb, et al., 2003), two population-based studies performed in the UK provide some clues as to the prevalence of this condition. One reported that neck pain affects 10-17% of adults at any one time and 71% of adults during a lifetime (Walker-Bone, Reading, Coggon, Cooper, & Palmer, 2004). This survey found that 17% of the representative sample had neck pain that made it difficult or impossible to carry

out normal daily activities. Another study (Webb, et al., 2003) demonstrated that 5.9% of a representative sample of the United Kingdom population experienced chronic neck pain, while 2.9% found their neck pain intense, disabling, and chronic. This study also found that 78% of people with back pain and 88.7% of people with neck pain also reported pain at other sites of the body. The survey did not distinguish whether pain at other sites occurred before or after the spinal pain became chronic. Within the KP Pain Clinic, chronic neck pain is the third most frequently seen diagnosis after FM and chronic low back pain.

Chronic widespread pain

WSP, one of the defining components of FM, is typically diagnosed using the WSP component of the 1990 ACR criteria for FM (Wolfe, et al., 1990). These criteria state that WSP is diagnosed when a person experiences pain in three out of four body quadrants including axial pain. This diagnosis is made through a review of a body drawing in which the patient shades the areas in which s/he experiences pain. Epidemiological studies show that approximately 10-11% of the US population has WSP (Clauw & Crofford, 2003). The presence of eleven or more tender points (out of 18 designated points) separates a diagnosis of WSP from that of FM. Given that these disorders are both characterized by WSP, it is not surprising to note that they share several common risk factors (Macfarlane, 1999). In fact, epidemiological studies of WSP are often used to infer information about FM since diagnosing WSP from a body drawing does not necessitate a physical exam of participants, allowing for much larger sample sizes. Despite the commonalities between the two disorders and the likelihood that they exist on a continuum, a diagnosis of one does not constitute a diagnosis of the other. One recent study examined the difference in prevalence and impact of these disorders. They performed a tender point exam on 125 participants who demonstrated WSP on a body drawing and found that 56% met diagnostic criteria for FM (Coster, et al., 2008).

Fibromyalgia

FM is characterized by chronic widespread pain including axial pain and musculoskeletal tenderness (Wolfe, et al., 1990). Diagnosis of FM requires the presence of WSP for three months or more and pain on palpation of 11 out of 18 tender points. Several rigorous epidemiological studies reveal that FM prevalence in the general population ranges from 1.3% to 10.5% with a common finding of 3% in the female population. One group estimated that FM carries an economic burden of at least $20 billion in annual direct costs alone (Wolfe, Ross, Anderson, Russell, & Hebert, 1995). Patients with FM are routinely seen in rheumatology and pain clinics; in fact FM is the most frequent diagnosis made by rheumatologists (White & Harth, 1999). Within the KPNW Pain Clinic, FM is the second most frequently seen diagnosis behind chronic low back pain.

Clinical presentation

Along with a clinical presentation of WSP and tenderness throughout the body, most patients with FM also present with a variety of comorbid conditions and symptoms. Individuals with FM report the presence of WSP at a rate of 100%, fatigue at a rate of 96-100%, and disturbed sleep at a rate of 86-98% (Jones, Adams, Ross, & Bennett, 2006), representing the three most common symptoms of FM. Other common comorbid conditions include depression, migraines, chronic fatigue syndrome, irritable bowel syndrome, irritable bladder syndrome, tempromandibular joint disorder, hypermobility, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, and Sjorgren's syndrome. Numerous studies have investigated the presence of FM in these disorders and the presence of these disorders in FM. For instance, 22% of FM patients also have depression (Aaron & Buchwald, 2001), up to 80% have headaches (Aaron & Buchwald), 40-70% of FM patients meet chronic fatigue syndrome criteria (Aaron & Buchwald), 30-50% have irritable bowel syndrome (Aaron & Buchwald), 13-21% have irritable bladder

syndrome (Aaron & Buchwald), and 16% of FM patients have osteoarthritis (White & Harth, 1999). Many studies have also looked at the prevalence of FM in autoimmune conditions and have found that 20-60% of patients with lupus qualify for an FM diagnosis (Buskila, Press, & Abu-Shakra, 2003; Staud, 2006), 25% of patients with rheumatoid arthritis have FM (Wolfe, Cathey, & Kleinheksel, 1984), and 50% of patients with Sjorgren's syndrome have FM (Bonafede, Downey, & Bennett, 1995). In regards to overlap among viral illnesses, the literature shows that 26% of people with human immunodeficiency virus have chronic musculoskeletal pain while 41% of these individuals qualify for an FM diagnosis (Staud, 2004) and 16% of patients with hepatitis C fulfilled the FM criteria (Buskila, et al., 1997).

Chronic low back pain, chronic neck pain, WSP and FM represent the majority of the population of patients seen in pain clinics around the country. The high prevalence and poor clinical outcomes of these chronic pain diagnoses highlights the importance of the current study. More specifically, there is a need to know what factors influence the progression of chronic neck and back pain into the chronic widespread pain of FM with the aim of preventing this transition.

Impact

Although chronic low back and neck pain exhibit an increased prevalence over WSP and FM, the social costs and personal impact of WSP and FM has been demonstrated to outweigh that of these CRSP disorders. One study (Bergman, 2005) demonstrated that individuals with WSP and FM, as compared to individuals with no pain and chronic regional pain, demonstrated a more severely impaired health status as measured by the short form-36 health survey (SF-36). This study indicated that individuals with FM and WSP presented with significantly more impaired physical functioning, role functioning, bodily pain, general health perception, vitality, social functioning, and mental health. In comparing SF-36 scores on most of these subscales (higher scores indicate better

functioning), the chronic regional pain group had the highest scores at approximately 25% above the score of the WSP group, which had the second highest scores at approximately 20% above the FM group.

A similar study explored the consequences of developing WSP as compared to the development of regional pain in 275 consecutive patients presenting to a hospital for treatment of whiplash associated pain (Peolsson, et al., 2007). The authors compared three groups of participants; those who had developed WSP following a whiplash injury (defined as having pain in eight to eleven pre-defined body region), those who had pain in four to seven body regions, and those with pain in zero to three body regions. As compared to the groups with regional pain or no pain, the group of participants with WSP demonstrated significantly higher pain intensities, greater depression as measured by the Beck Depression Inventory, greater sleeping difficulties, more fatigue, and more overall non-pain related physical symptoms. Participants with WSP also demonstrated significantly decreased life satisfaction, worse health functioning as measured by the SF-36, and poorer quality of life as measured by the EuroQol instrument.

Another study investigated quality of life among patients with FM and other chronic illnesses including osteoarthritis, rheumatoid arthritis, insulin dependent diabetes mellitus, chronic obstructive pulmonary disease, and patients with an ostomy (Burckhardt, et al., 1993). The results of this study showed that, as measured by the Quality of Life Scale, FM patients presented with significantly lower quality of life scores as compared to the osteoarthritis, rheumatoid arthritis, ostomy, and healthy control groups. The FM quality of life scores were similar to those found in the insulin dependent diabetes and chronic obstructive pulmonary disease groups. It is of note that 75% of the diabetes group presented with complications and a majority of the COPD patients were in advanced stages of the disease. In further comparing these three chronic illness groups, FM patients had higher incomes, higher education levels, and were more often

married; all factors that have been found in other studies to improve quality of life. This study demonstrated that FM patients have decreased quality of life as compared to many chronic conditions and similar levels of quality of life as compared to individuals who are significantly impaired by their disease. While the authors did not compare the quality of life measures of FM patients to those with CRSP, one might relate patients with CRSP to osteoarthritis patients in terms of disease impact on life activities. The study demonstrated that FM patients had significantly lower quality of life scores than the osteoarthritis patients (Burckhardt, et al., 1993). Taken together, the Bergman (2005), Peolsson et al. (2007) and Burckhardt et al. (1993) demonstrate that having WSP and FM is associated with more impaired life satisfaction, physical functioning and psychosocial factors as compared with many chronic illnesses, including CRSP disorders. This increased impairment not only has a significant impact on the individual's life but also impacts society in a global manner.

Impaired functioning associated with FM commonly affects an individuals' ability to work and participate in society. One study demonstrated that 63% of individuals with FM reported an episode of sick leave as compared to 47% of individuals with CLBP (Boonen, et al., 2005). A survey of FM patients seen in American academic centers reported that 70% of individuals with FM perceived themselves as disabled (Wolfe, et al., 1997). Sixteen percent of these FM patients were receiving Social Security benefits; this is compared to 2.2% in the general US population. FM patients report an inability to hold regular work due to difficulty in carrying out repetitive motor tasks, reduced work efficiency, lack of mental sharpness, presence of workplace stressors, prolonged sitting or standing, and inability to conform to standard working hours due to fatigue (Bennett, 1996).

These studies demonstrate a more pronounced financial, social, economic and personal impact in WSP and FM as compared to chronic neck and back pain. The

potential for individuals with CRSP disorders to transition to a syndrome with significantly poorer outcomes represents an important area for research. While not all CRSP patients make such a transition, those who do constitute a high-risk group. This study aimed to discover predictive factors that increase the likelihood of transition from CRSP to WSP and FM. These findings will aid in the identification of high-risk individuals and could be useful in preventing this downward progression.

Theoretical Framework

Central sensitization represents a possible key link between CRSP disorders, WSP and FM. While understanding central sensitization in these painful disorders remains to be fully elucidated, preliminary evidence of this pain processing abnormality in relation to chronic low back and neck pain and FM will be discussed. Some researchers have proposed that a subset of the CRSP population develop central sensitization over time due to their ongoing painful condition. Several FM researchers have noted that central sensitization may play a key role in the WSP and sensitivity of this syndrome. This study proposes that this common underlying central nervous system abnormality might represent one mechanism placing patients with CRSP at risk for transitioning to FM.

Central sensitization

Central sensitization represents the pain processing abnormalities that can result from changes in the central nervous system in some chronically painful disorders. This phenomenon could represent one mechanism behind the extreme sensitivity of FM and can also occur in some individuals with regional pain syndromes like chronic low back and neck pain. In normal pain processing, a painful stimulus, or nociceptive input, is conveyed from the periphery to the central nervous system primarily by unmyelinated C-fibers or thinly myelinated A-delta fibers (Katz & Rothenberg, 2005). C fibers and A delta fibers represent the two types of primary afferent neurons that are predominantly responsible for carrying painful input to the central nervous system. The neurons first

synapse in the dorsal horn of the spinal cord while their second synapse occurs in the thalamus, then onto the primary sensory cortex and other supraspinal structures. It is here that the brain determines the type of pain experienced; the affective and emotional component of the pain experience, however, is perceived in the limbic cortical areas (Katz & Rothenberg, 2005). In acute pain situations, where neuroplastic changes, or changes in the nervous system, have not occurred, perception prompts automatic behaviors that work to diminish the painful input such as increased heart rate, perspiration, and breath rate (Bennett, 1999). This series of events typically follows an established pattern of spinal pathways that connect with their designated receptive fields, representing a linear relationship between painful input and the pain experience. In a person with chronic pain, this linear relationship does not exist. Due to the changes in pain processing that occur in some chronic pain experiences, nociceptive input does not always result in the same pain experience for individuals with some types of chronic pain.

Central sensitization occurs due to ongoing C-fiber stimulation, or painful input, resulting in sustained increases in the excitability and responsiveness of neurons in the spinal cord (Zusman, 2002). Central sensitization can manifest as hyperexcitability, increased spontaneous activity, or increased receptive fields of these spinal cord neurons (Eide, 2000). Repetitive stimulation of peripheral C-fibers can lead to hyperexcitable spinal cord neurons, which produces an enhanced responsiveness to painful and non-painful input (Mendell, 1966). This phenomenon is termed wind-up and means that a low level of stimuli can produce high levels of pain. Wind up is considered to be one of several initiators of central sensitization.

Neuroplastic changes characteristic of central sensitization occur in two types of spinal cord neurons: nociceptive-specific neurons that respond only to nociceptive (painful) input and wide dynamic range neurons that respond to a wide variety of stimuli,

both painful and non-painful (Bennett, 1999). Both types can be sensitized. Following sensitization, wide dynamic range neurons respond as intensely to non-nociceptive input as they had to nociceptive input prior to sensitization. This results in the experience of pain from non-painful input (allodynia). While wide dynamic range neurons are in this hyperexcitable state, A-beta fibers that are not normally involved in nociception may produce responses that are normally produced by A-delta or C-fibers (Eide, 2000).

In response to the barrage of C and A-delta fiber stimulation, an increased and prolonged release of peptide neurotransmitters (substance P and calcitonin gene-related peptide) and excitatory amino acid neurotransmitters (glutamate) occurs (Urban & Gebhart, 1999). Substance P, for example, facilitates nociception by alerting the spinal cord neurons to incoming painful stimuli. Substance P also can extend long distances to sensitize dorsal horn neurons at a distance from the initial locus of nociceptive input, thereby resulting in an expansion of receptive fields. Dorsal horn neurons that have receptive fields adjacent to an area of injury expand their receptive field to incorporate the sight of injury (Coderre, et al., 1993). This means that even if the initial pain originated in a specific area such as the neck, pain might be perceived in the head, shoulders, and upper back.

Since all neurotransmitters must bind to specific receptors, understanding the activation of these receptors is an integral component an enlightened understanding of pain neurophysiology. N-methyl-D-aspartate (NMDA) receptors, for example, are one subtype of glutamate receptors that play an important role in chronic pain states. In the presence of persistent noxious stimuli, glutamate and substance P activate NMDA receptors (Bennett, 1999; Dessein, Shipton, & Budd, 2000). Studies have confirmed the role of NMDA receptors in central sensitization by demonstrating that NMDA receptor antagonists can inhibit the increased excitability caused by repetitive C-fiber stimulation, thereby inhibiting windup (Eide, 2000). Wind-up was described more than 30 years ago

as progressively increasing activity in dorsal horn cells following repetitive activation of primary afferent C-fibers (Mendell & Wall, 1965) and is a critical event in the development of central sensitization.

Researchers also point to a disruption of the descending inhibitory system in individuals with central sensitization. One part of pain processing involves modulation of the pain response in which anti-nociceptive mechanisms in the central nervous system work to minimize the intensity of pain perception. This aspect of pain perception is termed the descending inhibitory system. A disruption in this system may enhance the facilitation of noxious stimuli, adding to the development and maintenance of central sensitization (Zusman, 2002). Deficiencies in one such inhibitory mechanism, diffuse noxious inhibitory control (DNIC), have been postulated to lead to increases in temporal summation (Marchand, 2008). In healthy males, DNIC can effectively inhibit windup and reduce C-fiber mediated second pain. Staud and colleagues (Staud, Robinson, Vierck, & Price, 2003) demonstrated that DNIC is effective in inhibiting windup only in healthy males but not in healthy females or females with FM. These findings suggest that a disruption in DNIC might not be unique to patients with FM but might instead be a phenomenon associated with the female gender. Staud and colleagues question whether ineffective DNIC predisposes the female gender to FM.

Central sensitization in fibromyalgia

It has become a generally accepted paradigm that central sensitization may be one underlying mechanism of abnormal pain processing in FM (Perrot, et al., 2008). The advances in FM research have lead scientists and practitioners to believe that there may not be one pathophysiologic mechanism underlying this syndrome but there are more likely several biological alterations that explain the symptomatology. This discussion will focus on evidence that could support central sensitization as one mechanism of the disease process. Attributes of FM that could support the role of central sensitization

include decreased pain thresholds, enhanced sensitivity outside of tender points, expansion of pain receptive fields, increased substance P in the cerebral spinal fluid, abnormal windup, prolonged pain after cessation of painful input, allodynia, and hyperalgesia (Dadabhoy, et al., 2008). Researchers have also demonstrated visible changes in the blood flow in the brain during resting states and painful states in patients with FM. These alterations will be discussed in greater depth in an attempt to outline some of the potential evidence for central sensitization in FM.

Numerous FM studies have demonstrated enhanced pain sensitivity and decreased pain threshold among most FM patients (Price & Staud, 2005; Staud & Rodriguez, 2006). Nearly all al these studies have documented abnormalities of pain sensitivity with various types of stimuli (heat, cold, pressure) and a multitude of sensory testing (Staud, 2007). Several mechanisms of central sensitization have been proposed to underlie this finding. Central sensitization denotes an increase in the excitability of spinal and supraspinal neurons and pathways (Eide, 2000). Ongoing nociceptive input; increased excitatory amino acids, neuropeptides, and neurotransmitters; and decreased analgesic neurotransmitters can lead to sensitization of spinal cord neurons. Bennett (1999) outlined two types of spinal cord neurons involved in central sensitization, nociceptive specific neurons and wide dynamic range neurons. As discussed previously, once sensitization of the central nervous system has occurred, wide dynamic range neurons respond to non-noxious stimuli as intensely as they previously had to noxious stimuli, representing a lowered firing threshold. This hyperexcitability of the spinal cord neurons and pathways manifests as neuronal discharges beyond the time of the stimuli, increased response to painful and non-painful stimuli, spread of sensitivity outside the initial pain locus (known as expansion of receptive fields), and generation of pain by normally silent mechanoreceptors (Arendt-Nielsen & Graven-Nielsen, 2003; Staud & Rodriguez, 2006). A clinical consequence of this altered neurophysiology is that sensory

impulses arising from low intensity activities will be perceived as painful. In fact, researchers theorize that this enhanced sensitivity represents a heightened responsiveness to all sensory stimulation. Recent research studies have documented abnormalities in central processing of other sensory stimulation such as auditory stimulation, perhaps indicating a global disturbance in sensory processing (Geisser, et al., 2008).

While several studies have documented enhanced sensitivity, one group of authors set out to demonstrate that this sensitization occurs primarily in the central rather than the peripheral nervous system (Desmeules, et al., 2003). These authors investigated central sensitization in 85 FM subjects and 40 matched controls using the nociceptive flexion reflex. This involves direct electrical stimulation to the sural nerve, which in turn results in activation of a spinal reflex causing contraction of the biceps femoris muscle. This methodology bypasses stimulation of peripheral nociceptors. Sensitization at the level of the spinal reflex is demonstrated by observing activation of muscle contraction at a lower current than in control subjects. The median threshold for contraction in FM patients was 22.7 mA and 33 mA in controls. A cutoff value of <27.6 mA provided sensitivity of 73% and specificity of 80% for detecting alloldynia in FM patients. In the same study the thermal detection thresholds in FM patients were about equal to the healthy controls; thus confirming the absence of peripheral nerve fiber pathology. The authors also reported that DNIC, measured as a reduction in the nociceptive flexion reflex by stimulation of the ipsilateral elbow tender point, was activated in a larger portion of FM patients than in healthy controls. DNIC is typically activated in response to intense painful stimulation whereas non-painful stimuli cause no effect on this inhibitory system. The fact that a low level of stimulation caused activation of DNIC indicates the presence of allodynia and an alteration of central inhibitory mechanisms (Desmeules, et al., 2003). Allodynia represents a central sensitization mechanism resulting from increased

excitability and enlarged receptive fields of spinal and supraspinal neurons. In summary, this study demonstrated several alterations in central nociceptive processing while demonstrating that these changes were unlikely to be a result of peripheral nerve dysfunction.

Several researchers have also described abnormal windup as a part of central sensitization in FM (Arendt-Nielsen & Graven-Nielsen, 2003; Bennett, 1999; Price & Staud, 2005; Staud & Domingo, 2001; Staud & Rodriguez, 2006). While windup is not equivalent to central sensitization, it seems to represent one mechanism related to central sensitization as it results from central rather than peripheral mechanisms (Price & Staud, 2005; Staud, et al., 2004). Following ongoing nociceptive input, the dorsal horn neurons exhibit increased excitability, enhanced responsiveness to painful and non-painful input, and an increase in spontaneous activity (Staud, et al., 2004). This phenomenon can occur in all humans but FM patients demonstrate enhanced windup with a greater degree of neuronal excitability and prolonged after sensations (Staud, 2007). This means that the wide dynamic range neurons have a lower firing threshold and take longer to resolve following cessation of the stimuli. Following central sensitization in FM patients, only low levels of stimuli are needed to maintain windup and produce high levels of nociceptive input (Staud & Rodriguez, 2006). Clinically this means that seemingly non-painful activities, including normal daily activities, provide enough stimuli to produce high levels of pain and therefore maintain a sensitized nervous system.

Staud and colleagues (2004) demonstrated these findings in a study comparing windup and windup maintenance in FM patients and healthy controls. The researchers applied computer controlled thermal stimulation to the subjects and had them rate their late pain sensations, the dull, aching, burning pain carried by C fibers that comes after the initial pain carried by A-delta fibers. The subjects also rated the pain 15-30 seconds

after resolution of the thermal stimuli, a measurement of the after-sensation. The authors found that FM patients demonstrated abnormal windup and prolonged windup after-sensations. The FM patients demonstrated the occurrence of windup at lower intensities and once the initiation of windup occurred, a lower level of stimuli was needed to maintain central sensitization. The prolonged windup after-sensations demonstrate that the wide dynamic range neurons in FM patients take longer to resolve following the thermal stimuli. These findings also imply that once central sensitization is established it may be maintained by the neural input from everyday activities and account for the pain experienced from relatively low levels of exertion.

Research has also demonstrated that abnormal levels of neurochemicals in FM might have an impact on the development and maintenance of central sensitization. Many discussions of FM include the finding of elevated levels of substance P in the cerebrospinal fluid of patients with FM (Dadabhoy, et al., 2008). Studies have demonstrated that substance P levels in FM patients are two to threefold that of healthy controls (Russell, 1998; Russell & Bieber, 2006). Substance P, along with excitatory amino acids, such as glutamate and aspartate, enhance the transmission of pain through the primary afferent neurons (Larson, Giovengo, Russell, & Michalek, 2000). Increased levels of substance P can induce hyperalgesia and allodynia by lowering the firing threshold of spinal cord neurons and extend long distances from the pain locus resulting in sensitization at sites distant from the pain locus (Bennett, 1999). These factors result in an expansion of receptive fields and cause wide dynamic range neurons to respond to non-painful stimuli as if it were painful. Substance P also stimulates an increase expression of cytokines, which have found to be elevated in patients with FM, resulting in further sensitization of peripheral nerve endings and perhaps is involved in activating the sympathetic nervous system (Staud, 2007).

Studies have demonstrated low levels of the serotonin metabolite 5 hydroxy-indole-acetic acid (5HIAA) in the CSF of FM patients (Russell, Vaeroy, Javors, & Nyberg, 1992) and an overall dysfunction in serotoninergic neurotransmission (Coaccioli, et al., 2008). Serotonin activates the descending inhibitory system and can inhibit the release of glutamate and substance P. This is the mechanism whereby medications that reduce the reuptake of serotonin (TCAs, SSRIs and SNRIs) are postulated to act in chronic pain states (Littlejohn & Guymer, 2006). Researchers have also discovered elevated levels of nerve growth factor in some individuals with FM and propose that this relates to central sensitization as nerve growth factor likely facilitates the growth of substance P containing neurons, allowing for increased production of this neuropeptide. Nerve growth factor also can facilitate neuplasticity, a critical feature of central sensitization. Researchers propose a role for cytokines in central sensitization. Studies demonstrate that serum Interleukin 8 and Interleukin 6 are significantly higher in patients with FM (Russell & Bieber, 2006; Staud, 2007). In fact, Interleukin 8 has been shown to correlate with symptoms of FM (Dadabhoy, et al., 2008). These finding are relevant to central sensitization as Interluekin 8 is stimulated in vitro by substance P and Interluekin 6 and other proinflammatory cytokines provide signals to the central nervous system creating another source of exaggerated pain.

Staud and colleagues (Staud & Rodriguez, 2006; Staud, Vierck, Robinson, & Price, 2006) propose that peripheral pain input plays an important role in the maintenance of central and peripheral sensitization in FM patients. In fact, some FM experts propose that regional pain precedes the development of WSP in most patients with FM (Nielsen & Henriksson, 2007). Staud, Vierck, Robinson, and Price (2006) tested this hypothesis by determining whether local pain intensity represented an important predictor of overall clinical pain in FM, thereby indicating the role of peripheral input in FM pain. The researchers investigated the pain ratings, local areas of the body with pain, and tender

point count in 277 FM subjects. The subjects reported an average of 20 painful body areas while 11 out of 18 tender points were located in these painful areas. Most common painful body areas included the shoulders (84.3%), the low back (64.3%), and thighs (67.4%). Using a hierarchical regression analysis, the authors found that the number of painful body areas; average and maximal pain ratings; and pain related negative affect accounted for 55% of the variance in overall pain intensity. The authors propose that the persistent activity in the peripheral nociceptive afferents caused by the peripheral pain generators serve to perpetuate central sensitization. This process also produces excessive pain responses to these peripheral inputs, thereby increasing the overall level of pain intensity.

The proposed neuroplastic changes that could result from central sensitization have been visualized with functional magnetic resonance imaging (fMRI), single photon emission computed tomorgraphy (SPECT) and positron emission tomography (PET) imaging. Gracely and colleagues (Gracely, et al., 2002) investigated fMRI changes in FM patients and healthy controls while applying slow, controlled pressure to the thumb nail. Another set of authors (Cook, et al., 2004) investigated this phenomenon using painful and non-painful heat stimuli while a third group made an incision on the volar forearm of FM patients and healthy controls (Burgmer, et al., 2009). All three groups discovered that a significantly lower level of stimuli produced pain in the FM patients and that higher pain ratings paralleled atypical brain activation in FM patients. When Gracely et al. and Cook et al. provided an equal level of stimuli that caused pain in the FM patients but not in the controls, the FM patients demonstrated activation of significantly more pain related brain areas as compared to the controls. These two groups also demonstrated that painful stimuli in healthy controls resulted in increased regional cerebral blood flow to the thalamus while this did not occur in the FM patients. Several other studies have documented reduced regional cerebral blood flow in the thalamus and caudate nuclei of

FM patients along with significantly lower total cortical blood flow (Mountz, et al., 1998; Wood, 2005). Taken together, these neuroimaging findings suggest augmentation of pain processing in the brain of FM patients and propose that amplified neural responses might maintain the abnormal pain responses produced in FM.

As discussed, several findings within the FM population point to the possibility that central sensitization represents one mechanism of abnormal pain processing within these individuals. Enhanced windup, hyperalgesia, allodynia, increased sensitizing neurochemicals, hyperexcitable spinal cord neurons, decreased pain thresholds, and changes within the brain all provide evidence of central pain processing abnormalities. While central sensitization has been proposed to represent one underlying mechanism of the FM syndrome, central sensitization could play a different role in other chronic pain syndromes. Central sensitization could come as a result of ongoing pain combined with other predictive factors.

Central sensitization in other chronic pain syndromes

Several researchers and experts have proposed that chronic pain syndromes, such as chronic low back and neck pain, might produce the sustained noxious input that results in hypersensitivity of the central nervous system (Lidbeck, 2002; Staud, 2007). This hypothesis proposes that longstanding bombardment of spinal cord neurons by A-beta and C-fibers as a result of this ongoing pain gives rise to the neuroplastic changes characteristic of central sensitization (Meeus, et al., 2007; Nielsen & Henriksson, 2007). In fact, generalized hyperalgesia has been described in individuals with regional pain syndromes such as whiplash, back pain, irritable bowel syndrome (IBS) and pelvic pain (Staud, 2007). One group of researchers (Flor, et al., 1997) proposed that repetitive and continuous noxious stimulation can result in cortical reorganization that has been described in the central sensitization section. Resultant changes in the central nervous system may first begin through more locally occurring changes that represent peripheral

sensitization. Tissue injury or inflammation that can occur in back or neck pain stimulates a release of potassium ions, substance P, bradykinin, prostaglandins, and other substances. These substances can sensitize peripheral receptors, which result in alterations in how they respond (Curatolo, 2004). These changes may stimulate normally inactive nociceptors and increase the production of nociceptors. The body not only produces more peripheral nociceptive receptors but the sensitization process also modifies these nociceptors. A-beta fibers, which are normally not involved in nociception, can start to adopt C fiber characteristics and transmit painful stimuli. These peripheral changes in conjunction with the ongoing nociceptive input lead to spinal cord and supraspinal changes described in the previous discussion of central sensitization.

One group of researchers substantiated this theory that regional chronic pain syndromes can be associated with generalized hyperalgesia and decreased pressure pain thresholds (Laursen, et al., 2005). They used pressure algometry to assess pain and pressure pain thresholds in patients with chronic low back pain, chronic whiplash pain and healthy controls. Pressure was systematically applied to seven body locations including sites in the arm, back, finger, and lower leg. The researchers found that patients exhibited significantly lower pressure pain thresholds in all locations as compared to healthy controls. This study provided evidence that regional pain disorders can produce generalized hyperalgesia. Demonstrating clinical evidence of this generalized hyperalgesia, one group of researchers quantified the frequency with which patients experiencing chronic disabling occupational spinal disorders exhibited WSP (Mayer, et al., 2008). In a consecutive group of 2,730 patients seeking treatment at a functional rehabilitation facility, the researchers found that 32% of patients with chronic disabling spinal disorders met the ACR criteria for WSP. This study provides substantial evidence that individuals with chronic spinal pain develop widespread hypersensitivity to pain.

Knowing that sensitization can occur peripherally or centrally, a valid question arises as to whether both can occur in chronic back and neck pain. Several studies have addressed this question, typically by applying a sensory stimulus at non-painful peripheral tissue and assessing pain detection and tolerance thresholds. Establishing the presence of hypersensitivity occurs when a person interprets a normally non-noxious stimulus as painful or a normally noxious stimulus produces a more intense level of pain (Curatolo, 2004). Peripheral sensitization is detected at the pain locus, such as the low back or neck whereas central sensitization is detected in healthy tissue distant from the pain locus, such as in the thumb or leg. Studies using this method, and others, to explore central sensitization in patients with CRSP disorders include studies exploring the presence central sensitization in chronic low back or neck pain and studies exploring the transition from these painful disorders to FM. A review of these studies will follow.

Studies Critical to the Theoretical Framework of this Investigation

Chronic low back pain and central sensitization

To examine central sensitization in chronic low back pain, researchers have used various mechanisms to capture the changes in the central nervous system. The mechanisms used in these studies varied in accordance to the purpose of the research but the underlying goal of demonstrating the central nervous system alterations remained similar throughout each study. Seven studies were identified that experimentally examined this phenomenon (Clauw, et al., 1999; Flor, et al., 1997; Flor, Diers, & Birbaumer, 2004; Giesecke, et al., 2004; Kleinbohl, et al., 1999; O'Neill, et al., 2007; Wilder-Smith, et al., 2002). The purpose of these studies was related to examining central sensitization changes as evidenced by hyperalgesia or allodynia at the site of the pain locus (the lower back) and also at a site distant from the pain locus, such as the arm or leg. Examination of this enhanced sensitivity was evaluated by functional magnetic resonance imaging (fMRI) (Giesecke, et al., 2004); patient report of pain

tolerance, pain detection, and pain threshold (Flor, et al., 2004; Kleinbohl, et al., 1999; O'Neill, et al., 2007; Wilder-Smith, et al., 2002), dolorimeter examination (Clauw, et al., 1999); and magnetic source imaging (Flor, et al., 1997).

The patients investigated in these studies all had chronic back or low back pain. Some of these studies compared this patient group with another patient group such as a headache group (Flor, et al., 2004; Kleinbohl, et al., 1999) or a FM group (Giesecke, et al., 2004). Four out of the six studies also employed a control group of age and sex-matched healthy participants (Flor, et al., 1997; Flor, et al., 2004; Giesecke, et al., 2004; Kleinbohl, et al., 1999; O'Neill, et al., 2007). One study (Wilder-Smith, et al., 2002) investigated patients pre-operatively before undergoing elective surgery for intervertebral disc prolapse. Four of the studies used small samples of approximately ten to fifteen patients per patient or control group (Flor, et al., 1997; Flor, et al., 2004; Giesecke, et al., 2004; Kleinbohl, et al., 1999) while the other two studies did not use control groups (Clauw, et al., 1999; Wilder-Smith, et al., 2002) but had larger samples of 90 and 52, respectively.

While the results of these studies varied somewhat due to the methods used, they all presented a similar underlying construct of peripheral and central nervous system alterations resulting in central sensitization in a subset of the chronic back or low back pain participants. The study performed by Giesecke and colleagues (2004) used fMRI to demonstrate pressure pain sensitivity at the left thumbnail in chronic low back pain and FM patients. The results confirmed that both of these patient groups demonstrated decreased pain thresholds at the thumbnail, indicating that these participants were more sensitive to pressure stimuli than healthy controls. The results produced by the fMRI provided revealing findings as well. This testing indicated that 2 kilogram (kg) of pressure at the thumbnail in the control group caused faint pain and resulted in an increase in the fMRI signaling at only one pain-related cortical region. This same amount

of pressure applied to the chronic low back and FM patient group resulted in moderate pain and produced increased fMRI signaling at five pain related brain regions. The authors concluded that a subset of individuals with idiopathic chronic low back pain display altered physiologic processing similar to that displayed in FM patients.

Flor and colleagues (1997) performed a similar study using magnetic source imaging instead of fMRI. This group used electrical bipolar pulses on the back and left index finger to assess tactile perception and pain threshold. Very similar findings resulted as compared to the previously described study by Giesecke et al. (2004) in that electrical stimulation in the back and finger resulted in enhanced cortical reactivity as compared to healthy controls. The authors also found that the magnitude of cortical response to the stimulation was positively correlated to the chronicity of the back pain. This finding indicates that cortical reorganization progresses over time of painful input. Finally, the study discovered that the brain's representation of the back had expanded into distant areas such that an exaggerated pain response was observed not only at the back but also at the leg or foot. This provides further evidence for the expansion of receptive fields into previously unaffected areas.

Flor and colleagues extended these findings in a 2004 study investigating pain tolerance, pain threshold, and perception threshold in chronic back pain patients, headache patients, and healthy controls. The authors used the same electrical stimulus as in their 1997 study (Flor, et al., 1997). The results demonstrated that the chronic back pain patients showed significantly lowered pain tolerance and thresholds as compared to the headache and healthy control group. In fact, the headache group demonstrated higher pain tolerance than the back pain and healthy control group. The researchers also investigated habituation to the electrical stimulus. Habituation in healthy individuals allows for the brain to ignore much of the non-noxious input associated with the environment. The research demonstrated that the chronic back pain group demonstrated

significantly less habituation than healthy controls, in that they experienced and were much more sensitive to non-noxious input that healthy individuals can ignore. This evidence points to the ongoing sensitivity to non-noxious stimuli that individuals with chronic back pain experience.

Another group of researchers (Kleinbohl, et al., 1999) also examined central sensitization in chronic back pain patients, chronic headache patients, and healthy controls using tonic heat stimuli at the thenar eminence of the thumb. The authors chose this site due to the dominant influence of C-fibers at this location. As in the other studies, the results demonstrated that both patient groups, but more so in the back pain group, exhibited low thresholds to tonic heat, presumably due to early sensitization. The researchers discovered that the chronic back pain patients began sensitizing to the stimuli well below the pain threshold. In further analysis controlling for covariates, the authors discovered that only the chronic back pain patients differed significantly from the healthy controls in terms of lowered pain thresholds. The authors proposed that this sensitization is more common in chronic back pain patients. They also proposed that there is a subgroup of chronic pain patients that are “extreme sensitizers” and that chronic back pain patients are over represented in this group due to their increased sensitivity.

Similar to the previously discussed studies, Wilder-Smith, Tassonyi, and Arednt-Nielsen (2002) assessed pain sensitivity and tolerance with electrical stimulation at the leg, back, and arm in a group of patients preparing for back surgery. Back pain patients were divided into four groups; no pain, leg pain, back pain, and both leg and back pain. As compared to the “no pain” group, results of the study indicated that pain thresholds, pain detection, and pain tolerance were lower in the back pain group, higher in the leg pain group, and similar in the back and leg pain group. To account for these results, the authors proposed that the leg pain group represented a more acute pain syndrome and

was associated with pain inhibition representative of an acute pain response. The researchers hypothesized that the back pain group had endured a more chronic course of pain and therefore had developed neuroplastic changes leading to hyperexcitability of their nervous system.

Clauw and colleagues (1999) also measured pressure pain sensitivity but instead used a dolorimeter (a pressure gauge) to measure sensitivity at the back, all eighteen designated tender points across the body, and the forehead and thumbnail (considered control points). MRI or X-ray results were used if available. Clinical status variables such as functional ability, depression, and aerobic exercise level were also collected. Results of the study indicated that X-ray results had no correlation between clinical status variables, pain, or function. No significant correlations were found for MRI testing although there was a modest correlation (r= .031) with the level of pain. These findings confirm that there is a subset of individuals whose pain and functional ability do not correspond to anatomic changes within the spine. This finding suggests that another process, possibly central sensitization, might maintain the increased level of sensitivity and pain in these patients.

In regards to the sensitivity testing in these individuals with chronic low back pain, the authors discovered that this group had a higher mean number of tender points than the general population, 5.2 to 5.4 in the back pain patients as compared to 1.0 to 3.5 in the control subjects (Clauw, et al., 1999). Thirty eight percent of the patients presented with eleven or greater tender points, in conjunction with WSP, which qualified them for a FM diagnosis. Measures of tenderness included not only a tender point count but also tender point threshold and tolerance and control point threshold and tolerance. The results indicated the existence of a significant correlation between pain and function and all measures of tenderness. In fact, in a regression analysis, tenderness accounted for 12% of the variance in pain and 12% of the variance in functioning. The findings of this

study indicate that a subset of patients with chronic low back pain experience increased overall tenderness throughout the body, not just at the low back. The authors determined that at both traditional tender points and at control points, participants had decreased pain threshold and tolerance, similar to findings in FM patients.

O'Neill and colleagues (2007) also used pressure algometry along with saline-induced muscle pain to examine deep tissue hyperalgesia in patients with radiculopathy due to lumbar disc herniation. This research group applied pressure pain and a saline injection to the tibialis anterior (on the leg without radicular pain) and the infraspinatus muscle on the participants with radicular back pain and age and sex matched healthy controls. As compared to healthy controls, patients reported significantly higher pain responses, longer pain durations, and more widespread referred pain. Areas of pain indicated on a body drawing were significantly larger for patients as compared to controls. The authors propose that these results add to the evidence that ongoing nociceptive input from chronic low back pain initiate and sustain central sensitization.

Taken as a whole, these seven studies provide persuasive evidence for the existence of central sensitization and neuroplastic changes in a subset of the chronic back pain population. Six of these studies (Clauw, et al., 1999; Flor, et al., 2004; Giesecke, et al., 2004; Kleinbohl, et al., 1999; O'Neill, et al., 2007; Wilder-Smith, et al., 2002) demonstrated decreased pain thresholds and decreased pain tolerance not only at the back but also at sites distant from the back. Two of the studies (Flor, et al., 1997; Giesecke, et al., 2004) provided evidence of cortical hyper-reactivity in response to painful stimuli, demonstrating confirmation of the neuroplastic changes possibly associated with central sensitization. These findings provide strong evidence that some patients with chronic back pain have undergone significant changes in the central nervous system in regards to nociceptive processing.

Transition of chronic low back pain to WSP and/or FM

While the previous studies provided evidence of central sensitization in some chronic back pain patients, other studies have examined the actual transition of individuals with chronic back pain to WSP or FM. An extensive literature search resulted in five such studies. All five studies utilized similar concepts and operationalized these concepts in a similar way to one another (see Table 2.1 at the end of this chapter for an evidence table of these studies). The core concepts used in these studies included chronic pain, chronic regional pain (including low back pain) and WSP. Two studies conceptualized chronic regional pain as chronic low back pain (Lapossy, Maleitzke, Hrycaj, Mennet, & Muller, 1995; Natvig, Bruusgaard, & Eriksen, 2001), one study conceptualized chronic widespread pain as FM (Lapossy, et al., 1995), and one study conceptualized chronic widespread pain and FM as distinct outcomes (Forseth, Husby, Gran, & Forre, 1999).

Four of the studies operationalized these facets of pain location through analyzing the areas shaded by participants on a body drawing and one study through participant examination and report. A body drawing consists of an outline of the back and front of the body on which the patient is asked to shade the areas of the body that are painful. Although the method for obtaining areas of pain was similar across studies, the method for determining which individuals were classified as having WSP varied. One of the studies (Natvig et al., 2001) classified participants as having WSP if their body drawing had four or more areas shaded out of ten pre-determined areas. The other four studies relied on the requirements outlined in the 1990 American College of Rheumatology criteria for FM (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenburg, et al., 1990) for the diagnosis of WSP. Three of these four studies (Forseth et al., 1999; Bergman et al., 2002 (Papageorgiou, Silman, & Macfarlane, 2002)) utilized the American College of Rheumatology for the diagnosis of WSP instead of FM by eliminating the tender point count and only utilizing the requirements of pain in three of the four body quadrants plus the presence of axial pain. Four of these five studies also assessed the clinical factors

associated with making this transition from chronic low back or regional pain to WSP or FM. One study instead focused on the factors that predicted persistent WSP (Papageorgiou, et al., 2002).

Four of the five studies utilized questionnaires sent to the general population to obtain information regarding the presence and type of pain and variables impacting the pain (Bergman, Herrstrom, Jacobsson, & Petersson, 2002; Forseth, et al., 1999; Natvig, et al., 2001; Papageorgiou, et al., 2002). Four studies sent questionnaires at baseline and follow-up, while one study (Natvig, et al., 2001) sent the questionnaire out only once. The questionnaires utilized by these five studies were quite similar. Four of the studies utilized body drawings and the participants were asked to shade in the areas that were painful. One study utilized a listing of different body regions to elicit the same information (Forseth, et al., 1999). This aspect of the questionnaire was the primary source of differentiating regional pain from WSP. The remainder of each questionnaire asked the participants questions about the experience of the pain and covariates that impacted the pain or the transition from regional pain to WSP. The particular aspects of the questionnaire will be discussed later. Although the design of the study by Lapossy et al. (1995) was not explicit, it is assumed that the researchers utilized clinical records and participant examination to collect the same information obtained by questionnaires in the other studies.

As noted above, all but one study (Natvig, et al., 2001) utilized two time points to gain a longitudinal picture of the course of chronic regional or WSP. In those studies utilizing two time points, the same questionnaire was sent out at baseline with follow-up at the end of the study period in three of the four studies. In the study that utilized two time points but did not use a questionnaire (Lapossy, et al., 1995), it appears that clinical records and examination were used both at baseline and follow-up. In the study that utilized only one time point (Natvig, et al., 2001), a control group of individuals with

localized chronic low back pain were utilized as a comparison to those individuals with chronic low back pain and WSP.

Upon receipt of the questionnaires or examination, all researchers divided their participants into groups based on the follow-up examination of pain. The groups created in all five studies were extremely similar. All studies had a chronic regional pain group and a WSP group. Two of the studies conceptualized the chronic regional pain group as particularly chronic low back pain (Lapossy, et al., 1995; Natvig, et al., 2001) whereas two of the studies conceptualized chronic widespread pain as FM (Forseth, et al., 1999; Lapossy, et al., 1995). All of the studies also had a group that did not have chronic pain or had chronic pain that had resolved.

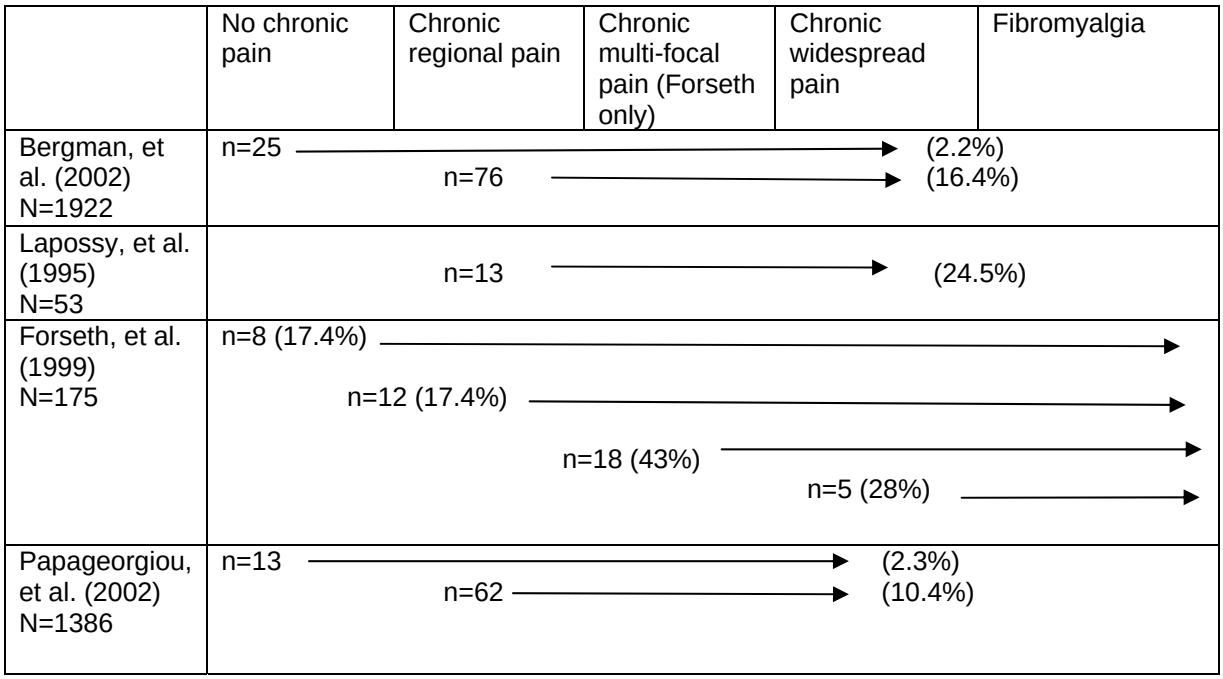
Four of the studies investigated variables that predispose and predict a transition from chronic low back or chronic regional pain to WSP or FM. All of the studies examined pain location, age, and gender. With the exception of the Bergman et al. (2002) study, the other studies analyzed the effect of pain intensity and duration, functional ability, sleep, and fatigue. All studies examined a myriad of other symptoms that often co-occur with pain, such as headache, orthostatic intolerance, and tremor (Lapossy et al., 1995), as well as symptom response to weather change, stress, irritable bowel symptoms, parasthesia, and pain at night (Forseth et al., 1999). Forseth et al. (1999) and Lapossy et al. (1995) also examined the symptoms of headaches and swelling in arms and legs. Bergman et al. (2002) looked at some unique variables as compared to the other investigators, examining the influence of socioeconomic status, housing area, educational level, smoking and alcohol habit, personal support, and family history of chronic pain. Only Forseth et al. (1999) examined depression as a covariate.

All studies in this synthesis utilized Chi-square to analyze the differences between the resulting groups. All but one study (Lapossy, et al., 1995) performed a multivariate

analysis using logistic regression to explore the association between the variables mentioned above and the outcome variable, WSP or FM.

With the exception of Natvig et al. (2001), which only measured one time point, the studies reported on all changes in pain status among the groups. For ease of discussion, this section will report on only the observed changes from chronic regional pain or chronic low back pain, to WSP or FM as opposed to discussing transition among all groups. Movement among these groups and other groups is documented in Figure 2.1. The four studies that looked at change in chronic regional pain over time found that in individuals experiencing chronic regional pain or chronic low back pain at baseline, 10.4% to 25% transitioned into experiencing WSP or FM. Lapossy et al. (1995) had the highest percentage of people who transitioned while Papageorgiou (2002) found the lowest percentage. Forseth et al. (1999) found that 17.4% transitioned from chronic regional pain to FM while Bergman et al (2002) documented 16.4% of participants who originally had chronic regional pain developed WSP.

Figure 2.1 The transition from chronic regional pain to WSP and FM among the studies utilizing a longitudinal design.



The second aim of four the studies was to determine the risk factors that could predispose a person for this transition from chronic regional pain to WSP. Two studies (Natvig et al., 2001; Forseth et al., 1999) found that having chronic low back pain for six or more years was a risk factor. These two studies also identified emotional difficulties or self assessed depression as a risk factor, while Bergman et al. (2002) found that personal support was a protective factor. Older age was also found to be a risk factor in the Bergman study (2002) and being female raised one's chances of developing FM in the studies done by Lapossy et al. (1995) and Natvig et al. The remaining risk factors were not shared across studies and included increased pain intensity and decreased self-rated general health (Natvig et al.), pain in the back as compared to other regional locations (Forseth et al.), family history of chronic pain and having greater than six regions of pain (Bergman et al.), and postural disorders of the spine (Lapossy et al.). Of

note, in the study done by Bergman et al. (2002), the researchers concluded that weekly or daily intake of alcohol was protective.

These five studies, which represent the findings of an intense literature search, demonstrate that there exists a subset of individuals who transition from chronic low back pain to WSP or FM. Most of these studies used similar designs with varied, but related findings. The risk factors predicting this transition were somewhat similar among the studies and represent the potential for identification of at-risk individuals. These studies, while small in number but robust in their findings, provide practitioners with more knowledge about the pain-related processes of their patients who progress from chronic low back pain to WSP and FM. The proposed project builds on these studies by placing a specific focus on determining predictive factors for the transition to both WSP and FM.

Central sensitization in chronic neck pain

Studies have also been performed that examine the role of central sensitization in patients with chronic neck pain. As noted earlier, the same pathophysiologic mechanisms that lead to central sensitization can occur with an original pain locus at the cervical spine. While this study proposes that this phenomenon can occur in various types of chronic neck pain, many of the studies investigate central sensitization in patients who develop chronic neck pain after whiplash. Whiplash causes chronic neck pain in approximately 20% of patients (Curatolo, et al., 2001; Herren-Gerber, et al., 2004) making this population a prime one to study the progression of chronic neck pain.

This discussion will include six studies that have investigated central sensitization in chronic neck pain (Banic, et al., 2004; Curatolo, et al., 2001; Herren-Gerber, et al., 2004; Johnston, et al., 2008; Koelbaek Johansen, Graven-Nielsen, Schou Olesen, & Arendt-Nielsen, 1999; Sheather-Reid & Cohen, 1998). Four of these studies investigated chronic neck pain patients that had experienced whiplash, one study (Sheather-Reid & Cohen, 1998) included not only whiplash patients but other sources of chronic neck pain

as well, and the most recent study investigated office workers with chronic neck pain (Johnston, et al., 2008). All of these investigations compared the chronic neck pain patients with healthy controls. These studies used similar methods as compared to the studies examining central sensitization in chronic low back pain. To investigate pain detection threshold, pain tolerance threshold, tenderness, and/or temporal summation, the researchers used one or a combination of three different stimulation methods. Three researcher groups used pressure stimulation with a pressure algometer (Banic, et al., 2004; Herren-Gerber, et al., 2004; Koelbaek Johansen, et al., 1999), while three groups used electrical stimulation (Banic, et al., 2004; Curatolo, et al., 2001; Sheather-Reid & Cohen, 1998). Johnston et al. investigated pressure pain thresholds, heat and cold tolerance, and vibration threshold. Herren-Gerber et al. and Curatolo et al. also injected the subjects with a local injection of Bupivicaine to assess the anesthetic's effect on pain while Koelback Johansen et al. used an injection of saline to assess muscle pain. Most of the studies used these stimulation methods on both neck sites and sites distant from the neck while Sheather-Reid and Cohen used only a neck site.

The five studies that investigated pain thresholds at the neck and at a site distant from the neck discovered decreased pain thresholds, including decreased pain detection and pain tolerance threshold whether they used electrical or pressure stimulation at both the neck and the non-painful site. These findings were significantly lower than pain thresholds of the healthy controls. The one study that investigated only the neck site discovered the same finding of decreased pain thresholds (Sheather-Reid & Cohen, 1998). Johnston et al. (2008) not only discovered decreased pressure, heat, and cold pain threshold but also found that individuals with neck pain had decreased sensitivity to vibration thresholds, suggesting hypersensitivity in large and small sensory fibers. Taken together, the findings of these studies demonstrated hypersensitivity not only at the pain locus but also at healthy tissue sites. This hypersensitivity that is not localized to the

painful area indicates underlying changes in the central nervous system that might be explained by central sensitization. Decreased pain thresholds at sites distant from the pain locus indicate that once central sensitization is initiated, hypersensitivity may be independent of peripheral input (Curatolo, et al., 2001).

Two of the studies used an injection of Lidocaine or Bupivicaine to assess the effect of this injection on pain (Curatolo, et al., 2001; Herren-Gerber, et al., 2004). Both groups of researchers examined the chronic neck pain patients for the presence of tender points and injected each point with one to four milliliters of Lidocaine or Bupivicaine. Despite the groups using similar methods and types of local anesthetic, the two groups of authors provided different results. Curatolo et al. found that the local injection of lidocaine provided no significant effect on pain intensity. The authors propose that this finding indicates that the overall pain of this condition does not stem from nociceptive input arising from the tender points. They suggest that if the pain arose from local tender points, the lidocaine injection would have blocked the pain. The authors propose that the true pain locus is deep within the structures of the neck and that the tender points associated with neck pain represent referred pain maintained through central mechanisms such as central sensitivity.

Although Herren-Gerber et al. (2004) used similar methods of injecting a local anesthetic into the tender points of chronic neck pain patients, this group found different results. The authors discovered that those individuals whose pain intensity increased following the injection (as measured by visual analogue scale) also demonstrated decreased pain thresholds and individuals who had decreased pain intensity following injection presented with increased pain thresholds. In other words, the authors found a negative correlation between increased pain intensity following injection and pain threshold. This group of authors proposed that the injection produces a localized trauma that summates to produce increased pain in patients who have already undergone

peripheral and central nervous system changes. These same patients who have undergone peripheral and central sensitivity also present with decreased pain thresholds, thereby explaining the negative correlation. This study demonstrated that this negative correlation presented at both the painful and non-painful neck sites. This occurrence at non-painful neck sites can be attributed to a spread of receptive fields in the neck causing hyperalgesia in the healthy areas of the neck.

Banic et al. (2004) used the nociceptive flexion reflex for demonstrating central sensitization in patients with neck pain after whiplash injuries. They found that, as compared to the control group, the current needed to evoke biceps femoris contraction in the neck pain patients was significantly decreased; indicating sensitization of the spinal reflex. This finding provides objective evidence that the spinal cord neurons in the central nervous system are indeed sensitized and that the peripheral nervous system does not necessarily maintain this sensitization.

Koelback Johansen, Graven-Nielsen, and Arendt-Nielsen (1999) used a different additional method to assess muscle pain intensity in chronic neck pain patients and controls. This group used a saline infusion into the infraspinatus (runs over the scapula) and anterior tibial (lower leg) muscles. As suspected, the authors found significantly more pain as a result of the infusion in the patient group at both muscle locations as compared to the control group. They also found that pain resolution following cessation of the stimulus occurred more rapidly in the healthy controls than in the chronic neck pain group.

These studies all provide preliminary evidence for the existence of central sensitization in some patients with chronic neck pain. The studies have provided this evidence through demonstration of decreased pain thresholds such as pain detection and pain tolerance thresholds, hyperalgesia and/or allodynia at both the neck and healthy tissue sites such as the lower extremity, and maintenance of sensitization

through central rather than peripheral mechanisms. Attention will now focus on the effects of this central sensitization, specifically whether central sensitization can lead to a transition from chronic neck pain to FM.

Transition of chronic neck pain to WSP and/or FM

A literature search uncovered six studies that address the course of chronic neck pain, particularly as it relates to the transition to FM or WSP (Andersson, 2004; Buskila, 1997; Holm, Carroll, Cassidy, Skillgate, & Ahlbom, 2007; Tishler, Barak, Paran, & Yaron, 1997; Visscher, Hofman, Mes, Lousberg, & Naeije, 2005; Wynne-Jones, Jones, Wiles, Silman, & MacFarlane, 2006). See Table 2.2 at the end of this chapter for a table of evidence for these studies. As noted in the previous discussion, studies describing the relation between chronic neck pain and FM frequently focus specifically on chronic neck pain originating from whiplash as was the case in four of the six studies found in this literature review (Buskila, 1997; Holm, et al., 2007; Tishler, et al., 1997; Wynne-Jones, et al., 2006). Three of the studies defined the outcome variable as FM (Andersson, 2004; Buskila, 1997; Tishler, et al., 1997) while the other three (Holm, et al., 2007; Visscher, et al., 2005; Wynne-Jones, et al., 2006) used WSP as a primary outcome variable. The studies had a stated purpose of investigating the incidence of FM or WSP in individuals with chronic neck pain. Three studies also set out to examine predictive factors for the onset of FM or WSP (Andersson, 2004; Holm, et al., 2007; Wynne-Jones, et al., 2006).

All of the studies divided the study participants into more than one group, which varied slightly among studies. Five of the six studies included a group of patients experiencing chronic neck pain as a result of whiplash (Buskila, 1997; Holm, et al., 2007; Tishler, et al., 1997; Visscher, et al., 2005; Wynne-Jones, et al., 2006) and two studies included patients with chronic neck pain not associated with whiplash (Andersson, 2004; Visscher, et al., 2005). At least one of the control group in three studies consisted of patients with pain or injury in locations other than the neck (Andersson, 2004; Buskila,

1997; Tishler, et al., 1997). Three studies had a control group consisting of individuals with no pain (Andersson, 2004; Visscher, et al., 2005; Wynne-Jones, et al., 2006). Most of the studies had moderate sample sizes of 150 to 250 participants while the study by Wynn-Jones et al. (2006) was based on a population based survey consisting of 695 participants.

To determine the presence of the outcome variable, FM or WSP, three of the six studies performed a tenderpoint examination (Buskila, 1997; Tishler, et al., 1997; Visscher, et al., 2005). Studies performed by Andersson (2004), Wynn-Jones (2006) and Holm et al. (2007) were based on mailed questionnaires and therefore the researchers did not perform a physical examination on participants. Andersson and Holm et al. utilized a body drawing to assess the presence of FM while Visscher et al. utilized questions regarding different body areas of pain to screen for WSP. Similar statistical methods were used for all the studies, namely t-test, chi squared, or ANOVA to assess differences between groups and logistic regression for determining predictive factors when appropriate.

Five of the six studies found similar results regarding the incidence of FM or WSP following chronic neck pain. Buskila and colleagues found that 22% of post-whiplash chronic neck pain patients transitioned to FM as compared to 1% of patients with leg fractures. Holm et al. (2007) also investigated individuals with neck pain immediately following a traffic accident and found that 21% developed WSP. Andersson (2004) reported an FM transition rate of 10% of patients who began with regional pain, predominantly neck/shoulder pain. Wynn-Jones and colleagues (2006) investigated 695 participants who had been in a motor vehicle accident and found that 8% of individuals who experienced whiplash pain presented with WSP after but not before the accident. Visscher et al. (2005) determined that a group of patients experiencing chronic neck pain as a result of a whiplash injury presented with significantly more tender points than a

group with no neck pain. The findings of one study (Tishler, et al., 1997) varied significantly from the findings of the other four studies. This group of authors compared patients who came into the emergency room following an accident resulting in whiplash with a group of patients from the orthopedic, surgery, and neurosurgery wards who had sustained severe trauma following a motor vehicle accident. The control group participants presented with injury to the neck (22%), injury to the upper limbs (28%), multiple trauma sites (25%), and other less frequent injury locations. The findings of this study demonstrated that only one participant in the whiplash group transitioned to FM and no patients in the control group made this transition. The authors of this study deny the link between chronic neck pain as a result of whiplash and FM. For studies that provided the percentages of people who made the transition, this information is summarized in Figure 2.2.

Figure 2.2: The transition from chronic regional neck pain to WSP or FM among the four studies that provided this information.

	Chronic neck pain	Chronic widespread pain	Fibromyalgia
Anderson (2004) N=141	n=7 →		(10%)
Buskila, et al. (1997) N=161	n=22 →		(22%)
Tishler, et al. (2006) N=206	n=1 →		(0.6%)
Wynne-Jones, et al. (2006) N=695	n=54 →	(8%)	
Holm, et al. (2007) N=266	N=266 →	(21%)	

Wynn-Jones and colleagues (2006) discussed possible predictive factors for the development of WSP following chronic neck pain as a result of whiplash. They

separated the predictive factors into pre-collision, collision, and post-collision factors. Their analyses demonstrated that no collision factors predicted onset of WSP. Pre-collision risk factors that predicted onset of WSP consisted of good, fair, or poor health (as compared to excellent health), frequent visits to a primary care provider, a high score on an illness attitude scale, high levels of health related anxiety, and the report of somatic symptoms. Post-collision predictive factors included the perception that the initial injury was more severe; report of any adverse physical symptoms; and occurrence of neck pain either before or after the accident was the strongest predictor.

Another study investigating the development of WSP following a traffic injury that produced neck pain was able to focus on other clinically relevant risk factors (Holm, et al., 2007). These authors asked participants to complete a questionnaire regarding pain, depression, and other clinical symptoms within 10 days of the accident. The authors then performed follow up assessments to establish the presence of WSP at 6 weeks, 4 months, 8 months, and 12 months. Using information obtained 10 days following the injury, the authors determined that depression at baseline (OR 4.6), moderate neck pain at baseline (OR 2.8), severe neck pain at baseline (OR 4.5), and having four or five painful areas at baseline (OR 3.1) were associated with the development of WSP.

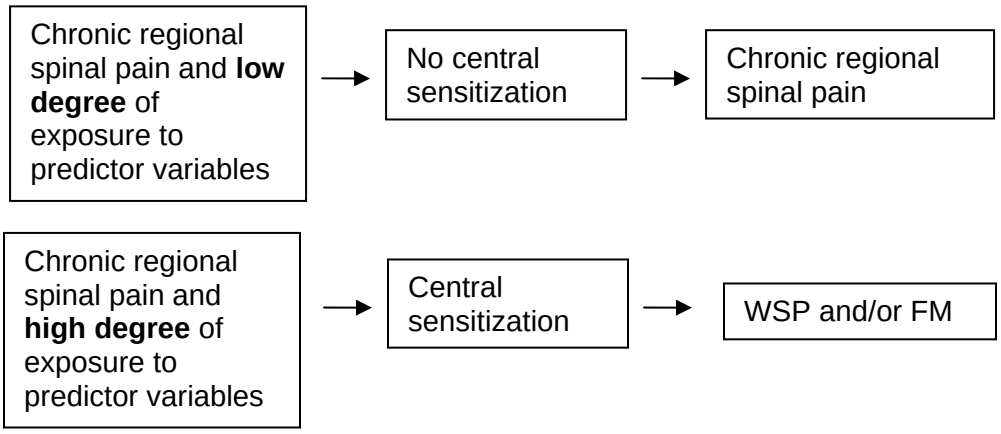
Five of the six studies demonstrated that some patients with chronic neck pain, often as a result of a whiplash injury, can transition from pain located specifically in the neck region to WSP or FM. The occurrence of this transition remains under debate, as evidenced by the study performed by Tishler and colleagues (2006) that did not find evidence of this transition. This study reiterates the importance of acknowledging that this transition does not occur in all patients experiencing chronic neck pain. While only two studies (Holm, et al., 2007; Wynne-Jones, et al., 2006) investigated predictive factors for this transition, there is no conclusive information as to which patients are most at risk and which baseline factors might predispose a person to this negative transition.

Overall the studies presented in both CRSP disorders offer evidence that this transition can occur in a subset of patients, thus providing a rationale for the further study of this phenomenon and an opportunity to take this concept one step further in investigating a multitude of predisposing factors.

Implications for this study

The studies that investigated central sensitization in CRSP disorders and the transition from these disorders to FM clearly found that central sensitization and transition to WSP or FM does not occur in every patient presenting with CRSP. This study hypothesized that certain predictor variables stimulate changes in the nervous system characteristic of central sensitization. In the absence of these predictor variables, CRSP will not lead to central sensitization and therefore these individuals will not transition to WSP or FM. Figure 2.3 outlines this hypothesis. The proposed predictor variables come from the literature describing the development of central sensitization, WSP and FM. A later discussion will discuss the rationale for each chosen predictor variable.

Figure 2.3: Hypothesis explaining transition from CRSP to WSP and FM



Variables Under Study

Outcome variable

The primary outcome variable in the current study was the development of WSP (Aim 1 and 2) or FM (Aim 3) during the study period (meets diagnostic criteria or does not meet diagnostic criteria). In the investigation of the neurobiology of FM researchers have provided preliminary evidence that the pain of this syndrome could be in large part a result of central sensitization and the central sensory abnormalities that cause central sensitization (Price & Staud, 2005). The clinical outcomes of central sensitization coincide with the symptoms characteristic of FM such as lowered pain thresholds and pain tolerance, allodynia, presence of tender points, and persistent pain after resolution of injury. As a result of this sensitization, individuals with FM present with WSP, one part of the FM diagnosis. A diagnosis of WSP occurs when an individual has pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist in addition to axial pain (Wolfe, et al., 1990). The FM diagnosis is based on the 1990 American College of Rheumatology guidelines and states that an individual must present with WSP of three months or more and the physical finding of eleven or more out of 18 specified tender point sites on digital palpation with an approximate force of four kilograms (Wolfe, et al., 1990). While the determination of the number of tender points requires patient examination, WSP can be determined through patient completion of a body drawing. The body drawing consists of a line drawing of the front and back of a human body. The directions ask the patient to shade in the areas of the body that they experience pain. Predefined body sections are superimposed on the body drawing to systematically determine the number of body areas containing pain. This method has been frequently used to determine WSP in individuals (Croft, Rigby, Boswell, Schollum, & Silman, 1993; McBeth, Macfarlane, Benjamin, & Silman, 2001; McBeth, Macfarlane,

Hunt, & Silman, 2001; Papageorgiou, et al., 2002). Physical examination of tender points can then confirm a diagnosis of FM.

Predictor variables

The current study investigated the interaction between having CRSP and the predictive value of certain baseline clinical features for the future development of WSP or FM. Discussion of these variables in the literature related to central sensitization, FM, and WSP propose that these particular variables place a person at greater risk for developing central sensitization, WSP, and FM. Data on each of these variables was collected at baseline (2001 or 2002) prior to a potential transition to WSP or FM. These variables preceded a transition to WSP or FM and therefore represent potential risk factors for transition versus consequences of such transition.

Duration and intensity of pain

Increased duration of pain is thought to enhance the development of central sensitization through long-lasting nociceptive input that sensitizes the spinal cord neurons to incoming stimuli (Flor, 2003; Katz & Rothenberg, 2005; Price & Staud, 2005; Zusman, 2002). The results of three studies support this finding. Flor and colleagues performed two studies (1997, 2004) demonstrating that chronicity of back pain symptoms correlated with the amount of cortical reorganization in the brain, indicating that changes in the central nervous system develop over time. Wilder-Smith and colleagues (2002) also demonstrated that central sensitization was associated with greater chronicity of back pain symptoms. In the specific investigation of chronic regional pain transitioning to WSP or FM, two sets of authors determined that prolonged duration of pain represented a risk factor for this transition (Forseth, et al., 1999; Natvig, et al., 2001).

Greater pain severity is also an important risk factor as intensity of pain messages can enhance the cumulative effect of persistent nociceptive input, thereby further

sensitizing the spinal cord neurons (Flor, 2003). In the study of the development of chronic pain following conditions such as herpes zoster, spinal cord injury, and amputation, severity of pain from the acute condition is the most consistent factor in the development of a chronic pain state (Edwards, 2005). Providing further evidence to this relationship, three research groups discovered that increased intensity of pain predicted or correlated with enhanced pain sensitivity, transition to FM, or central sensitization (Buskila, 1997; Clauw, et al., 1999; Flor, et al., 1997).

Researchers have also investigated the role of peripheral pain generators in the development of FM (Staud & Rodriguez, 2006; Staud, et al., 2006). These scientists proposed that the persistent activity in the peripheral nociceptive afferents caused by the peripheral pain generators serve to perpetuate central sensitization. This process also produces excessive pain responses to these peripheral inputs, thereby increasing the overall level of pain intensity. For this reason, the study utilized baseline reports of other painful body areas as a predictor variable, ensuring that there were not enough painful body areas to constitute WSP.

Genetic factors

Several studies have explored a potential genetic predisposition to central sensitization and the development of WSP and FM (Fillingim, Wallace, Herbstman, Ribeiro-Dasilva, & Staud, 2008). Studies of this link have indicated that there could be a genetic predisposition to central sensitization (Lidbeck, 2002), particularly in the catecholamine-O-methyltransferase (COMT) gene (Zubieta, et al., 2003) and serotonergic receptor genes (Dadabhoy, et al., 2008). Diathchenko and colleagues demonstrated this genetic predisposition when they performed a longitudinal study of 202 young, healthy, pain free women for two years noting that 15 of them developed chronic pain (temporal mandibular joint disease) and also had polymorphisms in the COMT enzyme, which correlates with abnormal pain thresholds on functional

neuroimaging (Diatchenko, et al., 2005). Another group of authors (Wiesenfeld-Hallin, Hao, Xu, Aldskogius, & Seiger, 1993) identified that genetic factors predisposed some animals to hypersensitivity of the central nervous system and proposed that this same phenomenon occurs in humans.

Due to the prohibitive cost of genetic testing, this study explored the possibility of genetics as a risk factor in the development of FM and WSP through family history. This proxy for genetics is commonly used in studies exploring a genetic predisposition to these disorders. Through an exploration of family history, it has been demonstrated that first degree relatives of patients with FM have up to an eight-fold risk of developing FM (Dadabhoy, et al., 2008). Research has also demonstrated that siblings of FM probands display significantly decreased pressure pain thresholds, even in the absence of persistent or recurrent musculoskeletal pain (Bradley, 2008).

Age and gender

Older age is also thought to be a predictor as more peripheral pain generators and comorbidities (osteoarthritis, plantar fasciitis, tendonitis, bursitis) develop with age (Jones, et al., 2006). In an epidemiological review of WSP and FM, it was noted that these disorders increase in prevalence until the seventh decade (Macfarlane, 1999). Correspondingly, Wolfe found that the prevalence of WSP increased progressively from the ages of 18 to 70 with a prevalence of 23% in the seventh decade of life (Wolfe, et al., 1990). Another study investigating the transition from chronic regional pain to WSP found that the oldest age group (age 59-74) represented a significant predictor for transition to WSP (Bergman, et al., 2002). These studies demonstrate that older age is associated with a greater risk for the development of WSP and FM.

Female gender has long been associated with a higher frequency of chronic pain, in fact prevalence of FM carries a nine to one female/male ratio (Wolfe, et al., 1995). Other disorders that seem to affect women more often than men include migraine headaches,

irritable bowel and bladder syndrome, TMD, and many others (Greenspan, et al., 2007). A recent consensus report on sex and gender differences in pain and analgesia outlines the multitude of studies documenting the differences in pain processing between males and females (Greenspan, et al.). This report outlines research demonstrating that women show greater temporal summation, lower pain threshold and tolerance to some types of stimulation, and larger referred areas of pain. Eide (2000) expands on this notion that females experience enhanced temporal summation, the clinical representation of wind-up. He noted that in one study, females presented with significantly increased thermal pain ratings as compared to males upon repeated painful thermal stimuli. This could represent a greater propensity for females to develop one component of central sensitization as compared to males. In the investigation of chronic regional pain transitioning to FM or WSP, the results of two research studies found that the female gender was a significant predictor for this transition (Lapossy, et al., 1995; Natvig, et al., 2001). A prospective study investigating the development of WSP in school-age children (10-12 years of age) also demonstrated that females were at a 40% greater risk of developing the disorder (Mikkelsson, et al., 2008). Taken together, there is substantial clinical and biological evidence that females are at an increased risk for the development of WSP and FM.

Lifestyle factors

Decreased physical activity has been associated with FM in several recent studies including a 2006 retrospective survey of 2,600 people with FM (Bennett, Jones, Turk, Russell, & Matallana, 2006). A study by Clauw and colleagues (1999) investigated sensitivity in patients with chronic low back pain. The study found that functional status significantly correlated with tender point threshold and tolerance, control point threshold and tolerance, and the number of tender points. While this study's design could not demonstrate a causal relationship, it did show an association between pain sensitivity

and functional ability. In a similar vein, increased body mass index (BMI) is linked with lower physical activity levels and is a common comorbidity in FM, though it is not clear whether increased BMI precedes the development of FM or is a consequence of pain and decreased physical activity. One group of researchers investigated this relationship by implementing a behavioral weight loss program in a group of women with FM (Shapiro, Anderson, & Danoff-Burg, 2005). Participants decreased their BMI by an average of 1.6 kg/m^2 and experienced significant improvements in the Fibromyalgia Impact Questionnaire (FIQ), Multidimensional Pain Inventory, and Beck Depression Inventory. Another study examined the impact of weight loss following gastric bypass surgery in morbidly obese individuals with musculoskeletal pain (Hooper, Stellato, Hallowell, Seitz, & Moskowitz, 2007). Subjects decreased their BMI from an average of 51 kg/m^2 to 36 kg/m^2. Following this significant decrease in BMI, only one out of the twelve participants who had originally met the ACR criteria for FM at baseline still qualified for an FM diagnosis. These studies demonstrate a relationship between BMI and FM although increased BMI as a risk factor for the development of WSP or FM has not been established.

The study also investigated smoking as a predictive variable since research has associated this behavior with spinal pain. One literature review found a positive association between smoking and non-specific back pain following the review of numerous studies (Goldberg, Scott, & Mayo, 2000). The authors specified several mechanisms that might be responsible for this association, specifically that smoking diminishes bone mineral content, increases coughing and intradiscal pressure, decreases blood flow to the vertebral bodies, and promotes fibrin deposition, which enhances the formation of scar tissue possible increasing pain and inflammation. Since most of the studies were cross sectional in design, they could not establish temporality,

and therefore causation, between smoking and FM. This study gathered data regarding smoking status at baseline, therefore providing evidence of temporality.

Psychological factors

The presence of depressive symptoms or psychological distress has been found to be associated with transition to FM (Forseth, et al., 1999; Lidbeck, 2002; Natvig, et al., 2001) and has been demonstrated to be more prevalent in FM than healthy controls (Yunus, 1994). Some researchers even propose that exposure to certain negative psychosocial factors might impact the development of FM (Bradley, 2008). Other authors (Gold & Chrousos, 2002; Stahl & Briley, 2004) have proposed that depression and FM share a similar biochemical profile in terms of neurotransmitters such as serotonin, corticotropin releasing hormone, growth hormone, epinephrine, and dopamine, perhaps offering evidence of a link between chronic regional pain, depression, and FM.

The connection between mental health disorders and WSP has also been extensively studied. Several studies have demonstrated that subjects with WSP more frequently present with depression and anxiety. One such study found that the prevalence of a mental disorder in participants with WSP was 16.9% compared to a prevalence of 6.5% in those participants with regional pain (Sidney Benjamin, 2000). Demonstrating that patients with WSP and FM have an increased incidence of psychological distress is important but does not clarify the role of psychological symptoms in the development of these disorders (McBeth & Silman, 1999). One prospective study investigating risk factors for the development of WSP found that participants who scored in the highest range of the Illness Behavior Subscale of the Illness Attitude Scale (asks questions such as “Do your bodily symptoms stop you from working?”) and the General Health Questionnaire (measures psychological distress) were significantly more likely to develop WSP (McBeth, Macfarlane, Benjamin, et al., 2001). These results were not duplicated when the same group set out to examine this relationship in the context of

studying the responsiveness of the HPA axis (McBeth, et al., 2007). In this prospective study they found that higher scores (indicating more severe psychological distress) on the General Health Questionnaire, Illness Attitude Scale, and Hospital Anxiety and Depression Scale were associated with a moderately, although not statistically significant, increased risk of WSP.

Another prospective study investigating the predictive nature of psychological distress on the development of WSP in the general population discovered a significant relationship between depression and anxiety and developing WSP (Gupta, et al., 2007). This group of researchers discovered that individuals scoring in the highest tier of the Hospital Anxiety and Depression Scale had a nearly three-fold risk of developing WSP as compared to those who scored in the lowest tier. These authors propose that psychosocial factors represent important risk factors for the development of WSP.

Emotional and/or physical abuse and its relationship with chronic pain has long been debated. A meta-analysis of studies that examined the relationship between childhood abuse and chronic pain in adulthood found that individuals who reported abuse and neglect in childhood had an increased risk for the development of chronic pain (Davis, Luecken, & Zautra, 2005). Another study looking at this relationship specifically in FM found that, except in cases of rape, there was no association between physical or sexual abuse and the development of FM (Ciccone, Elliott, Chandler, Nayak, & Raphael, 2005).

Ciccone et al (2005) discussed several previous studies that found a relationship between abuse and the development of FM but speculated that these findings might have been skewed due to reporting bias. This reporting bias has been one issue plaguing the relationship between abuse and chronic pain, specifically that perhaps individuals seeking care for their pain tend to more frequently report abuse (Raphael, 2005). Another methodological issue discussed by Raphael is the retrospective nature of most abuse and pain studies, and the potential for recall bias. While resolving this

dispute was beyond this study's scope, the study did incorporate a history of abuse as a possible predictor variable.

Physical comorbidities

Individuals with FM frequently present with other comorbidities that could be grouped into disorders that cause WSP, potential predecessors of FM, and those that share a similar underlying pathophysiology. Several systemic illnesses can present with WSP similar to that of FM and could present as predictors of FM. These illnesses include osteoarthritis, hypothyroidism, certain malignancies, osteomalacia, myopathy, polymyalgia rheumatica, rheumatoid arthritis, myopathy, and systemic lupus erythematosus (Kato, Sullivan, Evengard, & Pedersen, 2006; Staud, 2004; Weir, et al., 2006). Studies have demonstrated that several infectious diseases could also act as triggers for FM (Staud, 2004). These diseases include hepatitis C, Lyme disease, HIV and parvovirus infection and will also be considered possible predictor variables for transition to FM. Recent research has also begun to explore the common pathophysiology of several syndromes that commonly co-occur with WSP and FM. It has been demonstrated that disorders such as irritable bowel and bladder syndrome, migraines, restless leg syndromes, TMD, and vulvar vestibulities share a pathophysiological basis with FM and WSP, namely central sensitization (Clauw, 2002; Diatchenko, et al., 2006; Yunus, 2008). While it is clear that these syndromes, often called central sensitivity syndromes, frequently occur in tandem, the predictive power of having one syndrome on the risk of developing another syndrome is less clear. In an effort to elucidate this relationship, one prospective study demonstrated that childhood report of abdominal pain, headaches/migraines, or periodic vomiting is associated with an increased risk for the development of WSP in adulthood (Jones, Silman, Power, & Macfarlane, 2007). Children whose parents reported that they had experienced all three of these symptoms were 50% more likely to develop WSP in adulthood. The current

study also attempted to evaluate the risk associated with having one or more central sensitivity syndromes on the development of WSP and FM.

Finally, the number of spinal surgeries a person has undergone was investigated as a predictor variable. Surgery of the spine can cause scar tissue, which might provide a consistent nociceptive input into the spine and brain. Surgery of this nature might be considered as a trauma to the central nervous system, perhaps providing the input needed to enhance the process of neuroplasticity in the nociceptive system. One of the only studies to propsectively investigate the relationship between having surgery and the development of WSP found that children who had undergone a surgery or hospitalization were twice as likely to develop WSP in adulthood (McBeth, Morris, Benjamin, Silman, & Macfarlane, 2001).

Summary

Since CRSP, WSP, and FM share a common pathophysiological glue, namely central sensitization, this study hypothesized that individuals with chronic spinal pain were at risk for the development of WSP and FM. This fact has been demonstrated by several reputable researchers. More importantly, this study set out to determine the risk factors associated with this transition. Research regarding the development of central sensitization, WSP, and FM along with factors known to co-occur with these syndromes informed the variables chosen in this study. This study represented a unique opportunity to study a multitude of suspected risk factors in a group of individuals at risk for the development of these disorders. Determining which factors actually lead to a transition from CRSP to WSP and FM represents an important endeavor as this information will inform future research aimed at mitigating this transition in high risk individuals.

Table 2.1: Evidence table: Transition from chronic regional back pain to WSP or FM.

1. Citation	1. Purpose	1. Design 2. Sample	1. Variables/Measures 2. Statistical test	1. Findings 2. Limitations
Lapossey, E., Maleitzke, R., Hrycaj, P., Mennet, W., & Muller, W. (1995). The frequency of transition of chronic low back pain to fibromyalgia. *Scandinavian Journal of Rheumatology,* 24, 29-33.	1. To investigate how often CLBP converts to FM. To look for symptoms related to CLBP which can predict the occurrence of FM.	1. Retrospective study investigating a group of 53 patients with localized back pain on first presentation. Re-examined pts after an average disease duration of 18yrs. Does not specify time period between re-examination. 2. 18 males, 35 females, average age 57 years. CLBP defined as localized pain in lumbar region, duration > 3months, no severe pathology on x-ray, no radicular symptoms.	1. Pain intensity (VAS), regions of pain (pain score 0-4 in a 24 region body scheme), disease duration, functional and vegetative symptoms (17 variables: fatigue, trouble falling asleep, headache, lump in throat sensation, cardiac troubles, orthostatic troubles, dysesthesia of hand and feet, swelling of arms and legs, GI complaints, functional dyspnea, urinary urgency, cold extremities, hyperhydrosis, sicca symptoms, tremor, dermatogrphism), tender points 2. T-test, Mann-Whitney U test, Correlations Relative frequency of different parameters compared with Chi square.	1. Three groups: Still CLBP (32 (60%)), Now FM (13 (25%)), Neither CLBP or FM (8 (15%)). Significant for 'Now FM' group (from baseline): Female, slight postural disorder of spine (ex:scoliosis) Significant for 'Now FM' group as compared to 'Still CLBP' (current): Higher pain score, more tender points, fatigue, swelling hands and feet, GI complaints, higher number of functional and vegetative symptoms 2. Minimal description of sample, design, and procedures, or how variables were measured. Somewhat unclear as to which findings actually were present at baseline and could have perpetuated the change.
Natvig, B., Bruusgaard, D., & Eriksen, W.	1. Establish how often LBP is combined with	1. Cross sectional mailed questionnaire. Established two	1. Age (6 birth cohorts), Gender, Pain location (drawing and 10 area	1. LBP with WSP (sig.): More often female. Longer duration of pain.

(2001). Localized low back pian and low back pain as part of widespread musculoskeletal pain: Two different disorders? A cross-sectional population study. *Journal of Rehabilitation Medicine,* 33, 21-25.	WSP and to compare between individuals with localized LBP and those with LBP as part of widespread musculoskeletal pain.	groups: localized LBP and LBP with widespread musculoskeletal pain. 2. Questionnaires sent to individuals in a town in Norway. 2893 (63%) responded. From these, 222 had localized LBP and 281 had LBP with WSP.	checklist), Pain duration (less than 1 year, 6-10 years, greater than 10 years), Consistency of pain (In past year: less than a week, 1-8 weeks, more than 8 weeks, everyday), Pain severity (no pain, not so bad, moderate, bad, very bad), Physical leisure activity (how often do you strenuously use your body in your leisure time: non, less than 2hrs/week, 2-4hrs/week, more than 4hrs/week), Sleep problems (how do you usually sleep: well, fairly well, badly), Functional status (standard functional measure and 1-5 rating) 2. Chi square: comparison of two groups on each variable. Stepwise logistic regression: to explore associations between the variables and LBP with WSP.	More consistent pain. Greater severity. Decreased overall health. More impaired sleep. Higher or lower BMI. Decreased functional ability in all six dimensions. No difference in strenuous leisure activity. Regression: Having LBP with WSP associated with: female, pain intensity, emotional problems, reduced self rated general health, and chronicity of symptoms. 2. Possible selection bias (non-responders more often male and younger), functional questionnaire used designed to also pick up minor limitations, cut off point for WSP was 4 areas (another study used 5), study did not distinguish between lower extremity pain related to the LBP and other causes. LBP with radiation was not included in WSP though.
Forseth, K.O, Husby, G., Gran, J.T., & Forre, O.	1. To estimate the risk of developing FM and to find	1. The authors used a cohort study with a 5.5 year observation	1. FM as outcome variable. Predictor variables:	1. At baseline, 115 subjects with limited pain. Pain status 1: 46. Pain

(1999). Prognostic factors for the development of fibromyalgia in women with self-reported musculoskeletal pain: A prospective study. *The Journal of Rheumatology,* 26(11), 2458-2467.	predictors for FM in women with self-reported pain, particularly women with limited pain. 2.	period. In 1990, women received questionnaire to screen for regional pain or FM. Those subjects who indicated that they had FM were excluded. In 1995 subjects were classified into four groups: Pain status I: non-chronic pain (intermittent), Pain status II: chronic regional pain; Pain status III: more than regional but less than widespread (chronic multifocal pain); Pain status IV: WSP. Developers (developed FM), non-developers (did not develop FM) 2. Source population was 2498 women in southern Norway. 2038 women responded to initial questionnaire. 1168 (57%) answered that they had at least one area of pain (out of joints, muscles, back, and whole body). A representative sample of 214. After excluding women with FM, they	Chronicity (experienced pain for at least 4 out of 7 days per week for at least 3 consecutive months), WSP, pain duration (dichotomized at >6years or <6years), number of TP (dichotomized at >11 or <11) Associated sxs: Factors that aggravate pain (weather change, stress, unusual physical activity), pain at night, headache, poor sleep, not feeling refreshed in the morning, fatigue, irritable bowel symptoms, parasthesia, swelling in joints or muscles (associated sxs dichotomized at >4 or <4). Self assessed depression (feeling depressed at least once per week). Marital status, number of children, years of schooling, kind of education. 2. Absolute risk of FM was given for the presence or absence of each risk factor. Relative	status II: 69. Pain status III: 42. Pain status IV: 5. At follow up, 43 (25%) women developed FM. These 43 women at baseline: 8 (17.4%) were Pain status I, 12 (17.4%) were Pain status II, 18 (43%) were pain status III, and 5 (28%) were pain status IV. Risk factors for development of FM (Chi square): Pain >6years, back (RR 2.5) and lower part of arm (RR 2.4), 78% had localized onset of pain at baseline, greater than 4 associated symptoms (particular symptoms that were risk factors – alternately loose/hard stools, not feeling refreshed in the morning, and subjective swelling), self assessed depression Multiple logistic regression: Pain duration >6yrs (OR 3.5), pain in the back OR 3.2), and self assess depression (OR 6.3). 2. "The clinical heterogeneity of FM means that predictors

		were left with 175 women.	risk was assessed using Chi-square. Multiple logistic regression was used to identify predictors for FM with FM as outcome variable.	may vary from subgroup to subgroup and thus lose power in the analysis. Several clinically important predictors may be left out as predictors." (pg. 2464). High incidence of FM developers may be attributed to sample of only women and a sensitive screening questionnaire followed by detailed questions about pain. FM may be more frequent in this particular Norway county.
Bergman, S., Herrstrom, P., Jacobbson, L.T.H., & Petersson, I.F. (2002). WSP: A three year follow-up of pain distribution and risk factors. *The Journal of Rheumatology,* 29 (4), 818-825.	1. To study the longitudinal course of chronic regional pain (CRP) and chronic widespread pain (WSP) and to what extent CRP proceeds to WSP. A second aim was to identify risk factors that predicted the development or persistence of WSP.	1. Three year follow-up with a postal questionnaire in 1998 to subjects that initially responded to a cross sectional postal survey in 1995. Identical questionnaires were sent out at baseline and follow-up with the exception of questions concerning other health problems and socio-demographic status. Questionnaire had two parts. First was the Medical Outcomes Survey Short Form 36. The present study was	1. Variables: Sex, age (4 groups of ages ranging from 20-74), socioeconomic group (4 groups based on manual/nonmanual and assistant/high level and other), immigrant status (swede or immigrant), housing area (socially compromised or not), educational level (2 groups: two years after high school or not), smoking habit (never, former, current), alcohol (never/seldom, monthly, weekly/daily), personal support (no/yes), family	1. Subjects were classified into four groups: no chronic pain (NCP), CRP, WSP, and unknown. There were no significant changes in prevalence rates among the four groups between 1995 and 1998 but there was variability in individual status. 16.4% of individuals initially presenting with CRP transitioned to WSP. 2.2% of individuals originally presenting with NCP transitioned to WSP. Out of subjects initially

		based on second part of questionnaire which focused on the experience and location of chronic pain in the musculoskeletal system. The questionnaire was piloted and validated in a previous group of 50 patients. 2. 1995 sample consisted of 3928 subjects aged 20-74. 2425 (62%) responded in 1995 and received a follow-up questionnaire in 1998. 1922 (79%) subjects responded in 1998 and 1852 subjects were evaluated.	history of chronic pain (no/yes), regions with pain (based on outlined body drawing). 2. Statistical comparison of prevalence was done using Chi square. Multivariate logistic regression was used to compute odds ratios for risk factors.	presenting with WSP, 26.8% moved to CRP and 16.3% to NCP. Developing WSP from CRP or NCP was significantly predicted by the oldest age group (59-74), having a family history of chronic pain, and the presence of 1-12 "regions" with pain (highest OR was for 6-12 regions – regions defined by body map). Social support and weekly/daily intake of alcohol (as compared to monthly or never/seldom) were protective. 2. Selection bias: In the analysis of the 1995 survey it was discovered that people with chronic pain were more likely to respond. In 1998 survey, women responded at a significantly higher rate. Potential for misclassification despite best efforts but likely would distribute across groups. Recall bias could affect family history of chronic pain with individuals with chronic pain more frequently

				knowing if there was a family history.
Andersson, H.I. (2004). The course of non-malignant chronic pain: A 12-year follow-up of a cohort from the general population. *European Journal of Pain,* 8, 47-53.	1. To describe the long-term course of chronic pain and to analyze possible predictive factors for recovery from and persistence of chronic pain.	1. Sent a postal questionnaire in 1988 to residents in the south of Sweden. From the individuals who responded, four groups were derived: A. neck and/or shoulder pain; B. pain report from at least three body regions (WSP); C. no report of chronic pain; D. pain in other locations. From groups A-C, a random representative sample was drawn from each group to create a cohort. The cohort was examined and blood samples were taken. In 1990 the cohort received a follow-up questionnaire. Those who could be traced were sent another questionnaire in 2000. 2. Questionnaires were sent to the general population in south Sweden. Original randomly drawn cohort from 1988 included 100 women and 114 men.	1. Age, gender, having a close friend outside the family, smoking, working conditions (bent position, exhausted after workday, monotonous movements), fatigue, sleeping difficulties, chilliness, stiffness, number of painful areas (body drawing), hypertension, sick leave. 2. Chai squared was used to investigate hypotheses of difference between groups for categorical data. Correlation was also used. Stepwise logistic regression was used to evaluate the prognostic and predictive factors. Outcome variable in all models was report of chronic pain in 2000 and covariates were the variables mentioned above.	1. In 1988, 71 individuals presented with regional pain. Seven (10%) of those individuals transitioned to WSP by 2000. In 1988, 73 individuals presented with no chronic pain. Five (7%) of those individuals transitioned to WSP in 2000. It could be hypothesized that some of them might have transitioned to chronic regional pain, then onto WSP in the 12 years. ** The rest of the analyses were done looking at factors that predicted the onset of chronic pain or the persistence of chronic pain (not factors that predicted a transition to WSP). Among those reporting chronic pain in 1988, the factors that correlated with persistent pain in 2000 were age 40-59 and report of more than three areas of pain. In a model that predicted chronic pain 12 years later, there

		In 2000, the cohort that responded included 56 women and 85 men.		was an increased risk with the 1988 report of chilliness, stiffness, and chronic pain. Having a close friend outside the family was protective. The one factor predicting onset of chronic pain from no pain in 1988 was a bent position at work. There was a significant difference in mortality among the WSP group as compared to the no pain and regional pain group with the WSP having more deaths. 2. Limitations in regards to this synthesis: There was no examination of factors predicting the transition from regional pain to WSP. This group was not looked at in detail.
Papageorgiou, A.C., Silman, A.J., & Macfarlane, G.J. (2002). Chronic widespread pain in the population: A seven year follow up study. *Annals of Rheumatic Disease, 61*, 1071-	1. To document the natural course of WSP over a seven year period and to identify comorbities at baseline that predict poor long term outcomes in those with WSP.	1. In 1991 authors sent a survey to people registered with a general practice in England. Based on the body drawing, the authors created three groups; those with WSP, regional pain, and no pain. In 1998,	1. The seven page survey included questions regarding musculoskeletal aches and pains in the past month; questions taken from the Fatigue Questionnaire, the Somatic Symptom Checklist, and General	1. Of the participants who had WSP in 1991, 34% still had WSP in 1998, 51%% had regional pain in 1998, and 15% had no pain in 1998. Of the participants who had regional pain in 1991, 10.4% had WSP in 1998, 36% had regional pain in

1074.		the authors sent a follow up survey with questions regarding sites and duration of their pain. 2. Sample included 1,386 participants who returned both the 1991 and 1998 surveys.	Health Questionnaire; a body drawing on which participants shaded their pain; and a question asking about pain duration. 2. Logistic regression was used to determine prognostic factors with an outcome variable of WSP in 1998.	1998, and 34% had no pain in 1998. The focus of the study was on the predictors of persistent WSP. Participants over the age of 50 were three times more likely to have persistent WSP. Subjects who endorsed the statements “I ache all over” or “Pain keeps me awake at night” were twice as likely to have persistent WSP. Statements of being “too tired during the day” and having “dry eyes or dry mouth” were also significantly associated with having persistent WSP. 2. Measures were not used in their entirety; only select statements from the validated tools were used. The research group only looked at factors contributing to the persistence of WSP and did not report predictors for the development of WSP.

Table 2.2: Evidence table: Transition from chronic regional neck pain to WSP or FM.

1. Reference 2. Purpose/Hypothesis	1. Sample 2. Variables/Measures	1. Findings
Buskila, D., Neumann, L., Vaisberg, G., Alkalay, D., & Wolfe, F. (1997). Increased rates of fibromyalgia following cervical spine injury: A controlled study of 161 cases of traumatic injury. *Arthritis and Rheumatism, 40*(3), 446-452. 2. Hypothesis: The incidence of FM should be increased in persons with neck injury compared to those who have lower extremity injuries.	1. 102 patients with neck injuries (90% whiplash). Control: 59 patients with leg fractures. Prior to accident, none had WSP. 2. Tenderness assessment: Tenderpoint count to diagnose FM. Dolorimetry at 9 tenderpoint sites and 4 control sites to measure threshold of tenderness. Also measured symptoms (on VAS), physical functioning, and QOL. 3. T-tests and chi-square	FM prevalence rate in neck pain group was 13 times greater than leg injury group (22% of patients compared to 1%). Neck pain group had significantly more tender points (5.9 compared to 3.1). Neck pain group had significantly lower pressure pain threshold. Quality of life and FIQ significantly more impaired in neck pain group. Divided neck pain patients into those with FM and those without FM. FM group assessed impact of trauma worse in regards to functioning, physical independence, and mobility. FM group displayed significantly worse symptoms (not stated whether symptoms were present before or after transition to FM).
Andersson, H.I. (2004). The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. *European Journal of Pain,* 8, 47-53. 2. Purpose: To describe the long-term course of chronic pain and to analyze predictors of persistent pain (not transition to WSP).	1. Postal questionnaire sent out of the general population in the south of Sweden in 1988 (N=214). Four groups were identified: Neck/shoulder pain, WSP, no pain, pain in other areas. This study is the result of a 2000 follow up questionnaire sent to 1988 participants. This resulted in N=141. 2. Method = questionnaire 3. Chi squared for categorical data, correlation for non-categorical. Stepwise logistic regression for predictive factors. Dependent variable was the report of chronic pain in 2000; covariates were variables from 1988 questionnaire.	10% of patients who had chronic regional pain (predominantly neck/shoulder pain) transitioned to FM over the 12 years between studies. Variables were used to predict who would have persistent pain, not who would transition to FM, so not relevant.

Wynn-Jones, G., Jones, G.T., Wiles, N.J., Silman, A.J., & Macfarlane, G.J. (2006). Predicting new onset of widespread pain following a motor vehicle accident. *Journal of Rheumatology,* 33 (5), 968-974. 2. Purpose: To examine person's who have recently had a traumatic event and determine which factors predict the onset of widespread pain.	1. Recruited patients from a large, UK insurance database. 2. Postal questionnaire. Included in they did not present with WSP in month before accident. Questionnaire also collected data on risk factors for WSP. Asked about general health, health behaviors, and psych distress in month prior to accident. Asked about collision specific factors, and post-collision factors. No body drawing, just questions. 3. Regression used to determine which baseline factors associated with onset of WSP.	695 participants were eligible (had no WSP prior to accident) and returned questionnaire at 12 months. 54 (7.8%) reported new onset WSP. Prevalence of WSP significantly increased with age. Pre-collision predictive factors: Good, fair or poor health doubled risk (as compared to excellent health), frequent visits to PCP in past year, high score on illness attitude scale, high levels of health anxiety (not psychological distress), report of somatic symptoms. Collision specific predictive factors: None Post-collision predictive factors: Report of any adverse physical symptoms, perception of initial injury to be more severe, occurrence of neck pain whether that was either pre or post-collision. Highest predictive factor was neck pain at both time points. Regression model: number of physical symptoms post collision, pre-collision health behavior, pre-collision somatic symptom reporting, and perceived injury severity.
Tishler, M., Levy., Malakov, I., Bar-Chaim, S., & Amit-Vazina, M. (2006). Neck injury and fibromyalgia – Are they associated? *The Journal of Rheumatology,* 33 (6), 1183-1185. 2. To test prospectively whether there is a causative link between trauma and FM.	1. 153 patients who were discharged from ER between 8/03 and 1/04 after whiplash. Control: 48 patients hospitalized in ortho, surgery, or neurosurgery because of severe trauma following MVA. In Israel. 2. Recruited patients in ER. Follow up phone calls every 5 months. Follow up included questions about joint pains, dizziness, sleep disturbance, headaches,	Follow up period for patient group: 14 months. One patient in study group and none in control developed FM. Study patients had significantly worse QOL, more headaches. Control group: Hospitalized for average of 6 days, 22% had injury to neck and shoulders, 28% to upper limbs, 25% had multi-trauma.

	concentration problems. Questionnaires: Arthritis Impact Measurement Scale, FIQ, employment status, and insurance claims. 3. T-test and chi-square	Conclusion: Results do not support link between neck trauma and FM.
Visscher, C., Lofman, N., Mes, C., Lousberg, R., & Naeije, M. (2005). Is tempromandibular pain in chronic whiplash-associated disorders part of a more widespread pain syndrome? *Clinical Journal of Pain,* 21 (4), 353-357. 2. Determine the prevalence of TMD pain, WSP, and psychological distress in persons with whiplash associated disorders.	3 groups: study group of patient with whiplash associated disorders (WAD), no chronic neck pain, and chronic neck pain not due to whiplash. 2. Questions: Presence of trauma to neck or orofacial region, pain location, nature, duration, radiation, VAS. Physical exam, tender point assessment but excluded neck tender points (to determine WSP). 3. Chi squared to compare prevalence of TMD between the three groups. T-test to determine differences in pain intensity, ANOVA to test differences in number of tender points in each group.	Number of tender points: WAD had most tender points, which was significantly more than no neck pain. Chronic neck pain group had more than no neck pain but did not reach significance. Significantly increased prevalence of TMD pain in the WAD group as compared to no pain group. None of the others reached significance. Conclusion: Increased prevalence of TMD in WAD suggests that TMD pain is part of a more WSP disorder.
Holm, L.W., Carroll, L.J., Cassidy, J.D., Skillgate, E., & Ahlbom, A. (2007). Widespread pain following whiplash-associated disorders: Incidence, course, and risk factors. 2. To investigate the incidence and course of WSP after the occurrence of a whiplash associated disorder with localized pain in the neck following a motor vehicle collision (MVC) and to investigate factors associated with the onset of WSP.	1. 266 individuals who had indicated experiencing neck or shoulder pain following a MVC and completed a survey questionnaire within 22 days following the accident which gave the researchers baseline information on their pain and condition. Follow up at 6 weeks, 4 months, 8 months, and 12 months to determine the development of WSP. 2. Baseline questionnaire gathered information on neck pain and headaches before and after the MVC and other symptoms following the MVC. Pain drawings were included in the baseline questionnaire and all follow up questionnaires.	1. 21% of participants who presented with neck or shoulder pain following the MVC developed WSP at some point during the year following the accident. 63% developed WSP within 6 weeks of the MVC and 20% within 4 months. 64% of participants with WSP following the accident demonstrated improvement within the year-long study. Depressive mood, higher baseline neck pain intensity, reporting 3 or more health symptoms, and presenting with 4 or 5 painful body areas (out of 45) were associated with the development of WSP.

CHAPTER 3: RESEARCH DESIGN AND METHODS

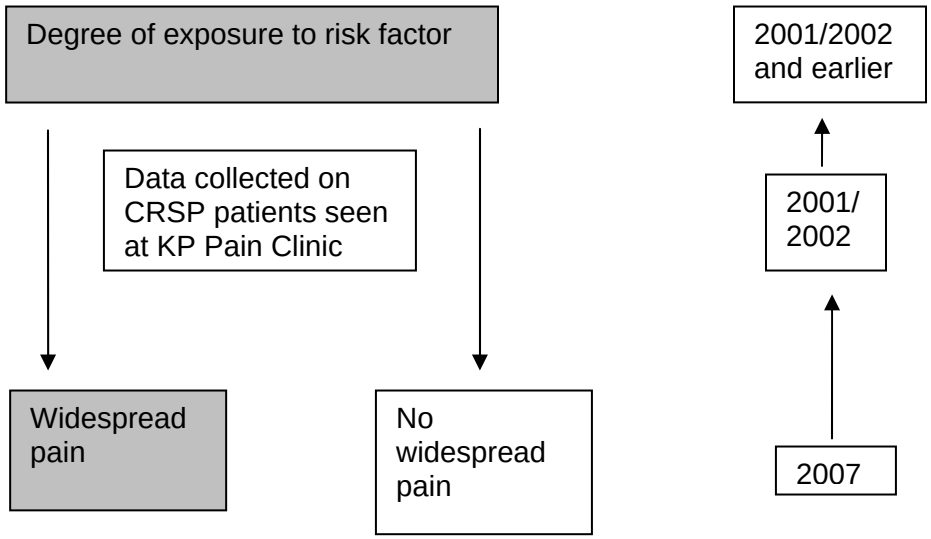
Design

This study employed two phases in order to investigate the transition from chronic regional spinal pain (CRSP) to widespread pain (WSP) and fibromyalgia (FM). The first phase utilized a retrospective cohort design to identify participants who transitioned from having CRSP in 2001/2002 to the development of WSP in 2007. The second phase entailed examining those participants who presented with WSP in 2007 to determine whether or not they qualified for a diagnosis of FM. After identifying the participants who had indeed transitioned to FM, a case control design was implemented to determine the risk factors associated with this transition. Details of these investigations are outlined below.

Retrospective cohort

This study utilized a retrospective (or historical) cohort design to investigate the transition from CRSP to WSP and to determine the factors that predispose an individual to this transition. The study used a population of patients seen in the Kaiser Permanente (KP) Pain Clinic in 2001/2002 for a diagnosis of chronic low back or neck pain (see Appendix A for a letter of support from the KP Pain Clinic). A survey sent to potential participants identified those participants who presented with a diagnosis of WSP in 2007, indicating that they transitioned from chronic low back or neck pain in 2001/2002 to WSP in 2007. Following the design of a retrospective cohort study, the principle investigator (PI) looked retrospectively to identify the presence of risk factors that might have predisposed these participants to a transition to WSP. The participant's status on the risk factors was found using a retrospective chart review focused on a questionnaire completed by the participants in 2001/2002 upon entering the KP Pain Clinic and from information gathered from a survey sent in 2007. Following is a diagram of the study's design:

Figure 3.1: Retrospective cohort design



The study team debated longer and shorter time frames and ultimately decided that based on the literature, the 2001-2002 subjects would be most likely to have adequate time to transition (Bergman, et al., 2002; Buskila, 1997; Lapossy, et al., 1995; Visscher, et al., 2005; Wynne-Jones, et al., 2006). Furthermore, the same medical intake form has been in place at the Pain clinic since 2000.

Case control

Implementation of the second phase aimed at identifying risk factors associated with a transition from CRSP to FM utilizing a case control design. Cases in this study consisted of participants who transitioned from CRSP to FM while controls were participants who had not developed WSP or FM. In order to identify which participants could be considered cases, the researchers had to determine which participants who demonstrated WSP in 2007 also qualified for a diagnosis of FM. To establish this, the study team invited the 129 participants who presented with WSP in 2007 but did not have a diagnosis of FM to Oregon Health & Science University (OHSU) to undergo a tender point examination. Details of this procedure are outlined below. The 22 individuals deemed to have FM by the tender point examination along with the 18 participants diagnosed with FM after 2003 by their Kaiser provider made up the cases

(total of 40 participants) for this case control portion of the study. For the control group, the author randomly selected 40 age matched participants who did not transition to WSP or FM. Comparison of the two groups allowed for the determination of odds ratios and relative risks of potential risk factors. Cases and controls were compared on current and past attributes and on exposure to particular factors. For example, they were compared on attributes such as pain severity in 2001/02, family history of WSP, and gender. Comparisons were also made on the exposure of the case and/or control to factors such as obtaining more than two spinal surgeries, previous experience of abuse, or exposure to certain syndromes. A discussion regarding analysis of these comparisons can be found in the Data Analysis section.

Sample

The study included participants seen in the KP Pain Clinic in 2001 or 2002 for one of the study diagnoses (see Table 3.1 at the end of this chapter for a list of all included diagnoses) and who met the study's inclusion criteria (discussed later). This sampling frame consisted of the 2,256 patients who were seen for any aspect of treatment within the Pain Clinic including visits for interventional procedures, consultation, medication management, and a multidisciplinary group series. Each of these patients was sent an invitation letter and study survey.

Inclusion criteria

For inclusion into this study, potential participants included adult men and women seen by the KP Pain Clinic in 2001 or 2002 carrying one of the study diagnoses. The study only included adults, defined as 18 years of age or older. The KP Pain Clinic only sees patients 18 and older. An upper age limit was not imposed as age was a potential factor affecting the transition from CRSP to WSP or FM. The study only included English-speaking participants as the number of non-English speaking patients seen in

the Pain Clinic is small and the primary study questionnaire was only available in English.

Exclusion criteria

This study aimed to investigate the transition from CRSP to WSP and FM in the years between 2001/2002 and 2007. Therefore, patients who had been diagnosed with FM in 2002 or earlier had to be excluded from the study. These patients entered the sampling frame because they were seen by the Pain Clinic in 2001/2002 for treatment of their spinal pain but also had a history of FM. This author excluded participants who either documented on the 2007 study questionnaire that they had been diagnosed with FM in 2002 or prior or if it was discovered, through a careful chart review, that they had been diagnosed or seen for FM in 2002 or earlier. This led to the exclusion of 80 patients. Participants presenting with WSP in 2001/2002 (through review of their body drawing on the 2001/2002 KP questionnaire) were not included in the analysis of aim 2 (as the outcome variable was WSP). This author did include them in the aim 3 analysis since the outcome variable was FM, not WSP.

Setting

Data collection for the proposed study took place in two different settings. The first phase of data collection, which consisted of a participant survey, took place at the participant's home at his/her convenience. The second phase of data collection consisted of a physical examination of participants who demonstrated WSP in 2007 but did not carry a diagnosis of FM. In order to determine whether these participants had FM, the study team performed tender point examinations on those patients who agreed to participate in this phase of the study. For the majority of these participants this took place at OHSU in a large room that accommodated a brief presentation and separate, small areas set up with a privacy screen for the tender point examinations.

Two sites were used for study activities not involving patient participation. The KP Pain Clinic was used for the collection of returned questionnaires, data entry and data storage. OHSU was the primary site for preparing study materials, consultation with FM and chronic pain research experts and data analysis.

Procedures

Recruitment

This author searched the KP Pain Clinic data records to identify all patients seen by the Pain Clinic in 2001/2002 for one of the included study diagnoses (Table 3.1). As noted, this consisted of 2,256 patients who were still living. This author recorded the patient's health record number, name, address and phone number for recruitment purposes. Each patient was assigned a unique study identification (ID) number which was kept in a password protected computer file that linked the study ID with the patient's identifying information. This author sent each of these patients an invitation letter signed by the PI and the manager of the Pain Clinic (see Appendix B) and a study questionnaire (see Appendix C). The invitation letter described the purpose of the study and what participation would entail. The letter also informed the potential participants that, upon return of their study questionnaire, they would be entered into a drawing for one of five $50 Fred Meyers gift cards. Lastly, the letter included the components necessary to gain consent for participation in the study. Instead of having the participant sign an informed consent document, the KP internal review board (IRB) recommended including the informed consent information in the letter and then consent was inferred with the return of the questionnaire. Therefore the participant's name was not associated with the data provided on the study questionnaire.

Sequence and procedures

As noted, this study consisted of two data collection phases. The first phase gathered data to investigate whether patients presenting with CRSP in 2001/2002 developed

WSP in 2007 and to assess potential predictor variables. In the second phase of the study, the research team determined which patients presenting with WSP in 2007 fulfilled a diagnosis for FM. This data informed analysis to identify the risk factors associated with the development of FM from a regional spinal pain disorder. Please see Table 3.2 for a timeline of the procedures.

Table 3.2. Timeline of study procedures.

Months 1-4	Months 3-6	Months 6-12
1. Determination of patients seen in Pain Clinic in 2001/02 with pertinent diagnoses. 2. Mail packets including invitation letter and Study Questionnaire	1. Collection of completed questionnaires. 2. Review participant's chart for KP Pain Clinic Questionnaire and medications used in 01/02. 3. Data entry for incoming data.	1. Data entry for incoming data. 2. Data cleaning and verification.
Months 13-14	**Months 15-17**	**Months 18-22**
1. Determination of participants eligible for second phase. 2. Invitation letter to those eligible participants. 3. Reminder letter and phone calls for patients who did not respond.	1. Examination of participants who have transitioned to chronic WSP. 2. Statistical analysis of results.	1. Statistical analysis of results. 2. Manuscript development. 3. Dissemination of findings at national conferences.

To achieve limited participant burden due to multiple mailings, the invitation packet included all necessary paperwork for the first phase of the study. The invitation packet included the invitation letter (Appendix B), one copy of the study questionnaire (Appendix C) and a self-addressed, stamped envelope. The invitation letter included the PI's telephone number for the participants to call and ask questions about the study. In order to ensure patient confidentiality, this phone had a private, secure voicemail that

only the PI could access. Patients choosing to participate completed the study questionnaire which likely took approximately 30 minutes. Upon completion of the study tool, the participants returned the questionnaire in the enclosed self-addressed, stamped envelope to the primary investigator at the KP Center for Health Research (CHR). Patients who returned a completed study questionnaire were entered into a drawing for one of five $50 gift certificates to Fred Meyer. Patients who did not return the study material were sent a second study packet including a revised invitation letter, the study questionnaire, and a self-addressed, stamped envelope.

Since the study questionnaires were sent to the KP CHR, the PI obtained a data transfer agreement in order to securely take the questionnaires to the KP Pain Clinic where data entry occurred. Prior to data entry, this author performed a chart review to ensure that the participant had not been diagnosed with FM during 2002 or earlier. This was accomplished by reviewing the participant's diagnosis list and determining whether the participant had ever been seen for a diagnosis of FM. Any participants who had a diagnosis of FM on their problem list or in their encounter diagnoses were excluded from further analysis. If the participant did not have a history of FM in 2002 or prior, this author continued with the chart review to locate the participant's 2001/2002 KP Pain Clinic questionnaire (Appendix D). When the author located the scanned KP Pain Clinic questionnaire associated with the Pain Clinic appointment in 2001/2002, this was printed and attached to the participant's 2007 study questionnaire. Approximately 18% of the participants' Pain Clinic questionnaires had not been scanned in 2001/2002. When this author could not locate the scanned questionnaire, the chart note associated with the 2001/02 Pain Clinic visit was printed and reviewed. The physicians typically documented aspects of this questionnaire into their chart note. Missing data associated with not having a scanned Pain Clinic questionnaire will be discussed in depth later. In the last phase of the chart review, this author identified the medications used by the participants

in the three months prior to and after the Pain Clinic appointment. This author documented these medications on the Medication Abstraction Form (Appendix E). The PI then organized this information into a study packet for each participant consisting of the 2007 Study Questionnaire, 2001/2002 KP Pain Clinic questionnaire, and the Medication Abstraction Form. Study packets were arranged by study ID numbers in a locked filing cabinet in a locked office. This author then began entering the information from these three data sources into Microsoft Excel.

In order to determine the presence of WSP in 2001/2002 and in 2007, this author reviewed the body drawing in the KP Pain Clinic Questionnaire (completed in 2001/02) and in the Study Questionnaire (completed in 2007). This author deemed the participant to have WSP if they met the American College of Rheumatology criteria of having pain in three out of four body quadrants and axial pain (Wolfe, et al., 1990). If this author had any question as to whether a participant's shading of pain on the body diagram constituted WSP, Drs. Bennett and Jones were consulted for their input. The chart and study documents were also reviewed to determine if the participant had been diagnosed with FM after 2002 (those patients diagnosed with FM in 2001/2002 or earlier were not included in the analyses). A diagnosis of FM could be determined in one of two ways. The 2007 Study Questionnaire asked the participants to document if and when they had been diagnosed with FM. If a participant endorsed being diagnosed with FM, this author confirmed this diagnosis and the date of diagnosis in the participant's health record. Every participant's problem list and visit diagnoses were also reviewed for a diagnosis of FM after 2002.

After receiving and documenting each participant's study packet into the Excel database, the study team was ready to move into phase 2 of data collection. This phase was necessary to determine which participants had developed FM between 2001/2002 and 2007. From the chart review, this author already knew that 18 participants had been

diagnosed with FM in this period. For the remainder of the 129 participants who demonstrated having WSP on their 2007 Study Questionnaire but did not have a documented diagnosis of FM, the study team needed to perform a tender point examination to determine whether or not these individuals qualified for a diagnosis of FM. These 129 participants were sent a letter inviting them to come to OHSU for a study visit involving an informational talk given by Dr. Robert Bennett and a brief tender point exam (see Appendix F for the phase 2 invitation letter). The letter informed the participants that the research team was offering two time options for the study visit, one in the afternoon and one at night. The letter also informed them that they would receive a $10 gift certificate to Borders Bookstore for coming to the study visit. The participants were asked to contact the PI with the particular visit they would attend. One to two weeks after sending this letter this author followed up with a phone call to all participants who had not responded (n=98). This phone call offered the opportunity for the participant to ask questions about the study visit or to inform this author why they were choosing not to attend. A reminder letter was also sent to all participants who had not responded or could not be reached by phone (n=24).

Following these recruitment efforts, the research team held the two study visits at OHSU. The study visit began with an information talk by Dr. Bennett regarding spinal pain, WSP, and FM after which he answered participants' questions. Following this segment, this author described the study in greater detail and reviewed the informed consent (Appendix G) with participants. After this author answered any questions about the study visit, four to five members of the OHSU fibromyalgia study team met individually with each participant. In this private meeting, the participants signed the informed consent and the investigator performed the tender point examination. The investigators documented the presence or absence of tender points on the study visit data collection tool (Appendix H). Participants also shaded in the body drawing found on

this data collection tool. Following the examination, the participants who met the diagnostic criteria for FM spoke with this author or the other investigators regarding the implication of this finding. This author also gave participants an informational sheet with information about FM, national and local resources for the management of FM, and specific information about resources within the Kaiser system for FM and chronic pain. This author documented this final outcome of development of FM into the study database and began analysis.

Measurement of variables

Data on the predictor variables/risk factors were obtained from a retrospective chart review of the participants' 2001/2002 Pain Clinic visit, medication use in 2001/2002 and from the 2007 Study Questionnaire. Table 3.3 presents a listing of each variable and the source of data collection. Since a majority of the data came from the two questionnaires, one completed in 2001/2002 and the other completed in 2007, these questionnaires will be discussed below.

Table 3.3. Variable data collection source and timing.

Variable	Data collection source	Scale of measure	Variable type	Collected in 2001/2002	Collected in 2007
Predictor variables					
Pain duration	Pain Clinic and Study Quest.	# of years	Continuous	X	X
Pain intensity	Pain Clinic and Study Quest.	0-10	Continuous	X	X
Presence of WSP	Pain Clinic and Study Quest. (body drawing)	Yes/no as to presence of WSP	Binary	X	X
Body mass index (BMI)	Pain Clinic and Study Quest.	BMI score calculated from height/weight	Continuous	X	X
General activity level	Pain Clinic and Study Quest.	0-10	Continuous	X	X
Depression	Pain Clinic and Study Quest. (PHQ-9 survey)	Number of symptoms endorsed or PHQ-9 score	Continuous	X	X
History of abuse	Pain Clinic and Study Quest.	Yes/no	Binary	X	X
Disability status	Pain Clinic and Study Quest.	Yes/no as to receiving disability benefits	Binary	X	X
Family history of fibromyalgia	Study Questionnaire	Positive or negative	Binary for each family member		X
Peripheral pain generators	Study questionnaire	Yes/no to having diagnoses	Binary for each comorbidity		X
Number of locations with pain	Study Questionnaire (Body drawing)	Number of shaded areas	Continuous		X
Use of tobacco	Pain Clinic and Study Quest.	Yes/no	Binary	X	X
Age	Study Quest.	Age over 21	Continuous		X
Gender	Study Quest.	Male or female	Binary		X
Diagnoses with WSP	Study Questionnaire	Positive/negative	Binary for each diagnosis		X
Viruses associated with FM	Study Questionnaire	Positive/negative	Binary for each diagnosis		X
Primary Outcome variable					
Diagnosis of WSP	Body drawing on Study Quest.	Positive/negative diagnosis	Binary		X
Diagnosis of FM	Physical exam or diagnosis in chart	Positive or negative diagnosis	Binary		X

2001/2002 KP Pain Clinic Questionnaire

The KP Pain Clinic has used this questionnaire since 2000 to obtain information from Pain Clinic patients regarding characteristics of their chronic pain experience (please see Appendix D for a copy of the KP Pain Clinic Questionnaire). The Pain Clinic scans completed questionnaires into the patient's electronic medical record. This questionnaire represented the primary source of data collection for baseline information on potential risk factors. It should be noted that this questionnaire was designed for clinical purposes, to obtain clinical information from patients that would inform the treatment of their chronic pain condition.

2007 Study Questionnaire

This Study Questionnaire was designed specifically for this study to gather data on variables of interest that were not collected (or not optimally collected) in 2001/2002 and to gain information on the participant's current pain status. Please see Appendix C for a copy of the 2007 Study Questionnaire. Examples of variables collected on this questionnaire in 2007 but obviously also pertinent to the participant's situation in 2001/2002 included family history of WSP and/or FM, age, gender, history of abuse, and the presence of certain relevant comorbities (year of onset was included). The other information gathered on this questionnaire allowed this author to determine the impact of either developing or not developing WSP and/or FM.

Measurement of Predictor Variables

Pain intensity

The 2001/2002 KP Pain Clinic Questionnaire and the 2007 Study Questionnaire elicited data regarding pain intensity by following the method used in the Brief Pain Inventory, which has been validated in the chronic nonmalignant pain population (Tan, Jensen, Thornby, & Shanti, 2004). The questionnaire asked patients to rate their worst, least, usual, and current pain intensity on a zero to ten pain scale with an anchor at zero

stating no pain and an anchor at ten stating unbearable pain. In deciding which variable to use as the most representative pain intensity measure, this author chose to use usual pain. This rating represents the pain level with which the person most often lives with. Worst and least pain levels represent a snapshot in time in which their pain level was not at the ordinary intensity. This author considered using the 'pain now' rating but felt that usual pain level was a more representative measure of the participant's pain. The resulting numbers from 0-10 were used both as a continuous variable and a categorical variable (separated into mild pain, moderate pain, and severe pain) in the statistical tests.

Pain duration

The 2001/02 KP Pain Clinic questionnaire asked the patient to state the year in which their pain started. This response was used to elicit pain duration; the number of years the patient had been in pain. To compute the actual number of years in pain from the stated year the pain began, this author measured this point from 2001. For instance, if a participant documented that their pain started in 1998, their pain duration would have been three years. This variable was used as a continuous variable in the statistical analyses.

Depression

In assessing depression, the 2001/2002 KP Pain Clinic questionnaire used a modified version of the Patient Health Questionnaire 9 (PHQ-9) whereas the 2007 Study Questionnaire used the PHQ-9 in its full form. The PHQ-9 is a standardized depression assessment tool used for clinical and research purposes designed for its ability to be self administered by the patient and quickly analyzed to grade depression severity. The PHQ-9 has demonstrated excellent internal reliability with a Cronbach alpha of 0.89 in a study of 3,000 primary care participants and a Cronbach alpha of 0.86 in a separate study of 3,000 obstetrics and gynecology patients (Kroenke, Spitzer, & Williams, 2001).

These two studies also demonstrated that a PHQ-9 score of greater than or equal to ten had a sensitivity of 88% and a specificity of 88% for major depression. The standardized version of the PHQ-9 lists nine symptoms of depression and asks the participant or patient to document how often, in the past two weeks, have they been bothered by each symptom. The options include not at all (associated with a score of zero points), several days (score of 1 point), more than half the days (score of 2 points), and nearly every day (score of 3 points). To determine the patient's depression severity, the researcher or practitioner totals the number of points associated with the frequency of symptoms to achieve a total score. Individuals with a total score of 0-4 are considered to have no depression, those with a score of 5-9 have mild depression, a score of 10-14 is considered moderate depression, 15-19 is considered moderately severe depression and a patient with a score of 20-27 is considered to be severely depressed. In using this tool for the 2007 Study Questionnaire, the author used the total raw score as a continuous variable. The author used information regarding depression severity in 2007 to assess whether having transitioned to WSP or FM was associated with increased psychological distress. In contrast, the 2001/2002 KP Pain Clinic questionnaire did not using the scoring mechanism and merely asked patients to indicate which of the nine depressive symptoms they had experienced nearly every day for the past two weeks. In analyzing this variable, this author used the sum score of the number of depressive symptoms (range of 0-9) experienced by the participant.

History of abuse

Status on this variable was collected on both the 2001/2002 and 2007 questionnaires. The question asked whether the participant had ever been a victim of abuse as an adult or as a child with a yes/no option for adult and child. This became a dichotomous variable for being abused as an adult or as a child. For analysis, this author

also created a new variable indicating whether or not the participant had been abused at any point in their life.

Disability status

The study collected information on participants' disability status both on the 2001/2002 KP Pain Clinic questionnaire to determine whether this impacted a transition to WSP or FM and on the 2007 Study Questionnaire to assess the implications of a transition to WSP or FM. Both of the questionnaires asked a two part question to determine whether or not the participant was receiving disability benefits and whether the disability was related to pain. The author used this information as a dichotomous variable.

Body mass index (BMI)

Both the 2001/2002 and 2007 questionnaires collected the participant's height and weight which was then used to calculate BMI. This author used the 2001/2002 information to determine whether BMI influenced a transition to WSP or FM whereas the 2007 BMI was used to establish the impact of transitioning to these disorders. To calculate the BMI, this author divided the weight in kilograms by the height in meters squared. This author decided that a one unit change in BMI would not be clinically significant so instead classified each participant's BMI into the categories established by the Centers for Disease Control (CDC). These categories define a BMI of 18.5 kg/m^2 as underweight, 18.5kg/m^2 to 24.9kg/m^2 as normal weight, 25kg/m^2 to 29.9kg/m^2 as overweight and 30kg/m^2 and above as obese. One will notice that the CDC uses categories separated by about 5kg/m^2 to define their categories until 30kg/m^2 where everyone over this mark is considered to have the same level of obesity. To capture the potential variance in this obese group, this author created a fifth category to specifically examine individuals with a BMI of over 40kg/m^2. This author used these five groups for all analyses of BMI.

Pain interference with general activity and sleep

Data on these variables was collected on both the 2001/2002 KP Pain Clinic questionnaire and the 2007 Study Questionnaire. Information collected in 2001/2002 was used to determine whether greater interference with general activity or sleep contributed to the development of WSP or FM while the 2007 information provided evidence into the impact of developing these disorders. This aspect of the questionnaire asked the participant to rate the level with which their pain had interfered with their general activity and sleep from zero to ten with zero labeled as no problem and ten labeled as cannot do or cannot sleep, respectively. The Brief Pain Inventory, previously discussed, uses this method to assess pain interference with these items. The participant's numerical response between zero and ten was used as continuous level data and categorical data separated into mild interference, moderate interference, and severe interference.

Tobacco usage

This information was collected on both the 2001/2002 KP Pain Clinic questionnaire and the 2007 Study Questionnaire. This author collected this information on the 2007 Study Questionnaire to obtain more detail regarding the participant's tobacco use. The 2001/2002 Pain Clinic questionnaire asked the patient to circle yes or no when asked if they use tobacco. The questionnaire then asked the patient to document the amount per day and the number of years tobacco was used. This information was used to calculate the number of pack years for each participant. For instance, if the participant documented smoking a ½ pack for 20 years, they would have a 10 pack year history. To analyze this information pack year history was categorized into five pack year increments.

The 2007 Study Questionnaire attempted to capture more detail in asking a two-part question. The questionnaire first asked the participant to document whether they

currently smoke, smoked in the past on a daily basis, or never smoked on a daily basis. The second part of the question asked those individuals who do or did smoke, to document the associated packs per day and the number of years smoked. This author again calculated the pack year history and categorized into five year increments. A separate analysis was used to assess the impact of currently smoking, quitting, or never smoking on the development of WSP or FM.

Pain management strategies used in 2001/02

On the 2001/2002 KP Pain Clinic questionnaire the participant was asked to mark, out of a list of 14 pain management strategies, which ones the patient had used to help manage their pain. For each strategy, this author documented whether or not the participant had indicated using this particular tool. To create a more meaningful variable out of this information, this author totaled the number of pain management strategies used. For this questionnaire, the possible range of values was zero to fourteen strategies. On the 2007 Study Questionnaire the author again asked the participant to document which strategies, out of a list of 13 tools, the participant had used in 2001/2002. A total composite score was again calculated representing the total number of strategies used. Although this method of collection carried the risk of problems with recall, the author felt that capturing this information would provide important information to the study. Data from the 2007 Study Questionnaire was used as the 2001/2002 KP Pain Clinic Questionnaire had more missing data for this variable.

WSP

The 2001/2002 KP Pain Clinic Questionnaire and 2007 Study Questionnaire contained a body drawing, which consisted of a line drawing of the front and back of a person's body. The line drawing of the body was divided into 50 different sections in order to accurately identify different areas of the body. The participant was asked to shade the places on the body that hurt. The body drawings of both the 2001/2002 and

2007 questionnaires were assessed for the presence of WSP. Shaded areas present in three out of four quadrants of the body and in the axial skeleton indicated WSP. Presence of WSP on the 2007 questionnaire warranted inclusion into the second phase of data collection. Presence of WSP on the 2001/2002 questionnaire excluded inclusion into the analysis of aim 1 or 2 (transition from CRSP to WSP) but was used as a dichotomous categorical predictor variable in the analysis of aim 3 (transition from CRSP to FM).

Other pain locations

While the body drawing used in the 2001/2002 KP Pain Clinic questionnaire did not include enough detail to document specific pain locations, this author used a more detailed body drawing for the 2007 Study Questionnaire. This body drawing was labeled with 50 numbers indicating 50 distinct areas of the body. This author created a variable for each 50 pain locations and documented whether or not the participant experienced pain at that location. A total number of pain locations was also created. This data was not used in the analysis because the number of pain locations did not reliably correlate with the overall area of the body that experienced pain. For instance, a participant might have shaded four areas of pain but really only experienced pain in their hands and feet. Alternatively another participant with four shaded areas might have experienced pain in the entire front and back of their torso. Although the author had planned that this information would correlate to the amount expansion of pain experienced by the participant, the data did not reflect this.

Family history of WSP or FM

The 2007 Study Questionnaire asked the participants to document their family history of WSP or FM. The questionnaire included a list of blood relatives (mom, dad, sister, brother, grandmother, grandfather, aunt, uncle, and first cousin) with four columns. These columns included yes/no responses to indicate whether or not the participant's

relatives experienced FM or WSP. The question included a description of FM and WSP in case the participant did not know the meaning of each of these diagnoses. For analysis, the author created a dichotomous variable for the presence or absence of WSP or FM for each relative. To create more meaningful variables, this author also created groups of relatives to be analyzed. For instance, this author created a variable called primary family which included the participant's mother, father, brother or sister. The variable elder family included the participant's grandmother, grandfather, mother or father. The female family variable included female family members while the sibling variable included only the participant's brother and/or sister. Each of these variables was a dichotomous variable that indicated the presence of any of these particular family members with WSP or FM.

Central sensitization syndromes

Assessment of the presence of central sensitization syndromes including migraines, irritable bowel syndrome, irritable bladder syndrome, and restless legs syndrome occurred by the participants answering yes or no as to whether they had been diagnosed with any of these conditions. These questions were part of the 2007 Study Questionnaire. If the participants answered yes, a follow up question asked the year of that diagnosis. These variables were entered separately as dichotomous yes or no categorical variables.

Infections associated with FM

The 2007 Study Questionnaire also determined the presence of infections that have been associated with FM. These diagnoses included hepatitis C, lyme disease, coxsackie B infection, and HIV. The form asked the participant whether he/she had been diagnosed with these conditions and the year of diagnosis. Each diagnosis became a separate dichotomous categorical variable.

Diagnoses that can present with WSP

The presence of diagnoses that can present with WSP was also assessed on the 2007 Study Questionnaire. These included myofascial pain syndrome, myositis (inflammatory myopathy), certain malignancies, hypothyroidism, osteomalcic myopathy, severe malnutrition, polymyalgia rheumatica, rheumatoid arthritis, osteoarthritis or systemic lupus erythematosus. The participant indicated whether he/she carried this diagnosis and the year of onset. Each diagnosis was entered as a separate dichotomous categorical variable.

Medications used to treat pain in 2001/2002

This author performed a chart review to determine the medications used by the participant to treat pain in 2001/2002. For each participant, this author located the medications used in the three months prior to and three months after the KP Pain Clinic appointment in 2001/2002. On a pre-determined list of medications of interest (see Medication Abstraction form in Appendix E) this author documented which medications the participant had used in this six-month period. For analysis, this author collapsed the individual medications down into classes of medications. Classes of medications included short acting opioids, long acting opioids, non-steroidal anti-inflammatories, steroids, selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, anti-epileptic medications, and topical medications. Each of these variables was a dichotomous variable indicating whether or not the participant used a medication from this class.

Measurement of outcome variable

Aim 1 and 2

Diagnostic criteria for WSP came from the 1990 ACR diagnostic criteria for FM (Wolfe, et al., 1990). According to these guidelines, diagnosis of WSP occurs in the patient with all of the following characteristics:

> “Pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine, or low back) must be present. In this definition, should and buttock pain is considered as pain for each involved side. Low back pain is considered lower segment pain.” (Wolfe, et al., 1990).

Review of the participants’ body drawing on the 2007 Study Questionnaire allowed for a diagnosis of WSP in participants meeting these criteria.

Aim 3

A diagnosis of FM consists of two main components; the presence of chronic WSP for greater than three months and greater than or equal to eleven out of eighteen tender points (Wolfe, et al., 1990). As discussed previously, presence of chronic WSP was assessed through response to the body drawing on the 2007 Study Questionnaire. This author performed a chart review on the subset of participants indicating the presence of WSP in 2007. This review looked for a diagnosis of FM as indicated by an ICD-9 code of 729.1 made subsequent to the 2001/2002 KP Pain Clinic evaluation. Those participants indicating the experience of WSP in 2007 but not carrying an FM diagnosis were invited to be physically examined for the presence of greater than or equal to eleven out of eighteen tender points. At this examination participants completed another body drawing to ensure they still met the second criteria of the FM diagnosis, the presence of WSP. The chart review or physical exam indicating a diagnosis of FM confirmed the presence of the outcome variable and indicated that these patients transitioned from CRSP in 2001/2002 to FM in 2007.

Data Verification and Cleaning

Prior to analysis a substantial amount of time was spent cleaning the data to ensure accurate and valid analyses. This author spent time ensuring the accuracy of the data,

evaluated the amount and pattern of missing data, and investigated the impact of outliers.

Data verification

Immediately following the first entry of data, this author verified the data by double entering 100% of all data. This was done in a second Excel database. After re-entering all data, the two databases were compared and all discrepancies were resolved by rechecking the hardcopy of the data and changing the erroneous entries. This was done until the two databases had no discrepancies.

Checking accuracy

Cleaning began by checking the accuracy of the data through evaluating the frequency charts, histograms and/or descriptive characteristic of each variable. This author examined frequency charts to ensure that all data values fell into the range of possible values for each variable and to identify outliers. Frequency charts were also used to ensure that individual coding for missing values matched the number of total missing values. For instance, the author summed the total number of values entered as -9, -8, -7, and -2 to ensure that this matched the total number of missing values. This author used the cross tab function to ensure that skip patterns were followed. For instance if 30 individuals reported not smoking, this author looked to find that 30 participants had -7 as a response to number of packs smoked per day. The descriptive values were examined to ensure that the range of values fell within the expected range and that the mean and standard deviation were such that the standard deviation did not exceed the mean. The author examined the histograms for large, continuous variables to visualize the distribution and identify potential outliers. Due to the thorough verification process, this author identified no data entry errors throughout this review.

Outliers

By reviewing the frequency tables and histograms the author was able to identify univariate outliers. The author identified three variables with potentially worrisome outliers which included the number of packs smoked per day (on the 2001/2002 Kaiser questionnaire), the number of years smoked (on the 2007 study questionnaire), and weight (on the 2001/2002 Kaiser questionnaire). This author recorded the outliers and rechecked them against the raw data, establishing that all were true responses. For each of these variables the author performed a sensitivity analysis to determine the effect of the outlier on the logistic regression analysis and the mean of the variable. To do this, this author first ran the logistic regression analysis and descriptive statistics on the variables, leaving the outlier at its original value. Then this author truncated the outlier by changing the value to one data point larger than the second largest value. For instance, the outlying value for number of years smoked was 70 years. The second largest value was 63 years. This author changed the outlying value to 64 years to bring it in line with the rest of the values while maintaining its rank order compared to the other values. In all three variables, this sensitivity analysis did not make a significant change in the odds ratio or the mean of the variables. This author decided to leave the values at their original numbers.

Multiple responses

In the data cleaning process, this author also had to decide how to handle multiple answers on a few different variables. Several participants marked multiple race boxes. Interestingly, the most common two boxes checked included American Indian/Alaska Native and White. Due to the frequency with which these two boxes were marked, this author decided to create a sixth race category of this combination. Participants marked multiple responses on the various 0-10 scales. When it seemed obvious that the participant was marking a range, the author took the average value of that range. For instance, participants would sometimes circle six and seven as their response to one of

these questions. In this instance, the author would determine the value to be 6.5. In instances where the participant marked two distinctly different values such as a two and eight, the author identified this as a multiple answer (-2) which was included as a missing value. The other instance where this author could not use an average of the response occurred on the 2007 Study Questionnaire PHQ-9 survey. Although a participant might circle a value of zero and one, these values indicated ‘not experiencing the depressive symptom at all’ or ‘experiencing this symptom on several days’; values that could not be averaged. Again, this author would mark multiple answers on this aspect of the questionnaire as a -2, a missing value indicating multiple answers.

Recoding and computing variables

Prior to analysis, this author had to recode or compute several variables to ensure accurate analyses. This author recoded several variables to create more meaningful one unit changes. For instance, after computing the variable for BMI, this author recoded participants’ values into five categories of underweight, normal weight, overweight, obese, and significantly obese. By doing this, the author could assess the difference between participants being of normal weight or overweight as compared to having a one unit difference in BMI which would be much less meaningful. Creating more meaningful one unit changes was the basis for recoding variables such as the total number of pain management strategies used in 2001/2002, age, tobacco years and pain levels rated on 0-10 scales.

New variables were computed to create a sum score from two or more variables or to create a new, more encompassing variable. For instance, this author computed new variables to score the PHQ-9 surveys on both the 2001/2002 and 2007 questionnaires. In working with the central sensitization diagnoses, this author summed the number of diagnoses to create a variable demonstrating the total number of central sensitization diagnoses a participant had and also created a variable that identified all participants

that presented with *any* central sensitization diagnoses. The same procedure was used to compute a variable that represented the participant having a history of abuse at any time in their life (as an adult *or* child). Recoding and computing variables allowed this author to create new variables that led to more meaningful analyses.

Missing data

The frequency of missing values varied substantially between the 2007 study questionnaire and the 2001/2002 Kaiser questionnaire. Prior to seeing the Pain Clinic in 2001/2002, patients would complete the Kaiser questionnaire and give this to the provider at the time of their appointment. The provider would use this questionnaire during the appointment to make treatment decisions. After the appointment, this questionnaire would be sent to the scanning department to be scanned into the patient's medical record. Approximately 18% of participants' 2001/2002 Kaiser Pain Clinic questionnaires had not been scanned into their medical record. If the questionnaire had not been scanned, this author reviewed the Pain Clinic visit and any other related visits (physiatry, neurosurgery) within one month of the Pain Clinic visit to gather information that would usually be retrieved from the Kaiser questionnaire. Some variables were easily retrieved in this manner. In most instances, the Pain Clinic provider would read part of the questionnaire into his/her dictation. The provider would always describe the body drawing pain distribution as this is a crucial factor in deciding whether or not to perform an anesthetic injection. He/she would often read the patient's stated pain level (0.4% missing data), the year the pain began (3% missing data) and reported height and weight (8% missing data). Variables such as depression level (20% missing data), pain interference (24% missing data), or strategies used to manage pain (22% missing data) were almost never read into the dictation and rarely available in chart notes from other disciplines. Since data missing from the Kaiser questionnaire was primarily due to the questionnaire not being scanned in 2001/2002, the data is assumed to be missing

completely at random. Whether or not the questionnaire got scanned did not vary based on patient characteristics.

Missing data from the 2007 study questionnaire was much more infrequent. All variables except family history of WSP/FM and history of abuse had a missing value frequency of two percent or less. Response rates on family history of WSP and FM and history of abuse as a child were the exception to this rule. The family history variables averaged a 15% missing value frequency. For these variables, the participant was asked to mark yes or no as to the presence of WSP or FM in their family members. Participants would often only mark yes when their family member had WSP or FM and not mark no when they did not. The participants might also have left these questions unanswered due to not knowing the history of certain family members. Although some participants wrote in that they did not know, adding a “do not know” column would have offered more accurate analyses.

An interesting pattern of missing data occurred with the variable “abuse as a child”. The 2007 study questionnaire question was displayed as follows:

11. Have you ever been the victim of physical abuse:

As an adult? Yes

No

As a child? Yes

No

Several participants who answered yes to “abuse as an adult” left the question of “abuse as a child” unanswered. Overall, the question, “abuse as an adult” had a missing rate of 3% while 9% of participants chose not to answer the question, “abuse as a child”. Although one cannot know the reason for this discrepancy in answering one question and not the other, this author speculates that answering yes to the first question was distressing enough that these participants chose not to answer the second question.

Despite the rationale for this pattern of missing data, it cannot be assumed to be missing at random. Due to this fact, caution must be used in interpreting this variable.

Assumptions of logistic regression

Unlike multiple regression, logistic regression does not require normal distribution of predictor variables. Some variables were mildly positively or negatively skewed as indicated by examining the distribution curve on the frequency histogram. For instance the variables, tobacco pack year and number of back or neck surgeries, was positively skewed due to the majority of participants with zero pack years or zero surgeries. The data did meet the one assumption of logistic regression which states that the same level of probability must be maintained across the range of predictor values.

Data analysis of specific aims

Aim 1: Describe the rate of transition to WSP in a cohort of adults originally presenting with CRSP.

Hypothesis 1: It was hypothesized that approximately fifteen percent of individuals with CRSP in 2001 or 2002 would have transitioned to WSP by 2007.

Analysis: The incidence of development of WSP in the study's sample was calculated by dividing the total number of participants who presented with chronic low back or neck pain in 2001/2002 and qualified for a WSP diagnosis in 2007 by the total number of participants. The 96% confidence interval for this estimate was also calculated indicating the range of transition to WSP that might occur in the general population. This descriptive aim adds to the literature regarding transition from a regional pain disorder to a WSP disorder and allows for comparison across other similar studies.

Aim 2: Identify risk factors that predisposed adults with CRSP to a transition to WSP.

Hypothesis 2: Based on a review of the relevant literature, it was hypothesized that risk factors would include presentation of the following variables in 2001/2002: increased

duration and intensity of pain, presence >4 symptoms of depression (from DSM-IV), tobacco usage, female gender, older age, positive family history for chronic pain, history of childhood or spousal abuse, high body mass index (BMI >30), low levels of physical activity, positive disability status, more than two spinal surgeries, presence of pain in other locations, and the presence of particular comorbid conditions.

Analysis plan: Logistic regression was used to determine which predictor variables represented risk factors for the transition to WSP. Those risk factors that demonstrated significant bivariate relationships with transition to WSP were included in a multivariate logistic regression model to determine the relative importance of the different factors.

Use of logistic regression occurs when a researcher wants to describe and test a hypothesis between a categorical outcome variable (transition to WSP or not) and continuous or categorical predictor variables (Peng, Lee, & Ingersoll, 2002). Use of logistic regression must occur when using this combination of outcome and predictor variables because use of a categorical outcome variable produces a nonlinear relationship. Because the value of the outcome variable was either one (transition to WSP) or zero (no transition to WSP), the plot of the relationship between the predictor variables and outcome variable is linear in the middle but curved at each end, creating an S-shaped curve. The same change in X (the independent variable) has a different effect on Y (the dependent variable) depending on how close the value of X is to maximum or minimum value of Y(Pampel, 2000). Using a linear regression equation, as is used in multiple regression, for this nonlinear relationship would provide inaccurate results. Logistic regression solves this problem by applying the logit transformation to the dependent variable. This is done by taking the natural logarithm of the odds (the probability of Y happening divided by the probability of Y not happening). Taking the antilog of this equation gives us a new equation to predict the probability of the

occurrence of interest (transition to WSP). This equation is represented as $\frac{e^{a+\beta X}}{1-e^{a+\beta X}}$, where e is the base of the system of natural logarithms, a is the Y intercept, β is the regression coefficient, and X is the continuous variable (Peng, et al., 2002).

Prior to entering the variables into SPSS, the dichotomous variables were coded for interpretation. For ease of interpretation, transition to WSP was coded as 1 as this was the response category of interest, while no transition to WSP was coded as 0 as this was the reference category. Coding the data in this manner enhanced interpretability, as the parameter estimates were positive (Tabachnick & Fidell, 2001). This same principle applied to coding the predictor variables. The response group, or the outcome of most interest, was coded as one and the reference group had a code of 0. Please see Table 3.4 for a listing of the codes for coded variables.

Table 3.4. Coding of categorical and binary variables.

Categorical variable	Coded value
Presence of WSP	1 = WSP
	0 = No WSP
History of abuse	1 = Yes, history of abuse
	0 = No history of abuse
Disability status	1 = Receiving disability benefits
	0 = Not receiving disability benefits
Family history of chronic pain	1 = Yes, family history
	0 = No family history
Irritable bowel syndrome	1 = Presence of IBS at baseline
	0 = No IBS at baseline
Osteoarthritis	1 = Presence of OA at baseline
	0 = No OA at baseline
Migraine	1 = Presence of migraine at baseline
	0 = No migraine at baseline
All comorbid diagnoses	1 = Participant has the diagnosis
	0 = Participant does not have the diagnosis
Use of tobacco	1 = Currently using tobacco
	2 = Used tobacco in the past
	0 = Never used tobacco on a daily basis
Body mass index	0 = Normal weight (18.5kg/m^2 -24.9kg/m^2)
	1 = Overweight (25kg/m^2 -29.9kg/m^2)
	2 = Obese (30kg/m^2 -39.9kg/m^2)
	3 = Morbidly obese (40kg/m^2 and above)
	4 = Underweight (below 18.5kg/m^2)
Gender	1 = Female
	0 = Male

The first step was to determine which predictor variables demonstrated a significant bivariate relationship with transition to WSP. The PI entered each predictor variable

separately into its own logistic regression model with the outcome variable of transition to WSP. Based on this analysis, this author examined the odds ratio, confidence interval, and significance level for each variable. Those variables demonstrating a significant association with transition to WSP in 2007 were deemed significant risk factors for this transition. Only those predictor variables found to have a significant association with transition to WSP were entered into the multivariate logistic regression model. The author decided to place all significant bivariate predictors into one block for the multivariate analysis. While the bivariate analysis determined which variables were independently associated with the transition to WSP, the multivariate analysis allowed the study team to assess the association of each variable while controlling for all other variables.

The output of both the bivariate and multivariate logistic regression produced several useful pieces of information. The first component of interest was to determine the significance of each predictor variable. This author used two ways to assess the significance. Each individual predictor variable had a Wald's statistic with accompanying significance level and an odds ratio with accompanying confidence interval. Assessing the significance level of the Wald's statistic determined if the predictor variable was significantly associated with transition to WSP. Assessing the confidence interval of the odds ratio associated with each predictor variable also indicated significance if the confidence interval did not cross one.

While logistic regression produces the odds ratio for each predictor variable, the relative risk holds more importance to this study. Instead of comparing the relative odds of transitioning to WSP, using relative risk compared the probability of transition to WSP. Odds ratios are more difficult to interpret when trying to determine the real impact a particular risk factor has on the development of a disease. While an odds ratio of five might indicate that a person has a five-fold increased risk of developing a disease, it is

difficult for most people to understand what a five-fold increased risk means. Alternatively, a relative risk of three indicates that a person is three times more likely to develop the disease. This provides a much more understandable way of interpreting the data. Despite the substantial difference between odds ratios and relative risks, many people misinterpret odds ratios for relative risks. This creates misinterpretation of data as the odds ratio overestimates the relative risk of most risk factors.

This author calculated relative risk from the odds ratio using an established equation (Zhang & Yu, 1998). This equation utilizes the odds ratio and the incidence of the outcome of interest in the non-exposed group. For instance, in calculating the relative risk for gender, this author entered into the equation the odds ratio of 3.14 and the incidence of men who developed WSP (.16). Calculating the equation gave the relative risk of 2.35; a female with a history of CRSP is 2.35 times more likely to develop WSP as compared to a male with CRSP. Note that the relative risk is lower than the odds ratio which was the case for all the variables. This reinforces the misinterpretation of data that occurs when people interpret the odds ratio as the relative risk.

Aim 3: Identify the proportion of people with WSP who developed FM and compare the associated risk factors for development of FM with those risk factors identified for the development of WSP.

Hypothesis 3: It was hypothesized that risk factors associated with a transition to FM would be similar to those proposed for the development of WSP (Aim 2).

Analysis plan: This aim utilized a case control study design which was analyzed using logistic regression to determine the odds ratio for the proposed risk factors. In the case control design, the odds ratio represents the ratio of the odds of the disease in exposed individuals relative to the unexposed individuals. Cases consisted of the 40 participants who had been diagnosed with FM since their 2001/2002 KP Pain Clinic visit. Forty

participants matched on age were randomly selected who had not developed WSP to constitute the control group. To do this, the author identified the age of each participant with FM then lined up all the study IDs for participants of that same age who had not developed WSP. Using a computerized random number generator, this author was given a number (n) and chose the n^{th} non-WSP participant with that age. A new database was created with these 80 participants in order to utilize logistic regression to determine the odds ratios of suspected predictor variables. The same procedures were followed as outlined in aim 2 to determine the odds ratios, significance levels, and relative risks of the same proposed risk factors.

Because this analysis only included 40 cases and 40 controls, the study team suspected that there might have been inadequate statistical power to detect a relationship among several risk factors and the development of FM. To evaluate this lack of adequate statistical power, the study team performed a power analysis. The OR and number of participants in each response group was used to determine the sample size needed to have statistical power of .80, the power needed to detect an effect if one truly exists. If the sample size needed to have a power of .80 was approximately 500 or less, it is reasonable to assume that the small sample size of Aim 3 led to those particular non-significant findings.

To determine the impact of developing WSP and FM, analyses were performed assessing the differences between those participants who transitioned to WSP and/or FM and those who did not. All analyses utilized data collected from participants in 2007. This data assessed the participants' current situations, following the transition to WSP and/or FM for some participants. Using the 2007 data allowed this author to determine the impact of the development of a widespread pain disorder as compared to participants who had not undergone such a transition.

Impact of developing WSP

To determine the impact of developing WSP, two groups were compared for this analysis; the 114 participants who transitioned from CRSP in 2001/2002 to WSP in 2007 and the 398 participants who had CRSP in 2001/2002 but did not develop WSP. These two groups were compared on the variables of average pain intensity, pain interference with general activity and sleep, BMI, PHQ-9 score, age, gender, and receipt of disability benefits for pain. Mean differences between the groups were analyzed using T-tests for continuous variables and chi square for categorical variables.

Impact of having FM as compared to WSP

The second outcome analysis was performed to assess the impact of having FM as compared to having WSP. This author compared the 40 participants who had developed FM within the study time period to the seven participants who had WSP but did not qualify for an FM diagnosis. Given the small sample size and discrepancy between the sizes of the groups, this analysis did not have the power to detect any significant differences. Analysis with t-tests for continuous variables and chi square for categorical variables did allow the author to describe the differences between the two groups on the variables described above.

Protection of human subjects

Potential risks and protections

The potential risks to participating in this study were 1) unwanted feelings arising from completing questionnaires, 2) slight pain during tender point examination, and 3) security of study data. To respond to the potential for unwanted feelings while completing the questionnaires, the PI's private phone number was included in the invitation letter. Participants were encouraged to contact the PI with any questions or concerns regarding the study. Participants were also advised of their right to leave any question unanswered or to withdraw from the study at any time. This author has extensive experience in

working with chronic pain patients experiencing distress, health problems, and/or concerns. Throughout the study, the PI responded to participants' questions in a sensitive and respectful manner. No participant contacted this author regarding the sensitive nature of any questions on the 2007 Study Questionnaire. This author received 34 calls from study participants, the majority were made to inform this author that the patient was choosing not to participate in the study. Ten patients called with clarifying questions regarding the Study Questionnaire while three asked to be resent the survey.

In order to minimize the physical discomfort experienced during the tender point exam, experienced clinicians performed this examination using published standardized testing criteria in order to enhance proficiency and efficacy of the assessment. The examiner used his/her thumb to press on 18 specified muscle tendon junctions for three seconds. The total time of the test typically took less than five minutes. The study team also did their best to educate the participants as to what to expect during the exam. Dr. Bennett performed a physical exam on this author in front of all participants to show them the location and intensity with which these sites would be pressed. Prior to being examined, participants were encouraged to ask questions about the exam and were reminded that they could opt out of the examination at any time. During the tender point examination, each investigator warned the participant before placing pressure on each site. The investigators allowed time to pass between stimulating each point to allow the participant to recover. This author also encouraged participants to contact this author if they needed assistance due to increased pain as a result of the exam. None of the participants followed up with this author for that reason.

In order to maintain confidentiality, each study participant was assigned a study ID. As part of the study protocol, only the PI had access to the master list containing names and code numbers. The master list was kept in a computer file on a password protected computer in a locked office. All completed informed consents, questionnaires, and data

were kept in a locked file cabinet at the KP Pain Clinic in a locked office. This author kept the cabinet locked at all times except when she was within direct line of sight of the data and the file cabinet. This data will be kept until deemed no longer usable or until five years, whichever occurs first. It will then be destroyed via crosshatched shredding procedures.

For the majority of the study time period, computer data remained at the KP Pain Cilnic and access to this data was limited to the PI. This data was password and firewall protected. Following the completion of data entry, this author needed to transport the excel file containing the data to OHSU for analysis. This was done using a KP Center for Health Research secure website. This author uploaded the necessary Excel file to the secure website and, the next day, downloaded it onto a secure, password protected computer in a locked office at OHSU. This author deleted the file from the secure website immediately after downloading it. Only the PI and one committee member had access to this data.

Informed consent

The invitation letter (appendix B) sent to all potential participants included a section containing the necessary components of an informed consent for the first phase of the study. This included the study's purpose, procedures, potential risks and benefits, alternatives to participating in the study, and how the participant's confidentiality would be maintained. The KP IRB decided not to have participants sign and return a formal consent as this would place their identification and study responses in the same envelope, leaving confidential information at risk of being intercepted. In the invitation letter the name and phone number of the PI was highlighted to encourage all potential participants to call with any questions related to his/her participation. By mailing back a completed 2007 Study Questionnaire, participants implied consent to participate in the study.

For the second phase of the study, the research team used a formal informed consent which was signed by all those participating in the FM tender point examination. At the beginning of the study visit, the study team gave all participants two copies of the informed consent. With the participants in a group, this author discussed the informed consent and authorization to use protected health information. After this discussion, participants had an opportunity to ask questions regarding the informed consent in the group setting. When each participant met with one of the study team to be examined, they had an opportunity to ask questions in private or choose not to participate. All participants chose to participate and signed the informed consent with the investigator as their witness. The participants turned in one signed informed consent and kept one for their records.

Potential benefit to participants

Chronic low back and neck pain are common chronic pain diagnoses that have been demonstrated, in some instances, to transition to WSP and/or FM. This transition to WSP and FM represents a worsening clinical picture as these conditions are associated with increased disability rates and greater costs to society from lost productivity, increased medical costs, and loss of revenue. Participants in this study had the opportunity to contribute to knowledge regarding this transition. Information regarding the risk factors associated with the development of WSP and FM will inform future interventions and research aimed at preventing this transition, thereby minimizing human suffering and further disability.

A potential benefit to participants of this study included a finding of previously undiagnosed WSP or FM. This diagnosis could lead to a greater understanding of the individual's pain and an expansion of his/her treatment plan that includes management strategies thought to assist in WSP and FM. Participants who had WSP and came to the

study visit to be examined for FM received a list of available resources within Kaiser and the community for the treatment of chronic pain and FM.

These potential benefits to the involved participants, future chronic pain sufferers, and society in general were felt to outweigh the potential discomfort caused by answering two questionnaires, a short travel distance, and brief tender point examination. Also five randomly chosen participants received a $50 gift certificate to Fred Meyers and all participants who came to the FM tender point examination received a $10 gift certificate to Borders Books. It is also possible that the subjects gained no benefit from participating in this study.

Inclusion of women and minorities

The inclusion of women in the proposed study is important to the subject matter under study. Chronic low back and neck pain are prevalent in both men and women and FM and WSP tends to present with a higher frequency in women. Due to this higher presentation of WSP and FM in women, the female gender actually was a significant risk factor for the development of both disorders. This study population was made up of 57% women. Pregnant and non-pregnant women were included in the proposed research, as the study posed no increased risk to the pregnant woman or fetus.

English speaking men and women of all racial and ethnic groups who fulfill the inclusion criteria were recruited to participate in the proposed study. All races and ethnicities demonstrate the experience of chronic pain and were therefore important to the phenomenon under study. Kaiser Permanente consists of a predominantly white population (88-90%) with 10-12% of minorities. The minority population of KP Northwest is proportionally representative of the Portland/Vancouver area with approximately 5% Hispanic or Latino patients, 3% Asian patients, 3% African American patients, 1% American Indian/Alaskan native patients, and 0.5% Native Hawaiian/Pacific Islanders enrolled. This study achieved a slightly less diverse sample with 90% of participants

identifying themselves as white. One and a half percent identified themselves as Hispanic or Latino while 29% did not declare their ethnicity. Two and a half percent identified themselves as American Indian/Alaska native and white, one percent identified as black or African American, one percent identified as Asian, and half a percent identified as native Hawaiian or other Pacific Islander.

Inclusion of children

Children, defined as individuals under the age of 21, were not be included in this study for two primary reasons. While there has been a significant amount of evidence demonstrating the development of central sensitization in adults with chronic low back and neck pain and identifying central sensitization as a predominant characteristic in adults with FM, most studies have not examined this phenomenon in children. The evidence discovered in the adult studies provided the foundation for this research. Therefore, without this evidence in children, it was not appropriate to include children in this study. Also, since retrospective data collected in the KP Pain Clinic was used to monitor the transition of pain disorders and clinical characteristics and the KP Pain Clinic only sees adults, not data on children was available.

Summary

This study utilized a retrospective cohort and case control study design to investigate the transition from CRSP to WSP and FM. Data collected in 2001/2002 and 2007 allowed the study team to assess this transition over a six year period. Logistic regression was used to determine the risk factors associated with this transition. Findings from these analyses are discussed in Chapters 4 and 5.

Table 3.1. Diagnoses included in the study.

Diagnosis code	Diagnostic title
	Cervical and Lumbar back pain
306.0	Low back pain (Musculoskeletal disorder, psychogenic)
336.2	Subacute combined degeneration of spinal cord
353.0	Brachial plexus disorder
353.0	Cervical (Thoracic outlet syndrome)
353.1	Lumbar (lumbosacral plexus lesion)
353.2	Neuropathy, cervical root
720.0	Ankylosing spondylitis
720.1	Spondylopathies (Spinal enthesopathy)
720.2	Spondylopathies (sacroiliitis)
720.81	Spondylopathy in other disease
720.9	Spondylitis
721.0	Spondylosis cervical joint w/o myelopathy
721.1	Spondylosis of cervical joint w/ myelopathy
721.1	Cervical spondylosis (Compression syndrome of anterior spinal artery)
721.1	Spondylogenic compression
721.3	Spondylosis of lumbar joint w/o myelopathy
721.42	Spondylosis of lumbar joint w/ myelopathy
721.5	Spondylosis (Kissing spine)
721.6	Ankylosing hyperostosis of vertebra
721.7	Traumatic spondylopathy
721.90	Arthritis of the spine (sponylarthropathy)
721.90	Spondyloarthropathy
722.0	Spine (Displacement of cervcial intervertebral discu w/o myelopathy)
722.0	Displacement of cervical intervertebral disc w/o myelopathy
722.10	Displacement of lumbar intervertebral disc w/o myelopathy
722.10	Spine (Displacement of lumbar intervertebral discu w/o myelopathy)
722.4	Spine (Degeneration of cervical intervertebral disc)
722.4	Degeneration of cervical intervertebral disc
722.52	Lumbar (degeneration of lumbosacral intervertebral disc)
722.52	Spine (Degeneration of lumbosacral intervertebral disc)
722.7	Displacement of cervical intervertebral disc w/ myelopathy
722.70	Back pain (aka Disorder of the intervertebral disc w/ myelopathy)
722.71	Back pain (aka Disorder of cervical intervertebral disc w/ myelopathy)
722.72	Back pain (aka Disorder of thoracic intervertebral disc w/ myelopathy)
722.73	Displacement of lumbar intervertebral disc w/ myelopathy
722.80	Postlaminectomy syndrome
722.81	Postlaminectomy syndrome of cervical region
722.83	Postlaminectomy sydnrome of lumbar region
722.93	Low back pain (aka Disorder of the lumbar intervertebral disc)
722.93	Disorder of lumbar intervertebral disc
723.0	Stenosis of cervical region
723.1	Cervicalgia
723.2	Cervicocranial syndrome

723.4	Cervical radiculopathy
723.5	Torticollis
723.7	Spine (ossification of posterior longitudinal ligament, cervical region)
723.7	Ossification of posterior longitudinal ligament, cervical region
723.8	Cervical syndrome
723.9	Cervicalgia (Musculoskeletal disorder of neck)
724.00	Cervical (spinal stenosis)
724.02	Spinal stenosis lumbar (Stenosis of lateral recess)
724.02	Spine (spinal stenosis of lumbar region)
724.2	Low back pain
724.3	Lower back pain (sciatica)
724.3	Spine (sciatica)
724.4	Lower back pain (Lumbar radiculopathy)
724.5	Back pain (aka backache)
724.6	Low back pain (aka Disorder of sacrum)
724.8	Low back pain (aka Facet syndrome)
724.9	Spine stiffness
737.12	Kypophosis postlaminectomy
737.21	Lordosis postlaminectomy
737.30	Spine (scoliosis)
737.9	Abnormal curvature of spine
738.4	Spondylolisthesis, acquired
738.5	Deformity of spine, acquired
739.1	Somatic dysfunction of cervical region
739.3	Somatic dysfunction of lumbar region
742.59	Spine (spinal cord anomaly)
742.9	Spine (spinal defect, congenital)
754.1	Torticollis, congenital
754.2	Spine (scoliosis, congenital)
756.10	Anomaly of spine
756.10	Cervical (anomaly of spine)
756.10	Spondylosis (Anomaly of spine)
756.11	Spondylosis lumbar (lumbosacral spondylosis, congenital)
756.11	Lumbosacral spondylolysis, congenital
756.12	Spondylolisthesis lumbar (spondylolisthesis)
756.12	Spondylolisthesis
756.12	Cervical spondylolisthesis, congenital
756.15	Lumbarization (Fusion of spine, congenital)
756.15	Fusion of spine, congenital
756.2	Cervical rib
805.00	Spine (Closed fx vertebra, cervical, w/o spinal cord injury
805.00	Closed fx vertebra, cervical, w/o spinal cord injury
805.10	Spine (Open fx vertebra, cervical w/o spinal cord injury)
805.10	Open fx vertebra, cervical w/o spinal cord injury
805.4	Fx vertebra, lumbar
805.4	Spine (fx verterbra, lumbar)
805.5	Open fx vertebra, lumbar
805.5	Spine (open fx vertebra, lumbar)
806.00	Spine (Closed fx vertebra, C1-4 level, w/ spinal cord injury)
806.05	Spine (Closed fx vertebra, C5-7 level, w/ spinal cord injury)

806.4	Closed fx vertebra, lumbar, w/ spinal cord injury
806.4	Spine (Closed fx vertebra, lumbar, w/o spinal cord injury
806.8	Cervical (closed fx vertebra column, w/ spinal cord injury
839.00	Spine (Closed dislocation vertebra, cervical)
839.00	Closed dislocation vertebra, cervical
839.20	Closed dislocation vertebra, lumbar
846.0	Pain - low back (sprain back, lumbosacral ligament)
846.0	Sprain back, lumbosacral ligament
846.1	Sprain of sacroiliac ligament
846.9	Sprain back, sacroiliac region
847.0	Sprain or strain of cervical spine
847.0	Cervical sprain (injury neck, whiplash)
847.2	Strain of lumbar region
847.9	Strain of back
922.31	Contusion back (back interscapular lumbar sacral trunk contusion)
952.00	Spine (spinal cord injury C1-4 level)
952.05	Spine (spinal cord injury C5-7 level)
952.2	Spinal cord injury, lumbar
952.2	Spine (spinal cord injury, lumbar)
953.0	Injury of cervical nerve roots
954.0	Injury of cervical sympathetic nerves
V13.5	Cervical (Hx of musculoskeletal disorder)
V45.89	Hx of cervical spine surgery

CHAPTER 4: RESULTS

Sample characteristics

A total of 2,256 patients who were seen at Kaiser Pain Clinic in 2001 or 2002 for a diagnosis of chronic low back or neck pain were invited to participate in this study by receiving an invitation letter and study questionnaire in June of 2007. From this initial mailing, a total of 436 (19.33%) patients responded in some form. Twenty nine patients responded saying they could not or would not like to participate. Table 4.1 outlines the rationales given for not participating by those who responded that they did not want to participate in the study. A chart review on all 436 participants was conducted to determine if these patients had been diagnosed with FM prior to 2001/2002. The 58 participants who had a diagnosis of fibromyalgia (FM) prior to 2001/2002 were excluded from the sample. This initial mailing produced 349 eligible participants.

Table 4.1. Reasons for patients not wanting to participate (mailing 1)

Rationale	Frequency
Deceased	4
“Do not wish to participate”	9
Cannot complete due to health condition (dementia or stroke)	3
No longer have pain	3
Returned survey uncompleted	2
Offered no explanation	2
Expressed anger at receiving survey	2
Requested that survey be resent but never returned resent survey	2
Did not know how to describe pain	1
Stated that he/she was never seen at Pain Clinic	1

A second mailing was sent out to the 1,820 patients who had not responded to the first mailing. From this second mailing, a total of 246 (13.5%) patients responded. Twenty patients responded to say they would not or could not participate. Table 4.2

outlines the rationales given for not participating. Twenty three participants who returned the survey had a diagnosis of FM prior to 2001/2002 and therefore were not eligible for inclusion in the study. The second mailing produced an additional 201 eligible participants for a total of 550 participants. The participant flow chart documented at the end of this chapter outlines this information.

Table 4.2. Reasons for patients not wanting to participate (mailing 2)

Rationale	Frequency
Deceased	5
“Do not wish to participate”	3
No longer have pain	4
No longer a Kaiser member	5
Reported that pain was different due to having cancer	1
Does not remember 2001/2002	1
Stated that he/she was never see at Pain Clinic	1

The sample of 550 participants consisted of 57.0% female adults with an average age of 63.7 years (SD=13.7 years). The majority (69.8%) of the sample identified themselves as not Hispanic or Latino, 1.6% identified themselves as Hispanic or Latino, while 28.6% chose not to answer this question. In terms of race, 90.7% of the sample identified their race as white, 2.4% identified as American Indian or Alaska Native and white, 1.3% identified as Black or African American, .9% as Asian, 0.4% as Native Hawaiian or other Pacific Islander, 0.2% as American Indian or Alaska Native, while 4.2% chose not to answer this question. The 550 participants had an average pain level of 4.3 (SD=2.3) out of ten in 2007 with an average pain level of 5.8 (SD=1.9) out of ten in 2001. When asked to shade the areas of the body where they currently experienced pain, the sample shaded an average of 10.1 (SD=8.6) locations out of 50. In 2001 and 2007 their average body mass index (BMI) was 29.4 kg/m^2 and 29.1 kg/m^2 respectively (SD=6.3 kg/m^2 and 6.4 kg/m^2), which is classified as overweight but bordering on obese.

In 2001, 20.6% were receiving disability benefits but only 5.3% identified this disability as being related to pain. Conversely in 2007, 32.8% were receiving disability benefits and 15.2% identified this disability as being related to pain. Table 4.3 presents the demographic data for these 550 participants and documents the sample distribution according to the risk factors examined.

Table 4.3. Sample demographics

Demographic variable		n of sample (%) or mean (standard deviation)
Gender	Female	288 (56.3%)
	Male	223 (43.7%)
Ethnicity	Not Hispanic or Latino	384 (69.8%)
	Hispanic or Latino	9 (1.6%)
	Not reported	156 (28.6%)
Race	White	499 (90.7%)
	American Indian/Alaska Native and White	13 (2.4%)
	Black/African American	7 (1.3%)
	Asian	5 (0.9%)
	Native Hawaiian/Other Pacific Islander	2 (0.4%)
	American Indian/Alaska Native	1 (0.2%)
	Not reported	23 (4.2%)
Age		63.7 (13.7)
Number of shaded body areas		10.1 (8.6)
Average pain level in 2007		4.3 (2.3)
Average pain level in 2001/2002		5.8 (1.9)
Pain severity in 2001/2002	Mild	258 (50.4%)
	Moderate	213 (41.6%
	Severe	39 (7.6%)
Pain interference with activity in 2001/2002	Mild	88 (24.4%)
	Moderate	174 (48.2%)
	Severe	99 (27.4%)
Body Mass Index in 2001/2002		29.4kg/m^2 (6.3)
BMI in 200/2002	Normal	106 (23.6%)
	Overweight	171 (38.0%)
	Obese	148 (32.9%)
	Morbidly obese	25 (5.6%)
Use of tobacco	Never smoked	220 (43.2%)
	Currently smoke	59 (11.6%)
	Smoked in the past	230 (45.2%)

Disability benefits	Not receiving disability benefits	338 (66.8%)
	Receiving disability due to pain	74 (15.1%)
	Receiving disability unrelated to pain	78 (15.1%)
Abuse as an adult	Was abused	32 (6.5%)
	Was not abused	462 (93.5%)
Abuse as a child	Was abused	57 (12.2%)
	Was not abused	409 (87.8%)
First degree relative with WSP	Yes	209 (46.1%)
	No	244 (53.9%)

Aim 1

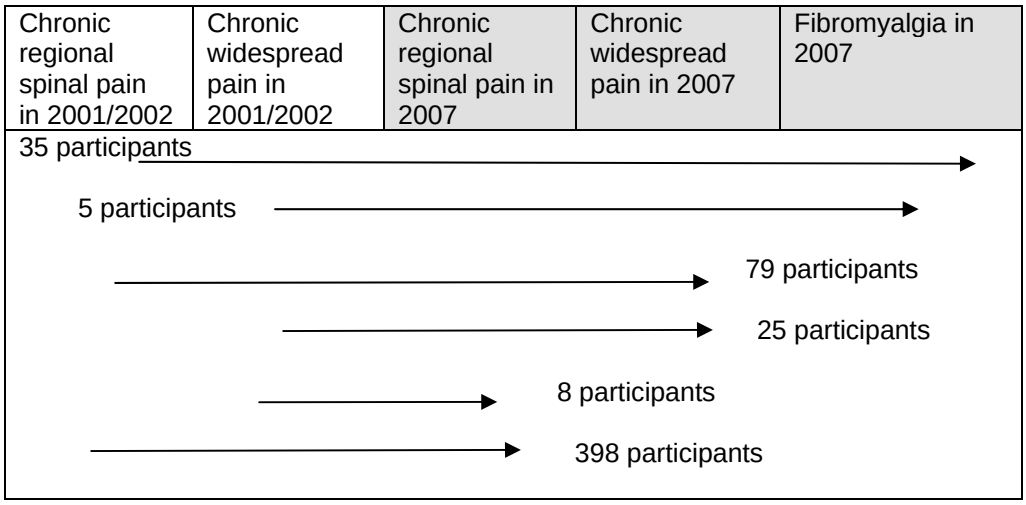
Describe the rate of transition to widespread pain (WSP) in a cohort of adults originally presenting with chronic regional spinal pain (CRSP).

Analyses for Aim 1 and 2 included only participants who presented with CRSP in 2001/2002 (N=512), excluding the 38 participants who presented with WSP in 2001/2002. This allowed for a clearer picture of the transition from CRSP to WSP. Out of the 512 participants presenting with CRSP in 2001/2002, 114 (22.3%) had developed WSP or FM by 2007 (79 to WSP, 35 to FM). The 96% confidence interval for the rate of transition to WSP is 18.4% to 25.6% meaning that the development of WSP from CRSP in the true population could fall between 18.4% and 25.6% with 96% confidence. Table 4.4 outlines the number of participants transitioning from CRSP to WSP and FM along with the progression of pain for all 550 participants. Figure 4.1 presents this information graphically to display the progression of the worsening clinical trajectory. A discussion of the transition to FM will follow under Aim 3.

Table 4.4. Progression of pain among all participants.

Pain status in 2001/2002	Pain status in 2007	Number of participants
CRSP	FM	35
CRSP	WSP	79
CRSP	CRSP	398
WSP	FM	5
WSP	WSP	25
WSP	CRSP	8

Figure 4.1. Progression of pain among all participants.



The differences between those with CRSP who transitioned to WSP (N=114) and those who continued to have regional pain (N=398) were examined using t-test and chi square analyses. The questionnaire data collected in 2007 was used for this analysis. Table 4.5 describes the specific differences between the two groups. In general, transition to WSP was associated with a substantially worse clinical impact. Data collected in 2007 indicated that the 114 participants who transitioned to WSP from CRSP presented with significantly higher pain ratings ($p<.001$), interference with general activity ($p<.001$), BMI ($p=.015$), PHQ-9 score (measure of depression) ($p<.001$), and

interference with sleep (p<.001). There was no difference between the two groups on the receipt of disability benefits (p=.853).

Table 4.5. Mean (SD) for participants who transitioned to WSP compared to those who did not (using 2007 data)

Clinical variable	Transitioned to WSP N=114	Did not transition to WSP N=398	p-value	Possible Range
Pain severity	5.6 (1.8)	3.8 (2.3)	p<.001	0 - 10
Interference with general activity	6.1 (2.4)	4.1 (2.9)	p<.001	0 - 10
Body mass index kg/m^2	30.2 (7.9) (obese)	28.5 (5.7) (overweight)	p=.001	17 - 62
PHQ-9 score	10.3 (6.0) (moderate depression)	6.1 (5.7) (mild depression)	p<.001	0 - 24
Interference with sleep	5.9 (2.7)	3.7 (3.0)	p<.001	0 - 10

Aim 2

Identify risk factors that predispose adults with CRSP to a transition to WSP.

Logistic regression was used to determine the 2001/2002 predictive factors associated with a transition from CRSP in 2001/2002 to WSP in 2007. Analyses included the 512 participants that presented with CRSP in 2001/2002. Table 4.6 outlines the significant bivariate predictors for transition to WSP, the associated odds ratios (OR), relative risk (RR), and level of significance. Participants who presented with moderate or severe pain in 2001/2002 (as compared to those with mild pain) were three to five times more likely to develop WSP (moderate pain RR 3.22, p<.001; severe pain RR 4.94, p<.001) while severe interference with general activity (as compared to mild interference) increased the likelihood of developing WSP by two (RR 1.95, p=.015).

Females were more than twice as likely to develop WSP (RR 2.35, p<.001) as were participants whose BMI fell into the morbidly obese classification (BMI >40kg/m^2: RR 2.68, p=.002) compared to those of normal weight. Participants who had a history of abuse as an adult were two and a half times more likely to develop WSP (RR 2.63, p<.001) whereas participants who were abused as a child were 73% more likely to develop WSP (RR 1.73, p=.007). Analyses also demonstrated that family history was associated with the development of WSP. Having a family member (parent, grandparent, sibling, or female family member) with a history of WSP made a person twice as likely to develop WSP (RR 2.19, p<.001). When investigating comorbidities demonstrated to have some component of central sensitization (irritable bowel, irritable bladder syndrome, restless legs, migraine), having a history of one of these diagnoses made a person nearly twice as likely to develop WSP (RR 1.88 p=.002). If a participant had two or more of these diagnoses, their chances of developing WSP increased by nearly three (RR 2.79, p<.001). Despite discovering several significant bivariate predictors, several of the tested variables were not significantly associated with the transition to WSP. These 2001/2002 non-significant variables included the number of depressive symptoms, the number of back or neck surgeries prior to 2001/2002, number of classes of medications used for pain management, use of tobacco, receipt of disability benefits, age, and duration of pain. Details regarding the individual bivariate predictors are discussed below followed by a discussion of the multivariate predictors.

Table 4.6. Bivariate risk factors associated with a transition from CRSP to WSP (using 2001/02 data).

Predictor variable	Odds ratio	Relative risk	Significance
Pain severity (mild vs severe pain)	9.81	4.94	p<.001
Pain severity (mild vs moderate pain)	4.47	3.22	p<.001
Female gender	3.14	2.35	p<.001
BMI: Normal weight vs morbid obesity	4.23	2.68	p=.002
Abused as an adult	5.24	2.63	p<.001
Abused as a child	2.26	1.73	p<.001
Abused at anytime in life	2.65	2.016	p<.001
Severe interference with general activity	2.41	1.95	p=.015
Use of more pain management strategies	1.50	1.46*	p<.001
Member of primary family with WSP	2.41	1.90	p<.001
Female family member with WSP	2.98	2.20	p<.001
Elder with WSP	2.43	1.9	p<.001
Sibling with WSP	3.05	2.19	p<.001
History of irritable bowel syndrome	2.65	2.04	p<.001
History of irritable bladder syndrome	2.77	2.05	p=.001
History of restless legs	2.26	1.81	p=.002
History of migraines	1.81	1.56	p=.015
History of one of the above central sensitivity syndromes (vs no syndromes)	2.19	1.88	p=.002
History of two or more of the above central sensitivity syndromes (vs no syndromes)	3.96	2.79	p<.001
Non-significant variables			
Predictor variable	Odds ratio	Significance	
Age	.99	.260	

Pain duration	.96	.586
BMI (normal vs overweight)	1.31	.391
BMI (normal vs obese)	1.42	.273
Number of back or neck surgeries prior to 2001	1.12	.439
Depressive symptoms in 2001/02	1.10	.089
Number of medication classes used for pain in 2001/02	1.10	.147
Tobacco pack year history	1.01	.224
Receipt of disability benefits	1.01	.968

*RR calculated using dichotomized version of variable (use of zero pain management strategies versus one or more strategies used) whereas OR calculated with the continuous variable.

Individual predictor variables (bivariate analyses)

Pain severity in 2001/2002

The bivariate relationship between the participant's pain level in 2001/2002 and the development of WSP was explored using pain as a continuous variable, a dichotomous variable, and a categorical variable. To use pain as a dichotomous and categorical variable, the variable was recoded into mild pain (including pain levels of 0-4), moderate pain (pain levels of 5-7), and severe pain (pain levels of 8-10). The dichotomous variable grouped mild and moderate pain into one level and severe pain into the other level. All three ways of conceptualizing pain significantly predicted a transition to WSP. It was ultimately decided to use the categorical variable with three levels (mild, moderate, severe) as this is the most clinically relevant way of conceptualizing pain intensity. In 2001/2002, 50.6% of participants presented with mild pain, 41.6% with moderate pain, and 7.6% with severe pain. The OR for developing WSP in 2007 was 4.47 ($p<.001$) for moderate pain in 2001/2002 as compared to mild pain and 9.811 ($p<.001$) for severe pain as compared to mild pain. The corresponding RRs were 3.22 for moderate pain and

4.94 for severe pain. This means that someone with severe pain in 2001/2002 had a five times greater chance of developing WSP from CRSP compared to someone with mild pain. Conversely, someone with moderate pain in 2001/2002 had a 3.22 times greater likelihood of developing WSP.

Gender

As noted earlier, 56.4% of the sample of 512 participants was female. Females with CRSP were 2.35 times more likely to develop WSP as males with CRSP. Logistic regression revealed that being female was associated with an OR of 3.14 and an RR of 2.35 ($p<.001$).

Abuse

Although few participants were abused as an adult (6.5%), being *abused as an adult* (as compared to not being abused) significantly predicted transition to WSP with an OR of 5.24 and an RR of 2.63 ($p<.001$). Those individuals who were abused as an adult were two and a half times more likely to develop WSP. Twelve percent of participants had been abused as a child. *Abuse as a child* also significantly predicted the outcome of developing WSP with an OR of 2.26 and a RR of 1.73 ($p=.007$). While distinguishing between the timing of abuse adds detail to our understanding of abuse as a factor in the development of WSP, one must also consider whether abuse at anytime in one's life impacts this development. To make this determination, a new dichotomous variable was computed that was coded 1 if the participant had been abused as an adult *or* child. *Abuse at any point in one's life* was a significant bivariate predictor of WSP with an OR of 2.65 and RR of 2.02 ($p<.001$).

Number of pain management strategies used in 2001/2002

On the study questionnaire sent to participants in 2007, participants were asked to identify from a list of 26 common pain management strategies, which strategies they had used to manage their pain in 2001 and 2002. Participants used an average 3.9 (SD=2.0)

pain management strategies with a range of zero to fifteen strategies used. To determine whether the number of pain management strategies used in 2001/2002 was a significant predictor of the development of WSP, pain strategies was recoded so that a 1 unit increase represented the use of three additional pain management strategies. This variable significantly predicted a transition to WSP with an OR of 1.50 and an RR of 1.46 ($p<.001$). The RR was calculated using a dichotomized version of this variable (use of zero pain management strategies versus one or more strategies used). A relative risk of 1.46 indicates that using one or more pain management strategies increases a person's risk of developing WSP from CRSP by 46%. Interestingly, this indicates that the more pain management strategies used, the greater the likelihood of developing WSP.

Interference with general activity in 2001/2002

Interference with general activity in 2001/2002 was analyzed as a categorical variable with similar grouping as used for pain intensity (0-4 equals mild interference, 5-7 equals moderate interference, and 8-10 equals severe interference). Twenty four percent of participants identified themselves as having mild interferences with general activity due to pain, 48.2% as having moderate interference, and 27.4% stated that they had severe interference with general activity. As compared to having mild interference with general activity, a person who described having severe interference with their activity was twice as likely to develop WSP (OR=2.41, RR=1.95, p=.015). Having moderate as compared to mild interference with activity in 2001/2002 was not significantly associated with developing WSP.

Family history variables

Regarding family history, participants were asked to report whether or not their parents, grandparents, siblings, aunts, uncles, or cousins had a history of WSP or FM. Grouping these variables allowed for a better understanding of familial history than looking at each family member individually. Despite the grouping of the family history

variables, a person with a family history of WSP was twice as likely to develop WSP from CRSP. Numerous studies, including this one, demonstrate that WSP is more prevalent in females as compared to males. For this reason, female family history was examined as a predictor for the development of WSP. This was a dichotomous variable that indicated whether or not the participant had any female family members with WSP. Overall, 41.1% of the sample had a *female family member with WSP*. This variable significantly predicted transition to WSP with an OR of 2.98 and an RR of 2.20 ($p<.001$), demonstrating that if a person with CRSP has a female family member with WSP, s/he was twice as likely to develop WSP. Looking at the presence of WSP in a sibling offers a unique perspective as siblings not only share a genetic makeup but also share a physical and psychological environment perhaps influencing their pain experience. Thirty percent of participants had a *sibling with WSP*. This was a significant predictor for the transition to WSP with an OR of 3.05 and RR of 2.19 ($p<.001$). The predictive value of having a primary family member with WSP (mom, dad, brother, sister) was also examined. Have a primary family member with WSP was associated with a transition to WSP with an OR of 2.41 and an RR of 1.90 ($p<.001$). Another variable was created to investigate the history of elder family members (mom, dad, grandfather, grandmother) as these individuals shape the genetic makeup of the participant. Forty two percent of participants had an elder family member with WSP. Having an *elder family member with WSP* significantly predicted the development of WSP with an OR of 2.43 and an RR of 1.90 ($p<.001$).

Body mass index

BMI, calculated from height and weight in 2001/2002, was categorized into a healthy weight group (18.5-24.9 kg/m^2), an overweight group (25-29.9 kg/m^2), an obese group (>30 kg/m^2), and an underweight group (< 18.5 kg/m2) using the Center for Disease Control's classification of BMI. Healthy weight was used as the reference group in the

logistic regressions. BMI was not significant using this categorization. Since only four participants fell into the ‘underweight’ category, the underweight and normal weight categories were merged. The largest group of participants (38.6%) fell into the obese category so this category was reclassified into an obese group (BMI 30–39.9 kg/m^2) and a morbidly obese group (BMI 40 kg/m^2 and greater). After re-categorizing, 23.6% of the participants fell into the normal BMI category, 38.0% into the overweight category, 32.9% into the obese category, and 5.6% into the morbidly obese category. Entering these categories into the logistic regression analysis with normal BMI as the reference group indicated that participants who were morbidly obese were 2.68 times more likely to develop WSP (OR=4.227, RR=2.68, p=.002). None of the other BMI categories, as compared to the normal BMI group, predicted transition to WSP. Although analyses demonstrated that being morbidly obese was associated with a transition to WSP, one must interpret these results with caution. The morbidly obese group only had 25 participants and the odds ratio for this group was associated with a wide confidence interval (95% CI=1.67-10.70), indicating poor precision in the analysis, perhaps due to the small sample size.

Central sensitivity syndromes

As discussed in Chapter 2, research has demonstrated that changes in the central nervous system are important mechanisms that underlie the pain of WSP, FM, and some spinal pain disorders. A growing body of research demonstrates that similar mechanisms underlie other pain disorders including irritable bowel and irritable bladder syndromes, restless leg syndrome, and migraines (together called central sensitivity syndromes). Participants were asked to identify whether or not they had each of these syndromes. Twenty one percent of participants stated that they had migraines, 22.9% had irritable bowel syndrome, 10.0% had irritable bladder syndrome, and 14.6% had restless leg syndrome. Having any of these central sensitivity syndromes was

significantly associated with an increased likelihood of transitioning to WSP with an OR of 2.74 and an RR of 2.20 (p<.001). Having irritable bowel syndrome made a person twice as likely to develop WSP (OR=2.65, RR=2.04, p<.001). The same was true for irritable bladder syndrome (OR=2.77, RR=2.05, p=.001). If a participant had restless legs s/he was 81% more likely to develop WSP (OR=2.26, RR=1.81, p=.002) while a person with migraines was one and half times more likely to transition to WSP (OR=1.81, RR=1.56, p=.015).

Since central sensitivity is a relevant underlying mechanism in these syndromes and the diagnoses of interest (WSP and FM), the relationship between transition to WSP and number of central sensitivity syndromes a person reported. Fifty two percent of participants had none of the syndromes, 30.9% had one syndrome, 13.7% had two, 2.5% had three, and 0.6% had all four syndromes. In order to determine whether or not the number of central sensitivity syndromes significantly predicted a transition to WSP, a new three level categorical variable was created (0, 1, 2 or more central sensitivity syndromes). In logistic regression, with zero central sensitivity syndromes as the reference group, a person with one central sensitivity syndrome was 1.88 times more likely to develop WSP (OR=2.19, RR=1.88, p=.002) and a person with two or more syndromes was nearly three times more likely to develop WSP (OR=3.96, RR=2.79, p<.001). While these analyses provided insight into the impact of comorbid central sensitivity syndromes on the development of WSP and FM, it is important to recognize that WSP and FM are also considered to be central sensitivity syndromes. Therefore it is of interest to know the total number of central sensitivity syndromes demonstrated by each participant. This information is displayed in Table 4.7. This table displays the total number of central sensitivity syndromes, out of six (WSP, FM, irritable bowel syndrome, irritable bladder syndrome, migraine, and restless legs), that participants demonstrated. No participants presented with all six central sensitivity syndromes.

Table 4.7. Total number of central sensitivity syndromes

Total Number of Central Sensitivity Syndromes	Number of Participants	Percent of Participants
Zero	234	42.5%
One	157	28.5%
Two	93	16.9%
Three	44	8.0%
Four	17	3.1%
Five	5	0.9%

Total number of medication classes used in 2001/2002

Through a chart review of the participants' medication use in the six months prior to and after their visit to the Pain Clinic, the number and type of medication classes used by each participant was obtained. Out of a total of twelve medication classes, the average number of medication classes used by these participants was 2.4 classes (SD= 1.6). The most frequently used type of medication was short acting opioids with 70.4% of participants using this type of medication. Interestingly, only 15.8% of participants used long acting opioids, which are strongly preferred over the use of short acting opioids for the management of chronic pain. The number of medication classes used for pain management in 2001/2002 did not significantly predict transition to WSP (p=.147).

Number of back or neck surgeries prior to 2003

On the study questionnaire sent to participants in 2007, they were asked to report the number of back or neck surgeries they had undergone prior to 2003. A majority of the participants (66.6%) had not had any surgeries. The number of surgeries ranged from zero to eight surgeries with 18.9% having undergone one surgery. In order to avoid any one group having too few participants, this variable was re-coded based on the frequency table and histogram distribution. The new variable had three levels: no back or neck surgeries, one surgery, and two or more surgeries. With no surgeries as the

reference group, number of surgeries was not a significant predictor of transition to WSP (p=.335).

Pain duration

The number of years participants had been in pain was calculated. Years in pain ranged from zero years (3-11 months) to 39 years. The average number of years that participants experienced pain was 3.0 years (SD= 0.41). The largest majority of participants (26.3%) reported being in pain for one year and 68.7% reported being in pain for 3 years or less when they were seen at the Pain Clinic in 2001/2002. Due to the large number of participants having a pain duration of zero, one, two, or three years, this variable was recoded into five groups (zero to 11 months, one year, two years, three to four years, and five or more years). Contrary to the hypothesis that the more years a person experiences chronic pain, the more likely they are to develop WSP, pain duration was not found to be a significant predictor of transition to WSP (p=.586).

Depression

On the 2001/2002 KP Pain Clinic questionnaire, patients were asked to place a check mark by the depressive symptoms they had experienced in the past two weeks (instead of the typical scoring method used in the official PHQ 9). This created a sum score based on the number of symptoms the patient endorsed. Participants marked an average of 2.6 depressive symptoms (out of nine symptoms) (SD=2.1). The number of depressive symptoms was not a significant predictor for the development of WSP (p=.089).

Tobacco pack year history

The study questionnaire sent to participants in 2007 asked participants to describe their smoking history including whether they were currently smoking, had smoked in the past, had never smoked and, if they had or were smoking, the number of packs per day and for how many years. 45.2% of the sample had smoked in the past, 43.2% had never

smoked, and 11.6% stated that they currently smoked. The most clinically relevant consideration, though, was the amount a person had smoked. Therefore tobacco pack years was calculated by multiplying the number of years smoked by the number of packs per day. For instance, if a person smoked a half pack per day for 20 years, they would have a 10 pack year history. As a one pack year difference would not likely be clinically relevant, the frequency distribution and histogram was examined to determine the appropriate groupings for this variable. Logical groups included a zero pack year group, a one to twenty pack year group, a 21 to 40 pack year group, and a 41 pack year or more group. Using this grouping, tobacco pack year history was not a significant predictor of transition to WSP (p=.224).

Multivariate analyses

The significant bivariate risk factors were included in a multivariate analysis to determine which variables significantly predicted transition to WSP when controlling for all other variables. When appropriate, only one variable was included to represent a set of bivariate risk factors. For instance, to represent the family history variables, it was decided to include the variable that denoted whether or not a participant had a primary family member with a history of WSP. To represent the abuse variables, whether or not a person had a history of abuse within their lifetime (as a child or adult) was chosen as a representative variable. For the central sensitization comorbidities, the variable stating whether the participant had no central sensitization diagnoses, one diagnosis, or two or more diagnoses was included in the model. These decisions were based on which variables, in theory, best represented the group of variables in question.

When including pain severity, family history of WSP, gender, number of pain management strategies used in 2001, history of abuse, and presence of a central sensitization syndrome in the multivariate logistic regression analysis, all risk factor remained significant except for history of abuse. See Table 4.8 for an overview of odds

ratios and significance for each variable. Of note, history of abuse was significantly correlated with three of the other risk factors including gender (r=.191, p=.01), number of pain management strategies used (r=.154, p=.01) and the presence of central sensitivity diagnoses (r=.093, p=.05).

Table 4.8. Multivariate analysis with all significant bivariate risk factors *except* extreme obesity (using 2001/02 data).

Predictor variable	Odds ratio	Significance
Pain severity	3.92	p<.001
Family history of WSP	1.92	p=.013
Gender	2.32	p=.003
Number of pain management strategies used in 2001	1.29	p=.016
History of having two or more central sensitivity syndromes vs having no syndromes	2.01	p=.039
History of having one central sensitivity syndrome vs having no syndromes	1.05	p=.883
History of abuse in lifetime	1.49	p=.221

Because of the large confidence interval associated with the comparison between having a normal BMI and being morbidly obese, the recoded BMI variable was not added into the initial multivariate model out of concern that it might make the model unstable. When adding the recoded BMI variable into the multivariate analysis, several other risk factors lost their significance including number of pain management strategies used in 2001, presence of central sensitivity diagnoses, history of abuse, and the BMI risk factor itself. Pain intensity, gender, and a family history of WSP remained significant. Interestingly, the variables that lost significance: number of pain management strategies used, presence of central sensitivity diagnoses, and history of abuse were not correlated with the BMI variable. BMI was correlated with pain intensity (r=.163, p=.01), gender (r= -

.108, p=.05), and having a family member with WSP (r=.174, p<.01). See Table 4.9 for details regarding this analysis.

Table 4.9. Multivariate analysis with all significant bivariate risk factors *including* obesity status (using 2001/02 data).

Predictor variable	Odds ratio	Significance
Pain severity	3.33	p<.001
Family history of WSP	2.18	p=.006
Gender	3.07	p<.001
History of having two or more central sensitivity syndromes vs having no syndromes	1.72	p=.150
History of having one central sensitivity syndrome vs having no syndromes	1.05	p=.888
Number of pain management strategies used in 2001	1.20	p=.102
History of abuse in lifetime	1.61	p=.171
BMI (overweight vs normal weight)	1.58	p=.229
BMI (obese vs normal weight)	1.30	p=.491
BMI (morbidly obese vs normal weight)	3.03	p=.069

Aim 3

Identify risk factors that predispose individuals with CRSP to a transition to FM.

The first step in Aim 3 was to determine which participants with CRSP had transitioned to FM. A diagnosis of FM was made if the participant presented with WSP and had 11 out of 18 tender points on a tender point examination. To determine which participants qualified for a diagnosis of FM, the research team needed to perform a tender point examination on the participants who demonstrated WSP in 2007. The sample for this third aim included 144 participants, 14 of whom already had a diagnosis of FM in the chart (diagnosed in 2003 or later) and therefore did not need to be tested for FM. One of the 144 participants was deceased and therefore was not included in the analysis for Aim 3. The remaining 129 participants who had presented with WSP in 2007

but did not already have a diagnosis of FM were invited to OHSU to be examined for FM. Forty two of these participants were scheduled for FM testing although only 29 (22.5%) showed up to be examined. Therefore, the research team was able determine if a participant had a diagnosis of FM for 43 (29.9%) of the 144 possible sample. Chapter 3 describes efforts to increase this response rate. Out of the 99 participants who chose not to participate in this second phase of the study, 55 gave some rationale for this decision. Table 4.10 outlines participants' rationales for not wanting to participate.

Table 4.10. Reasons for patients not wanting to participate in phase II.

Rationale	Frequency
Not wanting to drive or cost of gas	14
Unable due to health or advanced age	6
Not interested in participating	10
Busy or inconvenient timing	3
Did not remember originally participating	3
Indicated interest but never followed through	7
Scheduled but no showed visit	12
Never heard from despite two letters and a phone message	44

T-tests and chi square were used to investigate whether the participants who came in to be examined for FM differed significantly from those who chose not to be examined. Data collected in 2007 was used to determine if current differences in symptom severity affected a participant's ability to attend the FM examination. No differences were found between the two groups in terms of age, pain severity, BMI, depression, pain related disability, gender, or interference with sleep or activity. Table 4.11 displays the means for each group on these variables.

Table 4.11. Mean (SD) for participants who came to be examined for FM and those who did not (using 2007 data).

Variable	Attended FM exam N=29	Did not attend FM exam N=100	p-value	Possible range
Age	63.1 (11.3)	62.7 (13.3)	p=.885	22 - 97
Average pain severity	5.4 (1.8)	5.7 (1.8)	p=.392	0 - 10
Pain interference with activity	5.5 (2.5)	6.5 (2.3)	p=.052	0 - 10
Pain interference with sleep	5.3 (3.0)	6.4 (2.5)	p=.049	0 - 10
BMI (kg/m^2)	29.7 (5.3)	30.3 (8.1)	p=.728	17 - 62
PHQ 9 score	9.5 (7.3)	10.5 (6.4)	p=.480	0 - 24

As noted, 29 participants who had transitioned from CRSP in 2001/02 to WSP in 2007 agreed to undergo a tender point examination to determine whether or not they qualified for a diagnosis of FM. Out of these 29 participants, 22 met diagnostic criteria for FM and 7 did not. This indicates that 75.9 % of those participants who transitioned from CRSP to WSP and agreed to be examined did indeed have FM. As noted earlier, 14 participants who presented with WSP in 2007 had been diagnosed by a KP provider in 2003 or later. Four participants who did not present with WSP in 2007 were also diagnosed with FM by a KP provider in 2003 or later. These 18 participants with FM were added to the 22 participants that the research team diagnosed with FM.

The 40 participants who were diagnosed with FM were compared to the 7 participants who had WSP but did not qualify for a FM diagnosis on age, average pain intensity, pain interference with general activity, pain interference with sleep, BMI, depression, and gender (on data collected in 2007) using t-tests and chi square analyses. No significant differences between the two groups were detected although the analyses did not have sufficient statistical power due to the small sample sizes. Table

4.12 outlines the means for each group on these variables. Interestingly, when the two groups were compared on the presence and number of central sensitivity diagnoses, the difference did approach significance at p=.051, indicating that participants with more central sensitivity diagnoses could have been more likely to develop FM.

Table 4.12. Mean (SD) for the 40 participants who transitioned to FM and the 7 participants who transitioned to WSP but not to FM (using 2007 data).

Variable	Transitioned to FM (N=40)	Transitioned to WSP but not FM (N=7)
Age	59.8 (12.8)	65.4 (11.6)
Average pain severity	5.4 (1.9)	5.1 (2.0)
Pain interference with activity	5.7 (2.5)	3.9 (2.9)
Pain interference with sleep	5.4 (2.9)	4.1 (3.4)
BMI kg/m^2	31.8 (7.5) (obese)	30.2 (6.5) (obese)
PHQ 9 score	10.5 (6.6) (moderate depression)	4.0 (1.6) (minimal to no depression)

In an effort to determine the risk factors associated with a transition from CRSP to FM, the research team decided to utilize a nested case control, matching by age, the 40 participants who transitioned from CRSP to FM to 40 participants who did not transition to WSP or FM in 2007. Logistic regression (bivariate analysis) was used to determine the risk factors associated with a transition from CRSP to FM over a six-year period. Analyses demonstrated that having moderate or severe pain (compared to mild pain) in 2001/02, being of female gender, having been abused at any point in one's life, having a central sensitivity syndrome, using more pain management strategies in 2001/02, and having a sibling with WSP significantly predicted a transition to FM. Table 4.13 outlines

the individual odds ratios, relative risk ratios, and significance level for each predictor variable. This table demonstrates that a patient with CRSP who presented with a moderate level of pain intensity had a two and a half times greater likelihood of developing FM than one who presented with mild pain (OR= 4.44, RR=2.57, p=.003), while a person who experienced severe pain on a regular basis was three times more likely to develop FM than someone with mild pain (OR=16.00, RR=3.18, p=.016). A female with CRSP was 3.35 times more likely to develop FM as compared to a male (OR=6.33, RR=3.35, p=.001) while a person who had been abused at sometime in their life was twice as likely to develop FM (OR=3.93, RR=1.94, p=.019). Participants who used two or more pain management strategies to control their pain in 2001/02 were 37% more likely to develop FM (OR=1.56, RR=1.37, p=.020). A person with CRSP who had a sibling with WSP was 1.76 times more likely to develop FM (OR=3.14, RR=1.76, p=.041). Finally, a participant with CRSP and two or more central sensitivity syndromes was twice as likely to develop FM (OR=4.20, RR=2.07, p=.023) as compared to a participant with no central sensitivity syndromes. A participant with one central sensitivity syndrome was 80% more likely to develop FM (OR=2.91, RR=1.8, p=.044). Variables that had represented significant predictors for WSP but did not demonstrate significance in the development of FM included abuse as an adult, abuse as a child, presence of individual central sensitivity syndromes (irritable bowel, irritable bladder, restless legs, and migraine), BMI, and family history of WSP in elder and female family members.

Table 4.13. Bivariate risk factors associated with a transition from CRSP to FM (using 2001/02 data).

Predictor variable	Odds ratio	Relative risk	Significance
Pain severity (mild vs severe pain)	16.0	3.18	p=.016
Pain severity (mild vs moderate pain)	4.44	2.57	p=.003
Female gender	6.33	3.35	p=.001
Abused at anytime in life	3.92	1.94	p=.019
Sibling with WSP	3.14	1.76	p=.041
History of having any of the central sensitivity syndromes	3.32	1.99	p=.013
Having one central sensitivity syndrome vs no syndromes	2.91	1.80	p=.044
Having two or more central sensitivity syndrome vs no syndromes	4.20	2.07	p=.023
Number of pain management strategies used in 2001/02	1.56	1.37*	p=.020
Variables that were non-significant for transition to FM (Aim 3) but significant for transition to WSP (Aim 2)			
Predictor variable	Odds ratio	Significance	N needed to have power of .80
Abused as an adult	2.009	.999	808
Abused as a child	2.448	.147	272
BMI (normal weight vs overweight)	.960	.955	78,711
BMI (normal weight vs obese)	2.0	.348	299
BMI (normal weight vs morbid obesity)	6.0	.152	161
History of irritable bowel	1.8	.230	437

syndrome			
History of irritable bladder syndrome	1.588	.502	1,370
History of restless legs	3.581	.072	176
History of migraines	2.067	.147	298
Member of primary family with WSP	1.490	.411	827
Female family member with WSP	1.47	.418	875
Elder family member with WSP	1.768	.240	399
Variables that were non-significant for both transition to FM (Aim 3) *and* transition to WSP (Aim 2)			
Age	1.0	.979	
Pain duration	1.108	.115	
Number of neck surgeries prior to 2001	1.440	.147	
Depressive symptoms in 2001/02	1.079	.501	
Number of medication classes used for pain in 2001/02	.930	.592	
Tobacco pack year history	.992	.587	
Receipt of disability benefits	.726	.691	

*RR calculated using dichotomized version of variable (use of zero pain management strategies versus one or more strategies used) whereas OR calculated with the continuous variable.

Due to the small sample size, the research team suspected that some predictive risk factors might not have been significant due to a lack of adequate statistical power. One indication that led the team to this conclusion was the fact that individual variables such as abuse in adulthood, abuse in childhood, and presence of individual central sensitivity syndromes were not significant in the bivariate logistic regression. When these variables

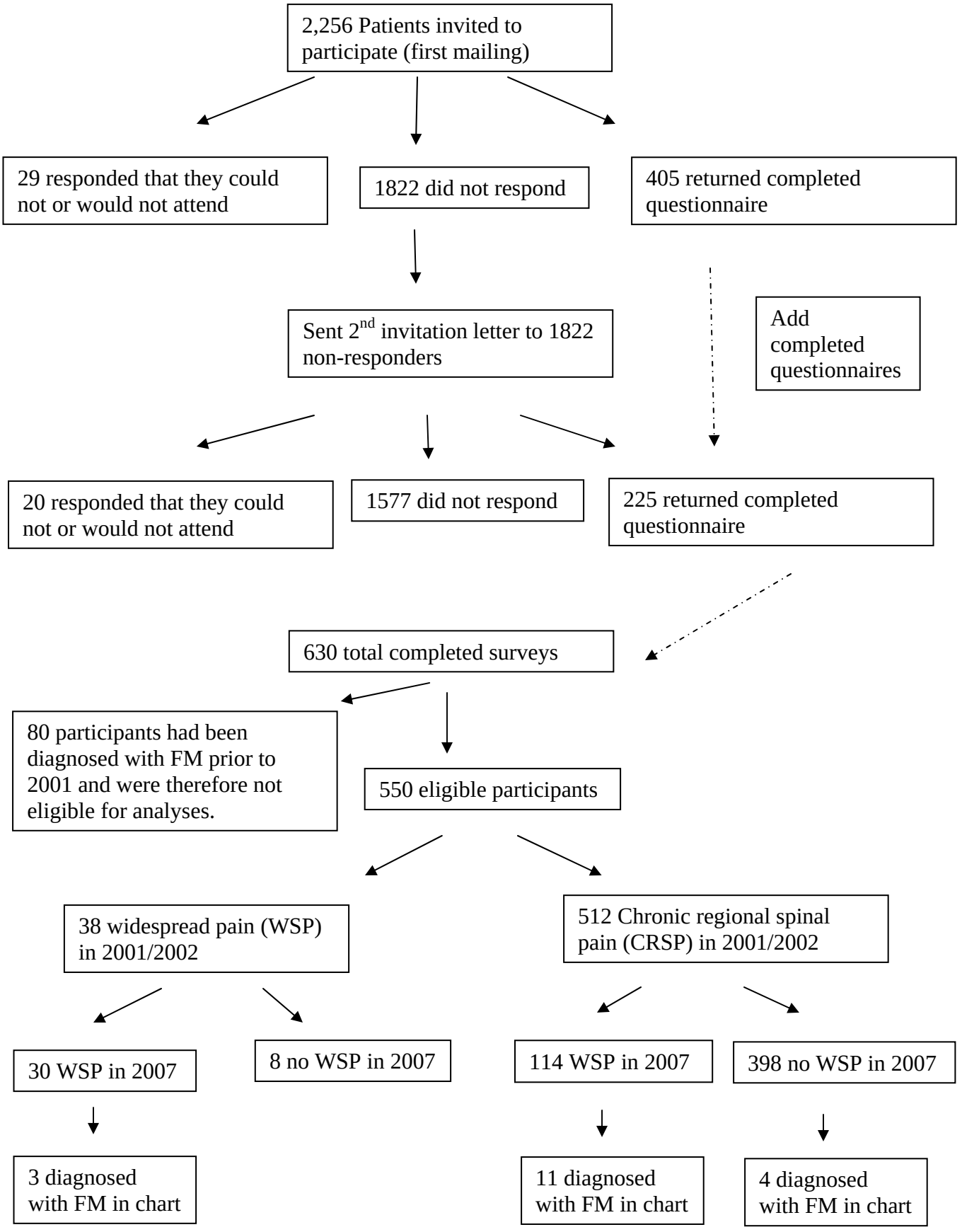
were collapsed into a variable containing more individuals (history of abuse at any time in life or presence of any central sensitivity diagnoses), they became significant. This indicated that a lack of significance in these individual predictor variables could have been due to inadequate statistical power. Because many of the individual risk factors had been significant with a sample size of 512 participants in Aim 2 (transition to WSP), but lost significance with a sample size of 80 in Aim 3 (transition to FM), the research team chose to conduct a power analysis to determine if sample size played a role in the non-significant findings.

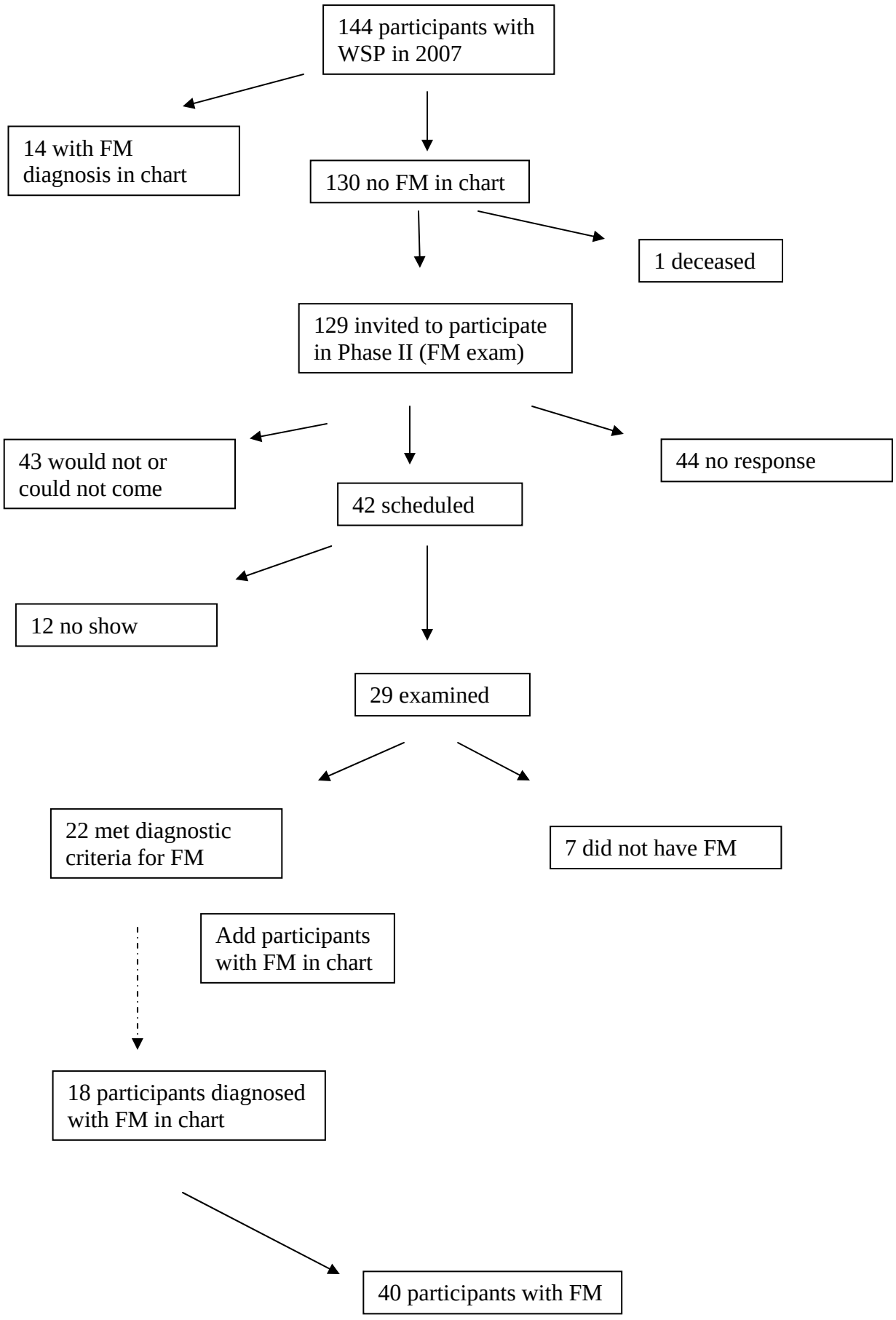
The OR and number of participants in each response group was used to determine the sample size needed to have statistical power of .80, the power needed to detect an effect if one truly exists. These sample sizes are displayed for each non-significant variable in Table 4.13. If the sample size needed to have a power of .80 was approximately 500 or less, it is reasonable to assume that the small sample size of Aim 3 led to those particular non-significant findings. Using this guideline, it is likely that being abused as a child (OR=2.45, RR=1.52), being obese (OR=2.00, RR=1.38) or morbidly obese (OR=6.0, RR=1.85) (as compared to being of normal weight), having a history of irritable bowel syndrome (OR=1.80, RR=1.32), restless legs (OR=3.58, RR=1.65), or migraines (OR=2.07, RR=1.4), having severe interference with general activity (OR=2.25, RR= 1.39) (as compared to having mild interference with general activity), and having an elder family member with WSP (OR=1.77, RR=1.32) would have been significant risk factors for the development of FM with a sample size similar to that used for Aim 2 (N=512). Even with a substantially larger sample size, a history of abuse as an adult, being overweight, having a history of irritable bladder syndrome, having moderate interference with general activity, or having a primary family member with WSP would not have been associated with a transition from CRSP to FM. Table 4.13 compares the risk factors associated with the development of WSP and FM.

Table 4.14. Comparing the risk factors associated with a transition to WSP to those associated with a transition to FM (using 2001/02 data).

Predictor variable	Transition to WSP (RR)	Transition to FM (RR)
Pain severity (severe pain)	4.94**	3.18*
Pain severity (moderate pain)	3.22**	2.57**
Gender (female)	2.35**	3.35**
Abused as an adult	2.63**	1.38[NS]
Abused as a child	1.73**	1.52[¥]
Abused at anytime	2.016**	1.94*
Morbid obesity	2.68**	1.85[¥]
Number of pain management strategies used	1.46**	1.37*
Severe interference with general activity	1.95*	1.39[¥]
History of irritable bowel syndrome	2.04**	1.32[NS]
History of irritable bladder syndrome	2.05**	1.24[NS]
History of restless legs	1.81**	1.65[¥]
History of migraines	1.56*	1.4[¥]
History of any of the above four central sensitivity co-morbidity	2.20**	1.99*
Having one central sensitivity co-morbidity	1.88**	1.8**
Having two or more central sensitivity co-morbidity	2.79**	2.07**
Member of primary family with WSP	1.90**	1.22[NS]
Female family member with WSP	2.198**	1.21[NS]
Elder family member with WSP	1.90**	1.32[NS]
Sibling with WSP	2.19**	3.14*

** Significant at the p<.01 level
* Significant at the p<.05 level
¥ Would be significant with 100-500 participants (based on power analysis)
NS: Not significant


2,256 Patients invited to participate (first mailing)
29 responded that they could not or would not attend
1822 did not respond
405 returned completed questionnaire
Sent 2nd invitation letter to 1822 non-responders
Add completed questionnaires
20 responded that they could not or would not attend
1577 did not respond
225 returned completed questionnaire
630 total completed surveys
80 participants had been diagnosed with FM prior to 2001 and were therefore not eligible for analyses.
550 eligible participants
38 widespread pain (WSP) in 2001/2002
512 Chronic regional spinal pain (CRSP) in 2001/2002
30 WSP in 2007
8 no WSP in 2007
114 WSP in 2007
398 no WSP in 2007
3 diagnosed with FM in chart
11 diagnosed with FM in chart
4 diagnosed with FM in chart


144 participants with WSP in 2007
14 with FM diagnosis in chart
130 no FM in chart
1 deceased
129 invited to participate in Phase II (FM exam)
43 would not or could not come
44 no response
42 scheduled
12 no show
29 examined
22 met diagnostic criteria for FM
7 did not have FM
Add participants with FM in chart
18 participants diagnosed with FM in chart
40 participants with FM

CHAPTER 5: DISCUSSION

This study adds five critical findings to the widespread pain (WSP) and fibromyalgia (FM) literature: 1) 22.6% of 512 of subjects with CRSP transitioned to WSP over six years, 2) subjects with WSP compared to subjects with CRSP had significantly poorer clinical outcomes and a greater symptom burden, 3) eight factors not including distress were closely associated with the transition from CRSP to WSP (moderate or severe pain severity, female gender, history of abuse, family history of WSP, severe interference with general activity, morbid obesity, having one or more central sensitivity syndromes, and using more pain management strategies), 4) 75.9% of the sample with WSP were diagnosed with FM based on a clinical exam in a subset of 23.6% of subjects who were willing to report to the study site for examination, and 5) six factors were significantly associated with the transition from CRSP to FM (moderate or severe pain severity, female gender, history of abuse, having a sibling with WSP, having one or more central sensitivity syndromes, and using more pain management strategies). While the development of WSP and FM has been demonstrated in past research studies investigating various forms of regional pain, this study proposed that the presence of chronic regional spinal pain (CRSP) places individuals at a unique risk for this downward clinical trajectory. This study not only demonstrated that these individuals are at an increased risk but also investigated the risk factors associated with the development of a widespread pain disorder. We were able to evaluate the rate of transition from CRSP to WSP, demonstrating that individuals with CRSP do develop this disorder at an increased rate compared to the general population and participants with other regional pain disorders. We also determined the risk factors associated with the development of WSP and FM in patients with CRSP. These findings should prove useful to health care providers in understanding the clinical issues that are important in the development of WSP and FM. Hopefully these results will inform future studies that evaluate pro-active

strategies for reducing the burden of chronic pain. These various issues are now discussed in more detail.

Rate of transition from CRSP to WSP

The rate of transition from CRSP to WSP in this study, 22.6%, compares well to the rate of transition identified in other studies, especially one study using a similar population. Lapossy and colleagues (Lapossy, et al., 1995) followed a sample of participants with chronic low back pain and found that 24.5% of those participants transitioned to WSP over an 18 year period. Three other studies that investigated this phenomenon in patients with chronic pain also found similar, but slightly lower transition rates. Bergman (Bergman, et al., 2002), Forseth (Forseth, et al., 1999) and Papageorgiou (Papageorgiou, et al., 2002) investigated participants identified as having chronic regional pain (any region of the body) over three, five, and seven years, respectively. Bergman discovered that 16.4% of participants with chronic regional pain had developed WSP while Forseth's group identified 17.4% of chronic regional pain participants as having transitioned to WSP. In Papageorgiou's sample, 10.4% originally presenting with chronic regional pain developed WSP. Although all of these studies investigated the trajectory of chronic regional pain, the current study and the Lapossy study examined this phenomenon specifically in spinal pain. Given the research identifying central sensitization as an important underlying mechanism in spinal pain, WSP, and FM, along with the increased rate of transition from CRSP to WSP, it is reasonable to conclude that individuals with CRSP have a greater propensity for the development of WSP or FM. This finding not only identifies a group of patients with chronic pain at higher risk for the widespread expansion of pain, it also has the possibility of providing insight into the mechanism by which a regional pain disorder develops into a widespread pain disorder. Compared to regional pain distant to the spine (ie. shoulder, extremity, or joint pain), CRSP directly affects the spine and perhaps

exhibits a greater influence on pain related plastic changes in the central nervous system. This speculation has yet to be substantiated but one study comparing patients with chronic low back pain to those with chronic muscle tension headaches suggests that individuals with spinal pain display enhanced cortical activation to noxious stimuli, decreased habituation to multiple stimuli, and greater sensitization to painful stimulation (Flor, et al., 2004). These findings, along with several studies demonstrating altered central pain processing in CRSP, similar to those changes found in WSP and FM, suggest that patients with CRSP are uniquely predisposed to the development of widespread pain disorders. This has significant implications, as developing a widespread pain disorder is associated with poor clinical outcomes, as will be discussed below.

Impact of developing WSP

Not surprisingly, this study demonstrated that those individuals who developed WSP presented with poorer health outcomes following the transition from CRSP to WSP. As compared to those participants with CRSP in 2007, participants with WSP in 2007 consistently showed that WSP is associated with more severe impairments. Participants who developed WSP had significantly higher average pain ratings, greater interference with general activity and sleep, higher levels of depression, and had higher body mass indexes (BMI). This clearly demonstrates that WSP represents a more severe clinical condition. These findings reiterate the relevance of this study, in that identifying risk factors associated with the development a worsening health condition can eventually help understand factors that are pertinent to preventing such a transition.

Other studies comparing individuals with regional spinal pain and those with WSP also consistently demonstrated poorer health status in WSP patients. Similar to the current study, Natvig (Natvig, et al., 2001) found that participants with WSP rated their overall pain severity, general health, and sleep quality as significantly worse as those

with chronic low back pain. They also reported that those individuals with WSP presented with significantly higher BMIs.

Another similar study demonstrated that individuals with WSP and FM, as compared to individuals with no pain and chronic regional pain, demonstrated a more severely impaired health status as measured by the short form-36 health survey (Bergman, 2005). This study indicated that individuals with FM and WSP presented with significantly more impaired physical functioning, role functioning, bodily pain, general health perception, vitality, social functioning, and mental health. In comparing SF-36 scores on most of these subscales (where higher scores indicate better physical functioning and well being), the chronic regional pain group had the highest scores at approximately 25% above the score of the WSP group, which had the second highest scores at approximately 20% above the FM group. In reviewing the findings from the current study and similar studies there is little doubt that developing WSP and/or FM represents a worsening clinical picture.

Assessing the transition to FM

After evaluating the transition from CRSP to WSP, the study team sought to determine the frequency and risk factors associated with a transition to FM. As noted in chapter 4, in order to determine which participants with WSP had developed FM, the research group invited the 129 participants with who presented with WSP in 2007 but did not carry a diagnosis of FM to OHSU to be evaluated for FM. Despite multiple invitations by mailing and phone, only 22.5% of those participants invited were willing to be examined. In retrospect, one wonders if more participants would have been willing to come in for an examination had the exams been held within a Kaiser facility closer to their homes. The participants were invited to come to OHSU during a time when gas prices were surprisingly high and individuals throughout the community were limiting their driving. To compound this effect, OHSU is notoriously difficult to navigate and find

parking. Nearly all participants were Kaiser members who are used to convenient clinic locations with nearby parking.

In order to assess the existence of a selection bias, the 2007 questionnaires of those who agreed to be examined compared to those who elected not to come to the study visit were analyzed. Those participants who declined to be examined did not significantly differ from those who were examined for FM. These two groups were compared in terms of age, gender, pain severity, pain-related disability, level of depression, BMI and pain related interference with activity or sleep. The results showing that responders did not significantly differ from non-responders on these variables, suggests that the two groups might be more similar than dissimilar. This could indicate that results found in the 22.5% of participants who were examined for FM might be extrapolated to the participants not examined.

Comparing FM participants to WSP participants without FM

As indicated by the diagnostic requirements of FM (necessitating the presence of WSP), WSP and FM are closely related on a continuum of disorders characterized by hyperalgesia and allodynia (Clauw, 2002). The presence of eleven or more out of eighteen designated tender point represents the one diagnostic criterion separating these two disorders. While some opinion leaders debate the diagnostic importance of these specified tender points (Clauw & Crofford, 2003), studies done to establish the diagnostic criteria found that the combination of WSP and eleven out of eighteen tender points provided the most sensitive, specific, and accurate criteria for diagnosing FM (Wolfe, et al., 1990). In fact, in the 1990 study that established the FM diagnostic criteria, tender points were the most powerful discriminator between patients with FM and control patients who had other rheumatic syndromes such as neck and back pain syndromes, rheumatoid arthritis and osteoarthritis. The research group also looked at symptoms

common to FM such as fatigue, morning stiffness, and sleep disturbance but found that these did not adequately discriminate between FM and the other rheumatic disorders.

While researchers call for a continued investigation into the physiological differences between these two similar disorders, two studies have set out to describe the clinical differences between patients with FM and those with WSP but not FM (individuals who present with less than eleven out of eighteen tender points). Using a sample from an epidemiological study of 7,637 individuals from the general population in Sweden, one study further investigated 345 participants who endorsed having WSP as indicated by a body drawing on a mailed questionnaire (Coster, et al., 2008). One hundred twenty five of these participants (36.2% response rate) agreed to a tender point examination. Out of the 125 participants, 70 (56.0%) fulfilled the ACR diagnostic criteria for WSP. When comparing these two groups of participants, those with FM and those with WSP but not FM (non-FM), participants with FM proved to be more often female and presented with significantly greater pain severity and interference, more severe depression and anxiety, worse FIQ scores, and worse health related quality of life as measured by the SF-36. Another study comparing these two groups investigated 192 patients seen in a rheumatology clinic (Pamuk, et al., 2006). While there was no estimation of what percentage of WSP patients had FM, the researchers did find similar results indicating that patients with FM demonstrated greater symptom severity and levels of distress. Specifically, this study found that patients with FM endorsed greater pain severity, more sleep disturbances, greater depression and anxiety, and greater neuropathic sensory disturbances as measured by the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS).

Similar to these studies, the current study demonstrated that these two groups differed on some clinical variables, albeit on a less clinically significant scale. The author compared the 40 participants diagnosed with FM to the seven participants who

presented with WSP but did not meet the diagnostic criteria for FM of eleven out of eighteen tender points. It should be emphasized that this small, uneven sample did not yield enough power to detect statistically significant differences, compelling one to consider the mean differences between the groups in terms of one's own judgment of clinical impact. Likely clinically significant differences between these two groups would include the finding that participants with FM presented with higher pain interference with activity (FM = mean of 5.7 on a 10 point scale (SD=2.5); non-FM = mean of 3.9 (SD=2.9)) and pain interference with sleep (FM = mean 5.4 on a 10 point scale (SD=2.9); non-FM = 4.1 (SD=3.4)) as compared to the non-FM participants. The two groups also demonstrated a likely clinically significant difference in depression severity. Participants with FM had a mean PHQ-9 score of 10.5 (SD=6.6) indicating a moderate level of depression, whereas non-FM participants yielded a mean of 4.0 (SD=1.6), indicating mild depression. Differing from the previous studies investigating this phenomenon, it seems that the two groups did not achieve a clinically significant difference in pain severity (mean average pain level: FM = 5.4 on a 10 point scale (SD=1.9); non-FM = 5.1 on a 10 point scale (SD=2.0)), BMI (mean BMI: FM = 31.8 kg/m^2 (SD=7.5); non-FM = 30.2 kg/m^2 (SD=6.5)), and gender (87.0% female in FM group and 71.0% female in non-FM group).

Interestingly, the current study differed substantially from previous estimates of the prevalence of FM in patients with WSP. The 129 participants in our study who demonstrated WSP but did not carry a FM diagnosis were invited to come to OHSU for a tender point examination. Although only 22.5% (29 participants) agreed to be examined, this response rate is moderately comparable to Coster et al. study (2006). Out of the participants willing to be examined, 75.9% (22 participants) met the ACR diagnostic criteria for FM. This rate of FM prevalence in participants with WSP is substantially higher than that found in the Coster et al. study. Even more disparate, two prominent FM

researchers estimate that only 20% of individuals with WSP meet the ACR criteria for FM (Clauw & Crofford, 2003). This author speculates that this disparity may be due to the stringent criteria used to identify participants with WSP in the current study. In examining body drawings on the 2007 questionnaires, this author strictly adhered to the ACR criteria defining WSP, and. only identified a participant as having WSP if they had true axial pain (shading of pain along the cervical, thoracic, lumbar, or sacral spine) and a prominent demonstration of pain in three out of four body quadrants. When examining the criteria used in the Coster et al. study, it seems that less rigid standards were used. For instance, Coster et al. used more encompassing sections of the body drawing when identifying spinal pain. The body drawing used in that study had 17 sections, whereas the body drawing used in the current study had 50 sections, allowing for a more detailed assessment of pain location. This author cannot compare diagnostic criteria used in the statement by Clauw and Crofford (2003) as these details were not provided. The specificity of pain locations and stringent criteria for the determination of WSP in this author's study could have lead to the less disparate findings between participants with FM and those with WSP but without FM. If this were the case, one might postulate that the current sample of WSP participants represent a group of patients closer to FM on the continuum of widespread hyperalgesia and allodynia.

Risk factors associated with a transition to WSP or FM

This study revealed that eight factors were associated with the transition from CRSP to WSP or FM. They included moderate or severe pain severity, female gender, history of abuse, family history of WSP, severe interference with general activity, morbid obesity, having one or more central sensitivity syndromes, and using more pain management strategies. Notably level of depression, pain duration, age, number of medication classes used, and receipt of disability benefits was not associated with this transition. Despite having fewer participants and therefore less power to examine the

risk factors for a transition from CRSP to FM, many of the risk factors associated with the development of WSP were comparable to the level of risk associated with the development of FM. As described in Chapter 4, a power analysis was done to examine the significance of these risk factors had more participants shown up to be examined for FM. As hypothesized, with similar levels of power, the risk factors for the development of both WSP and FM were relatively equivalent. Family history represented the exception to this similarity. This finding will be discussed in more depth below. The following sections discuss the risk factors associated with the development of WSP and FM in individuals with CRSP. These predictive variables represent possible areas for intervention or further understanding of this transition from a regional pain disorder to a widespread pain disorder.

Variables that predict a transition to WSP and FM can be broadly placed under the categories of gender, pain severity at baseline, history of abuse, pain interference with activity, pain management strategies used, BMI, family history of WSP, and the presence of other central sensitivity co-morbidities. The risk factors identified in this study compare well to the predictive variables found in other studies investigating this phenomenon, although this research team investigated a few unique factors. Common risk factors identified in studies investigating the transition to WSP and FM specifically in individuals with regional pain included higher pain intensity, gender, family history of chronic pain, gastrointestinal complaints, spinal pain, and impaired physical functioning (Bergman, et al., 2002; Forseth, et al., 1999; Lapossy, et al., 1995). Not surprisingly, studies investigating the transition to WSP or FM in individuals following a spinal injury also found pain severity following the accident to be a significant predictor (Buskila, 1997; Holm, et al., 2007; Wynne-Jones, et al., 2006).

While many of the predictive factors discovered in the current study compare to those of other studies, some variables that predicted the development of WSP or FM in other

studies did not predict this transition in the current study. One of the most prominent of these differences would be the finding in many studies that psychological distress predicts the onset of WSP and/or FM (Gupta, et al., 2007; Wynne-Jones, et al., 2006). While the current study did not replicate this finding, the author will discuss potential reasons for this discrepancy below. Similarly, some studies found that longer pain duration placed a person at risk for the development of WSP and FM (Forseth, et al., 1999; Natvig, et al., 2001), although this was not a significant predictor in the current study. The possible reasons why pain duration did not significantly predict the transition will be discussed in the following sections. Finally, some of the studies investigating the development of WSP or FM found that older age was a significant risk factor (Bergman, et al., 2002; Gupta, et al., 2007). Despite an accurate collection of this piece of data, the current study did not find this to be a significant predictor.

Seemingly unique to the current study was the investigation of central sensitivity co-morbidities and their association with the development of WSP and FM. While numerous investigators discuss the similar underlying pathology between these central sensitivity disorders, WSP, and FM, few have investigated the link between having these diagnoses and the development of WSP and FM. The current study found that the presence of these disorders did indeed impact the development of WSP and FM. A discussion of the implications of this finding will follow. Each predictive factor will be discussed individually in order to further explore the relationships established in this study.

Pain severity

In investigating the development of WSP and FM, the intensity of pain experienced by the participant with CRSP in 2001/2002 was the strongest predictor of developing both syndromes. As compared to a participant with mild pain, endorsing an average pain level in the severe pain range placed a person at nearly a five times greater likelihood of

developing WSP (OR=4.94, p<.001) and increased their risk of developing FM by 3.18 (p=.016). Alternatively, a person with moderate level pain had a 3.22 greater likelihood of developing WSP (p<.001) and a two and a half times greater chance of developing FM (p=.003). Increasing a person's odds of developing a pain syndrome associated with a significantly greater symptom burden by three to five times is a significant, clinically important finding. Studies investigating individuals with other regional pain disorders or neck injuries have also discovered the detrimental effects of enhanced pain severity, although not all such studies evaluated pain severity at baseline. In one study that also investigated a transition from chronic low back pain to WSP (Natvig, et al., 2001), patients who stated that they had "more than mild pain" were significantly more likely to develop WSP with an OR of 6.03, which is quite comparable to our findings. In two studies investigating the development of FM following whiplash in a motor vehicle accident, it was reported that the patient rated severity of the neck injury was significantly associated with the development of FM (Buskila, 1997; Wynne-Jones, et al., 2006). Another study investigating the same phenomenon specifically assessed baseline neck pain severity on a visual analogue scale (Holm, et al., 2007). The researchers demonstrated that, as compared to a pain rating of 0-30, having a VAS of 55-100 was associated with a 4.5 times greater likelihood of developing FM.

The clear finding that enhanced pain severity places a person at risk for the development of WSP and FM can also be supported by research findings in other arenas. Research demonstrates that increased intensity of pain messages can enhance the cumulative effect of persistent nociceptive input, placing a person at risk for increased sensitization of the central nervous system (Flor, 2003). This biological finding can support the clinical evidence that the development of chronic pain from acute pain states have also demonstrated that pain severity is the most consistent factor in the development of a chronic pain state (Edwards, 2005). This research time and again

demonstrates that in pain conditions such as herpes zoster, spinal cord injury, and amputation, severity of pain from the acute condition regularly predicts the development of persistent pain at a later time. This same phenomenon could explain why, in the current study, moderate and severe levels of spinal pain helped produced an expansion of chronic pain from the spinal region to the total body. While research in herpes zoster demonstrates that increased pain severity with the zoster rash produces persistent pain in that region, similarly increased pain severity in the spine might produce an ongoing sensitized state that translates to WSP.

Edwards (2005) presents one hypothesis that could explain the findings of the current study and those demonstrating that increased pain severity predicts the development of chronic pain. While past studies consistently demonstrate that people with chronic pain syndromes such as chronic low back pain and fibromyalgia present with decreased pain thresholds, enhanced temporal summation, and deficient endogenous pain inhibition (Giesecke, et al., 2004; Gracely, et al., 2002), these cross sectional studies leave one to wonder whether the altered pain sensitivity is a product of the chronic pain syndrome or, perhaps, preceded the syndrome and therefore is a risk factor for the development of WSP, FM, or associated disorders of pain processing. In his review, Edwards offers support for the latter, recognizing that there exists individual differences in the processing of noxious stimulation, even in healthy individuals, that might predict the development of disorders of altered pain sensitivity. This hypothesis can be used to understand the definitive findings in this study that increased pain severity preceded and predicted the development of WSP and FM. Using Edwards hypothesis, one might postulate that pain severity for some participants in 2001/2002 could be interpreted as a proxy for enhanced pain sensitivity and/or reduced endogenous inhibition of pain and therefore served as a predictor for the development of enhanced central sensitivity. While these biological individual differences would in no way account for all the variance

in pain severity (one would still need to account for behavioral aggravators and alleviators of pain); this hypothesis presents an interesting frame in which to view these results. If the research group, in 2001/2002, had performed testing to assess pain thresholds, temporal summation, and diffuse noxious inhibitory control, would these finding correlate with pain severity and also have served as a predictor for the development of WSP and FM? Logically the next step needed to answer this question would be a longitudinal, prospective study. Pain sensitivity measures such as those suggested would be performed at baseline on participants with spinal pain to identify those with enhanced pain sensitivity and deficient endogenous pain inhibition. Frequent follow up to assess for the development of WSP and FM would provide accurate knowledge regarding the timing of transition. Continued follow up and testing to evaluate pain sensitivity would provide information on changes in pain threshold with the establishment of WSP and/or FM.

Taking a more simplistic view of the finding that pain severity predicts the transition to WSP and FM, one cannot ignore the implications this has for the treatment of CRSP. Knowing that someone in severe pain is nearly five times more likely to develop WSP places a renewed commitment to the adequate management of pain in patients with chronic pain syndromes. Aggressive pain management in the form of physical modalities, self care management education, behavioral modification, and the proper use of appropriate medications might mitigate pain severity in CRSP.

Gender

Consistent with the knowledge that WSP and FM disproportionately affect women, being female seems to place one at a higher risk of developing WSP and FM. The current study found that females were 2.35 times more likely to develop WSP ($p<.001$) and 3.35 times more likely to develop FM ($p=.001$). This level of risk is consistent with the studies that found female gender to be a significant predictor for the development of

WSP from a chronic regional pain disorder, including Natvig (Natvig, et al., 2001) who found an OR of 3.71 for association of gender and the development of WSP (OR=3.14 in the current study). A prospective study performed in school age children also found female gender to significantly predict the development of WSP with an OR of 1.4 (Mikkelsson, et al., 2008).

With the confirmation that being female places an individual at a greater risk of developing WSP and FM, one naturally considers the mechanism behind this phenomenon. One reputable group that has performed many epidemiological studies investigating the risk factors for the development of WSP investigated this very question (Macfarlane, Blinkhorn, Worthington, Davies, & Macfarlane, 2002). Their research found that certain sex hormonal factors, including oral contraceptive use, hormone replacement therapy, age of onset or cessation of menstruation, duration of the menstrual cycle, or the presence of painful periods did not correlate with the development of WSP. A consensus statement on the research of sex differences in pain also noted that after an extensive review of studies, psychological and social variables might often explain more of the variance in pain than do biological variables (Greenspan, et al., 2007). That being said, the authors of this review do acknowledge and discuss the evidence of different clinical pain mechanisms operating in men and women, highlighting the complex intersection between biological and psychosocial factors. At the forefront of this research is the finding that temporal summation, a clinical correlate for wind-up, is enhanced in females. Wind-up can be seen as a precursor to central sensitization, the altered neurological processing thought to underlie some pain syndromes such as WSP, FM, irritable bowel and bladder syndrome. In fact, these disorders are decidedly more prevalent in the female population. Other research has demonstrated that females experience decreased thresholds of pressure pain, electrical pain and thermal pain although this finding could be interpreted through a biological lens of true physiological

differences or through a psychosocial lens of social acceptance of greater pain reporting by women.

Despite the ambiguity regarding the underlying mechanisms, the evidence of gender differences in chronically painful syndromes is clear given research such as this current study demonstrating a greater risk of the development of WSP and FM in women and studies demonstrating a greater prevalence of several pain disorders in the female population. The implication of this finding is significant given the personal, social, and financial impact of chronic pain disorders. The seriousness of this fact is reinforced by the recommendation of a recent consensus statement that all pain research include both sexes and if only one sex can be studied, the researchers choose to study females (Greenspan, et al., 2007).

Central sensitization syndromes

Recent research has begun to investigate a group of syndromes that seem to share a common pathophysiological basis. Although once described as psychosomatic syndromes, unexplained syndromes, or idiopathic pain syndromes, a shared background of central sensitization more accurately describes the unifying feature of these syndromes. Disorders typically falling under the umbrella of central sensitization syndromes include WSP, FM, IBS, irritable bladder syndrome, migraine, tempromandibular joint disorder (TMD), chronic fatigue syndrome, restless leg syndrome, and pelvic pain syndromes (vulvar vestibulitis, vulvodynia and prostodynia). As has been found in a subset of patients with CRSP and in all patients with WSP and FM, patients with other central sensitization syndromes experience enhanced pain perception as result of dysregulation in peripheral and central nervous system pathways (Diatchenko, et al., 2006). Specifically, these syndromes are characterized by hyperalgesia, allodynia, expansion of receptive fields, and prolonged nociceptive discharge. As research increases on these disorders and the central sensitization link

that binds them, Yunus proposes criteria for calling a disorder a central sensitization syndrome; namely that the specific disorder is associated with other central sensitization syndromes and has evidence of central sensitization (Yunus, 2008).

The four central sensitization syndromes investigated in the current study included IBS, irritable bladder syndrome, migraine, and restless leg syndrome. These four disorders meet the criteria specified by Yunus (2008) in qualifying as central sensitization syndromes. Extensive research has documented the presence of central sensitization in IBS and its common co-occurrence with FM. Several studies in patients with IBS have documented rectal and cutaneous pain hypersensitivity and allodynia in response to stimuli such as rectal balloon pressure and heat causing diffuse pain into the participant's perineum, lower abdomen, and low back (Yunus, 2007). Similar studies have been performed on patients with irritable bladder syndrome and found enhanced pain sensitivity in response to bladder distention and hyperalgesia on the forearm. In patients with migraines, researchers have documented evidence of central sensitization when demonstrating hyperalgesia in migraine patients with mechanical pressure, heat, and cold at cranial and extracranial sites (Yunus, 2007). Lastly, central sensitization in restless leg syndrome has been demonstrated through hyperalgesia found in the upper and lower extremities along with an enhanced nociceptive spinal reflex on the medial plantar nerve.

Another feature connecting these syndromes is the fact that they frequently co-occur, likely due to their common biophysical basis. It has commonly been understood that several disorders frequently present with FM. In a discussion of these disorders, Clauw proposes that pain and tenderness lie on a continuum within the population and that individuals presenting with central sensitization syndromes lie at one end of this spectrum (Clauw, 2002). This proposition is supported by evidence of their co-occurrence, perhaps demonstrating that a person with one central sensitization

syndrome is at risk for others due to an underlying pain and sensory processing disorder. One study demonstrated this phenomenon in an epidemiological study of the general population (Aggarwal, McBeth, Zakrzewska, Lunt, & Macfarlane, 2006). These authors found that 27% of their study sample presented with one or more of their identified central sensitization syndromes (TMD, IBS, WSP, and chronic fatigue syndrome). Demonstrating that these syndromes frequently co-occur, they discovered that 6% of the sample presented with two of these disorders, 2% with three disorders, and 1% had all four disorders. The current study also investigated this phenomenon looking at the central sensitization disorders of IBS, irritable bladder syndrome, migraine, and restless leg syndrome. In this population of participants with a history of CRSP, 47.7% presented with one or more central sensitization syndromes with 30.9% having one central sensitization syndrome, 13.7% with two syndromes, 2.5% with three syndromes, and 0.6% with all four central sensitization syndromes. Slightly more participants in the current study presented with central sensitization syndromes as compared to the Aggarwal et al. study, perhaps demonstrating a greater risk among participants with CRSP as compared to the general population.

While the co-occurrence of central sensitization syndromes has been relatively well established in the literature, less clear is the predictive nature of having one central sensitization syndrome on the development of another such syndrome. Theoretically, having one central sensitization syndrome should predict the onset of another if these conditions do indeed represent different manifestations of the same underlying pathophysiology, namely central sensitization. The current study added evidence to this theory by demonstrating that having a central sensitization syndrome predicted the onset of WSP and FM. Having any one of these syndromes made a person twice as likely to develop WSP or FM. Presenting with two or more of these syndromes made a person nearly three times as likely to develop WSP ($RR=2.79$, $p<.001$). This provides some

evidence that individuals with multiple regional central sensitization syndromes are at greater risk for expansion of receptive fields into the development of whole body sensitization.

Demonstrating that these co-morbidities co-exist and predict the onset of WSP and FM further validates the importance of investigating these conditions in relation to one another. Recognizing that there exists a continuum with patients affected by these central sensitization disorders allows one to identify a subgroup of patients who are at high risk for the development of various central sensitization disorders. Studying this group of patients could allow investigators to learn more about central sensitization and perhaps how to mitigate the worsening of this phenomenon. In terms of clinical care, practitioners should recognize that patients with one or more central sensitization syndromes are at risk for developing other associated syndromes and work to alter other risk factors amenable to treatment or lifestyle modifications. Mitigating the development of other central sensitization syndromes would significantly affect both the quality of life of patients and cost of care as one investigator notes that central sensitization syndromes represent the most common condition that a future physician will treat (Yunus, 2008).

History of abuse

As has been found in many other studies, the current study found a significant relationship between a history of abuse as a child and/or as an adult and the development of WSP and FM. To be specific, a participant with CRSP who had been abused as an adult was 2.63 times more likely to develop WSP ($p<.001$), while abuse as a child led to a 73.3% increased chance of developing WSP. This study also demonstrated that a history of abuse at any point in one's life made participants twice as likely to develop FM. As noted, these findings are consistent with several other studies that have documented a relationship between patients with chronic pain and a

retrospective account of having been abused as a child or adult. In a recent meta-analysis, results from nine studies confirmed that individuals who have experienced abuse or neglect in childhood are more likely to develop an increased number of pain symptoms in adulthood (Davis, et al., 2005). Alternatively, this meta-analysis documented, from eight studies, that individuals with chronic pain had a greater likelihood of having had experienced abuse or neglect as a child. Another study investigating pain and abuse in a community sample of psychologically distressed individuals demonstrated that the prevalence of a history of abuse was more than five times greater in those individuals who presented with a high number of tender points as compared to those participants with a low number of tender points (McBeth, Macfarlane, Benjamin, Morris, & Silman, 1999). Their multivariate analysis revealed that childhood abuse was the strongest predictor of a high tender point count. Not only is there significant interest in the association between abuse and generalized chronic pain, much interest has been devoted to the relationship between a history of abuse, WSP and FM. Studies investigating this relationship document that patients with FM more frequently report a history of childhood or adult-onset physical or sexual abuse as compared to healthy controls, patients with rheumatoid arthritis, or “explained pain” (Ciccone, et al., 2005). The current study, along with multiple other studies, clearly demonstrates a relationship between a history of abuse and pain; be it chronic regional pain, WSP, or FM.

That being said continued study into this documented association reveals a complex and not fully understood relationship. The current study, along with most other studies investigating this phenomenon, utilizes a retrospective review of abuse history in patients seeking care for their pain. Researchers investigating this relationship have documented some limitations of this kind of review. The first involves a potential for reporting bias among those individuals seeking care for their pain. This potential bias

suggests that treatment seeking individuals may be more likely to report a history of abuse or pain symptoms. While investigating this potential recall or reporting bias, McBeth and colleagues postulate that patients with chronic pain more extensively search past experiences in an effort to identify a cause for their symptoms (McBeth, Morris, et al., 2001). These authors termed this “effort after meaning”. In their investigation of adverse childhood events and the development of chronic pain (widespread and regional), they found that subjects with WSP over-reported the number of hospitalizations and operations they had undergone.

Another mechanism used to investigate biased reporting or recall is to compare treatment seeking individuals (patients) with non-treatment seeking individuals with similar levels of pain and functional interference (non-patients). A meta-analysis performed by Davis et al. (2005) reviewed two studies comparing chronic pain patients with non-patients. Indeed, patients were more likely to report a history of abuse. Utilizing a community sample is another mechanism by which researchers attempt to minimize response bias due to the seeking of treatment. A group of prominent researchers in this field used this methodology to gain greater insight into the relationship between abuse and FM (Ciccone, et al., 2005). They found that only rape victims were more likely to have FM as compared to controls; no other sexual or physical abuse events were associated with having FM.

This group also used a technique that enhances accuracy of recall regarding events of abuse, perhaps mitigating the challenge of response bias. In their study, Ciccone and colleagues (2005) used a structured interview that asks about specific events constituting sexual or physical abuse. For instance, the interview asks the participants whether anyone has succeeded in touching sex parts of their body, made them have sex or attacked them with the intent to seriously injure them. In contrast to simply asking about a history of abuse, using this form of questioning led to different, perhaps more

accurate results regarding the relationship between abuse and the development of FM. These authors found that only rape was more prevalent in the FM group as compared to the controls. No other physical or sexual abuse event was more prevalent in participants with FM. The meaning behind these findings could be interpreted in light of the phenomenon that McBeth and colleagues (2001) term “effort after meaning”. Perhaps patients with FM label the events in question as abuse whereas individuals without FM or non-care seeking individuals with pain would not identify themselves as having been abused despite also having undergone these same events. In the Ciccione et al. study (2005), 28.9% of women with FM responded that they had been physically attacked while 28.9% of women without FM also reported a history of being physically attacked. Perhaps if these same patients were merely asked about a history of physical abuse, the women with FM might endorse a history of physical abuse whereas women without FM might not identify this event as abuse. Perhaps women with FM label these events as abuse in an effort to ascribe a cause or meaning to their symptoms. It must be noted that the current study simply asked about a presence of being abused as an adult or child, allowing the definition of abuse to rely solely on the participant’s label of their past experience. Therefore the results indicating that a history of abuse is associated with the development of WSP and FM must be interpreted with caution.

Body mass index

While past descriptions of FM have noted a tendency for patients, on average, to be overweight, few, if any, studies have investigated whether being overweight places a person at risk for the development of WSP and/or FM or whether being overweight is a result of the pain, fatigue, and limited mobility that comes with such a pain disorder. This study has now provided one indication that morbid obesity might be associated with the development of WSP and FM. The currently study found that participants with a BMI of 40 kg/m^2 or greater had a 2.68 times greater chance of developing WSP (p=.002) and

had an 85.3% greater chance of developing FM (p=.152). Simply being overweight or moderately obese did not increase one's risk of developing WSP or FM, only the group of individuals who were morbidly obese where at a significantly higher risk for the development of these disorders. This finding is significant as it provides indication that extreme obesity does precede the development of WSP or FM and places one at risk for the transition to these disorders. Surprisingly, other studies investigating the development of WSP and FM have not looked at BMI as a potential risk factor. To this author's knowledge, it appears that the authors of these studies did not collect this measurement at baseline evaluations.

The relationship between BMI and the development of WSP or FM leads one to consider the impact of weight loss on these conditions. Two studies have investigated this very question in samples of individuals with FM. The first studied the impact that gastric bypass surgery had on morbidly obese individuals with FM (average BMI of 51 kg/m^2) (Hooper, et al., 2007). Twelve months following the surgery and decreasing the average participant's BMI to 36 kg/m^2, eleven out of the twelve participants with baseline FM no longer met the ACR criteria for FM. This study is limited by small sample size, lack of long term follow up or replication by other investigators. Although this study investigated a drastic measure for weight loss, the outcome has implications for the current study given that having a BMI over 40 kg/m^2 significantly predicted a transition to WSP. While it would not be prudent to recommend gastric bypass surgery for most patients with CRSP and morbid obesity, the results of the Hooper study and this author's study could imply that maintaining one's BMI under 40 kg/m^2 could decrease the risk of transitioning to WSP.

A second study investigating a more moderate approach to weight loss in FM, specifically a behavioral weight loss program, also found significant benefit with a decreased BMI (Shapiro, et al., 2005). With an average decrease in BMI of 1.6 kg/m^2,

participants experienced improvements in the Fibromyalgia Impact Questionnaire (FIQ) and pain severity. In fact, reduced BMI predicted improvements in both FIQ and pain scores. In contrast to these findings, when comparing FM patients with a BMI of below 25 kg/m^2 to those with a BMI of greater than 25 kg/m^2 Yunus et. al found that these two groups of FM patients did not significantly differ in terms of pain, fatigue, or global disease severity but that the difference in number of tender points approached significance at p= .015 (Yunus, Arslan, & Aldag, 2002).

A subset of studies, along with the results of the current study, suggests that BMI might have a relationship to the development and severity of WSP and FM. This knowledge should affect practice in a cautious but significant way. Patients with chronic pain too often hear from uninformed practitioners that if only they would lose weight, their pain would go away. The findings from these studies do not at all indicate that weight loss alone will lead to the resolution of their symptoms. The results from these studies do indicate that severe obesity leads to an increased risk for worsening of one's condition and weight loss might lessen the severity of the individual's symptoms. The message to patients must be one that encourages them to work toward an ideal weight, taking into consideration the limits placed on exercise by having a of a chronic pain condition.

Family history

Due to the inability to collect genetic information on the participants, this study used familial aggregation as a proxy for determining the genetic risk of developing WSP or FM. This method has been used in other studies to estimate the heritability of many disorders, including WSP and FM. Considerably more data exists on the genetic influences and heritability of FM as compared to WSP, in fact one article written in 2006 stated that no previous studies had demonstrated the familial risk of WSP (Kato, Sullivan, Evengard, Pedersen, et al., 2006). To investigate the genetic risk of developing

WSP, Kato et al. evaluated 15,950 twin pairs for the presence of WSP, using the standard ACR criteria. The investigators found that genetic factors accounted for 48-54% of the total variance in WSP with less variation coming from environmental factors. The authors note that this finding reflects similar genetic influences as compared to other illnesses such as rheumatic diseases and osteoarthritis, where familial aggregation has been more substantially demonstrated.

The current study adds to the minimal data on familial aggregation in WSP and demonstrates that having a family history of WSP places one at a significantly greater risk of developing WSP. In looking at the history of WSP in participants' immediate and extended family; having a family history of WSP made the participant twice as likely to develop WSP. This finding allows practitioners to easily identify patients with CRSP who are at risk for the development of WSP. Although one cannot modify this particular risk factor, knowing that a person is at increased risk for the development of WSP can increase the importance of mitigating modifiable risk factors.

As noted, familial aggregation in FM has been more consistently studied and documented. Buskila and Sarzi-Puttini reviewed the evidence demonstrating the high familial aggregation in FM (Buskila & Sarzi-Puttini, 2006). They noted that in one study the odds of a participant with FM having a relative with FM was 8.5. In another study described by Buskila and Sarzi-Puttini, 26% of patients with FM had blood relatives with FM. Despite the commonly held knowledge that FM is a hereditary disorder, the current study did not find that having a family history of FM predicted the development of FM. This negative finding is most likely related to the lack of clarity in collecting this variable. Participants were asked to identify (out of a list of relatives) which relatives described having pain and tenderness in many areas of their body along with being fatigued or tired much of the time. In parenthesis the questionnaire indicated that this described FM. To put this in context, one must recognize that the majority of the participants completing

this questionnaire did not have FM and might never have heard of this disorder. A surprising number of people indicated having a family history of FM. In fact, 41.3% of participants indicated that someone in their family had FM. This is well over the typical population prevalence of FM. This may or may not indicate a potential misinterpretation of the question. This author postulates that participants read the description of FM and had a vague memory of one of their family members describing aches and pains and feeling tired. In a future study investigating this phenomenon, one might simply ask if the participant's family members ever reported having FM or fibrositis. Presumably, if the participant truly had a family member with FM, they would recognize the word. While this would exclude the older relatives who might not have been diagnosed prior to the establishment of this diagnosis, this author suspects that under-representing the familial presence of FM would be more accurate than the over-representation that occurred.

While the current study used familial aggregation as a proxy for genetics, the finding of the heritability of WSP supports the evidence produced by numerous recent genetic studies. These studies have demonstrated that, compared to healthy controls, individuals with FM (and therefore WSP) have genetic polymorphisms in serotonin, dopamine, and catecholamine systems (Fillingim, et al., 2008). Specifically, patients with FM have been found to have a variant allele in the COMT gene which codes for an enzyme that degrades dopamine, epinephrine, and norepinephrine, all neurotransmitters involved in pain transmission. Genotyping of common single nucleotide polymorphisms (SNPs) across the COMT gene can also discriminate between individuals with low, average, and high pain sensitivity (Limer, Nicholl, Thomson, & McBeth, 2008); findings quite relevant to the study of disorders such as WSP and FM. Genetic studies have also identified several associations between FM and genes that regulate serotonin and variants of the serotonin transporter, supporting the notion that patients with FM have altered serotoninergic pathways. Specifically these studies have demonstrated

significantly different genetic polymorphisms in genes associated with serotonin transport and receptors. Alterations in the serotonergic pathways correspond well with the clinical finding that FM patients present with diminished diffuse noxious inhibitory control (DNIC) effects. Deficiencies in DNIC have been demonstrated in patients with FM in an experimental setting where DNIC reduced wind up in male healthy controls but not FM patients (Staud, et al., 2003). Given the importance of the serotoninergic inhibitory pathway to the efficiency of DNIC, genetic polymorphisms in the serotonin transporter gene and serotonin receptor subunits likely play a role in the altered pain modulation in FM. Another potential genetic contribution altered pain processing is the finding that one variant allele in the mu opioid receptor gene (OPRM1) has been associated with reduced pain sensitivity and has been found to be significantly lower in patients with chronic pain (Fillingim, et al., 2008). The multitude of findings demonstrating genetic variations associated with alterations in pain perception support the findings of heritability of WSP in this study. The clear demonstration of genetic contributions to the presence of FM reiterates the need for an improved measure of family history for FM.

Pain management strategies used in 2001/2002

Use of multi-modal strategies frequently throughout the day is the basic principle for managing persistent chronic pain. The pain management community educates patients to stay ahead of their pain by treating it continually with different modalities that address the various facets of chronic pain. The study team hypothesized that patients with more pain management tools would achieve more successful control of their pain and therefore be at less risk for the development of WSP and FM. Contrary to the hypothesis, analyses revealed a different relationship. Participants who used more pain management strategies in 2001/2002 had an increased risk of developing WSP and FM. Although unexpected, this finding is logical. It is likely that participants with more

extensive and intrusive pain utilized more pain management strategies in order to mitigate their pain interference. Participants with less bothersome pain would not need to implement as many modalities to successfully manage their pain.

A limitation of this variable was the need to recall the modalities used in 2001/2002. While the participants were likely accurate in describing modalities that they had used in the past, the exact timing of their use might have been less than accurate. Instead of describing the pain management tools used in this specific one to two year period, this variable likely captured the modalities used in a past two to three year period. One could argue that the exact timing of the participant's use of these strategies mattered less than being sure that their response reflected modalities used more than two or three years ago to accurately capture treatments used prior to a possible transition to WSP or FM. The wording of the question likely ensured that the participant understood the researchers' interest in past use of pain management strategies and not current use.

Medication usage

In a similar notion to the principle of using multi-modal pain management strategies to address the many facets of chronic pain, the pain management community advocates using medications with different mechanisms of action to treat the different physiological components of chronic pain. Using different classes of medications to treat a patient's pain ensures that the practitioner is addressing components such as inflammation, nerve irritation, muscle spasm, peripheral or central sensitization, mood disturbances and disturbances in general nociception. This principle would seem especially true for individuals with chronic spinal pain as this type of pain incorporates all of these mechanisms previously mentioned. Interestingly, the average participant in the current study only used two medication classes in 2001/2002. Perhaps due to the low number of medication classes used or the limited variance in number of classes used, this variable did not significantly predict a transition to WSP or FM. The study team had hypothesized

that using more medication classes would have served to moderately protect a participant from the expansion of central sensitization through minimizing the negative impact of inflammation, nerve irritation, and nociception on the central nervous system. Of note, the least frequently used medications were those to treat nerve irritation (tricyclic antidepressants, anticonvulsants, or selective serotonin and norepinephrine reuptake inhibitors). Therefore the nerve component of participants' pain may not have been adequately treated. An argument could be made that inadequately controlling nerve pain in chronic spinal pain might perpetuate central sensitization and the spread of receptive fields.

Another treatment recommendation advocated by the pain management community is the use of long acting opioids for the treatment of chronic pain, when opioids are needed on a regular basis. Although 50% of the sample described having moderate or severe pain and 75% expressed moderate or severe pain interference with general activity, only 16% of the sample was taking long acting opioids. The overwhelming majority (70%) was using short acting opiates, reiterating that the participants' pain severity was severe enough to warrant the use of opioids. Anecdotal evidence by practitioners suggests that around the clock dosing of opioids with long acting formulations provide more stable control of pain and improved adherence, although there has been a lack of reliable studies investigating this observation (Chou, Ballantyne, Fanciullo, Fine, & Miaskowski, 2009). While the scope of this study does not allow for understanding the impact of the limited use of long acting opioids and medications to treat nerve pain, future studies could substantially inform future treatment strategies regarding opioid usage in this population.

Depression

Mood disorders, such as a history of depression and anxiety, and psychological factors have been a somewhat consistent finding among predictors for the development

of WSP and FM. One study similar to the current one found that women with self assessed depression had an OR of 6.3; that is a six-fold risk of developing FM (Forseth, et al., 1999). Two studies investigating a transition to FM following a neck injury in a motor vehicle accident found that psychological factors such as health anxiety and an increased score on a validated depression screening tool to be significantly associated with transition to FM (Holm, et al., 2007; Wynne-Jones, et al., 2006).

Studies investigating the development of WSP in population studies of healthy individuals have also noted the increased risk in persons with psychological distress. One prominent group performed two large population based studies investigating risk factors for the development of WSP. Their prospective study demonstrated that scoring in the upper tertiles of the General Health Questionnaire (a measure of psychological distress) and a health anxiety measurement tool significantly predicted the development of WSP with an OR of between 1.5 and two, although these variables lost significance in the multivariate analysis (McBeth, Macfarlane, Benjamin, et al., 2001). Similar findings in their second large prospective study also demonstrated that increased levels of depression and anxiety as indicated by the Hospital Anxiety and Depression Scale predicted the development of WSP with ORs between two and three (Gupta, et al., 2007). These also lost significance in the multivariate analysis.

Despite a somewhat clear demonstration in other studies that some level of psychological distress is associated with the development of WSP and FM, the current study did not find a significant association. An explanation for this negative finding might be attributed to the measurement of this variable in 2001/2002. Collection of data in 2001/2002 was for clinical, not research purposes. The authors of this questionnaire wanted merely to get a rough picture of whether the patient was experiencing depressive symptoms. Although the questionnaire used phrases from the PHQ-9 depression screening tool, the patient was asked to place a check mark by the symptoms that s/he

had experienced in the past two weeks; not the way this tool has been validated for use in the clinical or research environments. To compound the less than ideal way this variable was collected, patients completing this clinical questionnaire frequently did not answer this series of questions. The rate of missing data on the depression questions exceeded 20%. While this would be an alarming rate of missing data on a questionnaire designed and distributed for research, the circumstances under which these patients completed this questionnaire in 2001/2002 is more forgiving. Most patients being seen by the Kaiser Pain Clinic have been in pain for years and have likely been told by more than one provider that pain is psychologically produced. These circumstances might influence whether or not someone answers questions about depressive symptoms prior to meeting with someone about their unrelenting pain. To reinforce the impact of these circumstances, when these same participants completed the validated form of the PHQ-9 in 2007, missing data was less than two percent.

Despite the negative findings of the current study, the impact of psychological distress on the development of WSP and FM remains important. To be sure, these findings do not perpetuate the ignorant and false belief that an individual's experience of WSP stems from psychiatric illness and imagined pain. The relationship between pain and depression more likely stems from the closely related neurotransmission of these two disorders. Feedback from the musculoskeletal system associated with routine functioning is normally suppressed by descending noradrenergic and serotonergic pathways so that attention can be placed on more important sensory information. Should a person experience dysfunction within these inhibitory pathways, as occurs in depression, routine sensory input from the musculoskeletal system is no longer suppressed and can be interpreted as painful (Stahl & Briley, 2004). The fact that both pain and depression respond to medications affecting serotonin and norepinephrine neurotransmission supports the likelihood of a common causal factor underlying these

disorders. This is only one mechanism connecting pain and psychological distress. As described in the section on genetics, researchers have identified variations in SNPs that are associated with pain regulation but also predict the occurrence of anxiety (Slade, et al., 2007). Despite this biological basis, one research group at the forefront of genetic research in pain advocates that psychological factors such as depression, anxiety, and perceived stress are risk factors for the development of TMD independent of this genetic variation (Slade, et al., 2007). Their study demonstrating the independent predictive nature of these variables highlights the complex nature of psychological distress and the development of disorders of altered pain sensitivity and reinforces the necessity of continued work in this area.

Other research into the relationship between psychological distress and the development of WSP and FM has investigated alterations in the hypothalamic-pituitary-adrenal (HPA) stress axis. While multiple studies have demonstrated HPA alterations in individuals already diagnosed with WSP or FM, one group prospectively examined HPA function in healthy adults prior to the development of these disorders (McBeth, et al., 2007). This group found that alterations in participants' HPA axis, as evidenced by higher post dexamethasone serum cortisol, lower morning salivary cortisol, and higher evening salivary cortisol, predicted the new onset of WSP. The authors propose that altered HPA axis function mediates the relationship between psychosocial risk factors and the onset of WSP. The evidence and theories that have come from extensive research on this subject confirm the need for a greater exploration into the mechanisms behind the association between psychological factors and the development of WSP and FM.

Researchers investigating another connection between psychological distress and pain demonstrate that cholecystokinin (CCK) may play a role linking anxiety and pain. This neuropeptide has been found to play a role in the generation of anxiety, pro-

nociception, and anxiety induced hyperalgesia (nocebo response) (Lovick, 2008). Animal and human studies have demonstrated both the anxiogenic effects of CCK injections and the ability of a CCK antagonist to block this reaction. The role of CCK in chronic pain states has also been discussed given the pro-nociceptive properties of this neuropeptide. Research documents that CCK blocks the anti-nociceptive effects of exogenous and endogenous opioids and could play a role in the decreased responsiveness of neuropathic pain to opioids (Wiesenfeld-Hallin, Xu, & Hokfelt, 2002). In neuropathic pain, it has been suggested that CCK may be one mechanism that enhances the facilitation of spinal nociception in the periaqueductal grey matter. While these studies demonstrate the effects of CCK on pain and anxiety independently, research on the nocebo response demonstrates that CCK might actually be one link between pain and anxiety. One group of researchers demonstrated that nocebo hyperalgesia is mediated by anticipatory anxiety through the blockade of the hyperalgesic response with diazepam (Colloca & Benedetti, 2007). These researchers were also able to block nocebo hyperalgesia with a CCK antagonist, indicating that CCK might play a role in mediating anxiety induced hyperalgesia. Animal models have also demonstrated that nociceptive stimulation causes a significantly larger increase in cortical CCK levels in stressed rats as compared to non-stressed rats (Lovick). These researchers have demonstrated that this enhanced responsiveness to nociceptive stimuli in stressed rats can be prevented with pre-treatment of a CCK antagonist. Taken together, these studies demonstrate yet another physiological link between psychological distress and chronic pain states.

Pain duration

Increased duration of pain is thought to enhance the development of central sensitization through long-lasting nociceptive input that sensitizes the spinal cord neurons to incoming stimuli (Flor, 2003; Katz & Rothenberg, 2005; Price & Staud, 2005;

Zusman, 2002). Studies performed by Flor and colleagues have demonstrated that patients with chronic low back pain undergo neuroplastic changes that alter the somatosensory representation of the back in the cortex. These changes lead to an expansion of pain sensitivity from the lower back to areas outside the original site of chronic pain. These studies demonstrate that the amount of expansion of the cortical representation is positively correlated with chronicity (Flor, 2003; Flor, et al., 1997). These findings could explain the mechanism causing increased duration of pain to be a risk factor for a transition from chronic regional pain to WSP and FM; a result found in two studies investigating the development of these two disorders (Forseth, et al., 1999; Natvig, et al., 2001).

Despite the evidence suggesting that pain duration is associated with enhanced central sensitization and therefore might help predict a transition to WSP or FM, this finding was not demonstrated in the current study. One explanation for this negative finding could be due to the lack of clarity of the question asked on the 2001/2002 questionnaire. Participants completed this questionnaire prior to being seen by the Pain Clinic in 2001/2002. The questionnaire asked, “When did your pain start”. While the question aimed to elicit the number of years the participant had been in pain, this author speculates that patients may have interpreted this question to mean how long the particular symptom for which they were seeking treatment had been present. For instance, although a participant might have experienced chronic back pain for years, a worsening of their radicular pain might have precipitated a referral to the pain clinic. The patient might have thought that their ten to twenty year history of back pain was less relevant to the consulting physician than the fact that their radicular pain had become severe eight months ago. The author suspects this due to the fact that the majority of patients (67.3%) reported being in pain for three years or less despite the fact that the Pain Clinic treats only patients with a known history of chronic pain and typically sees

the patients who are not successfully treated in the primary care or physiatry departments. In retrospect this author should have more clearly asked this question on the 2007 study questionnaire which was devised purposefully for this research study.

Relation of Findings to Conceptual Framework

The diagnoses studied in this investigation share a common pathophysiological process, namely central sensitization. It is through the altered pain processing caused by central sensitization that the regional disorders of chronic spinal pain develop into a widespread pain disorder. Variables thought to perpetuate this transition were drawn from three categories of risk factors; those known to influence the development of central sensitization, factors that precede the occurrence of WSP and FM, or characteristics that co-occur in patients with WSP and FM. Significant risk factors found in the transition from CRSP to WSP or FM were represented in each of these three categories. Development of WSP and FM was significantly predicted by pain severity, family history, gender, and history of abuse; all factors known to influence the development of central sensitization. Variables known to precede WSP and FM also significantly predicted a transition to these disorders, including family history, being of female gender, and a history of abuse. Results of this study also demonstrated that having one or more central sensitivity syndromes, being morbidly obese, and pain interference with general activity were also significant predictors that fell within the category of variables that frequently co-occur with WSP and FM. Non-significant predictive factors were also represented in all three over-arching categories of variables. Out of factors thought to cause central sensitization, duration of pain, number of spinal surgeries, history of smoking, or number of medication classes used was not found to predict the development of WSP or FM. Age of the participant or a history of depression were also not risk factors which would represent the categories of variables that can precede the development of WSP or FM. These results demonstrate that all three

categories of risk factors were pertinent to CRSP transitioning to a widespread pain disorder. Further research is needed to understand why particular factors in each category were not associated with the development of WSP and FM.

Study limitations

In that a retrospective chart review was used to collect the Kaiser Pain Clinic questionnaires, allowing the study team to complete a six-year follow up, this aspect of the study design became the root cause of most of the study limitations. Two significant limitations from this aspect of the design included missing data from questionnaires that were not scanned into the electronic chart in 2001/2002 and the inability to investigate all potentially relevant risk factors. As discussed in Chapter 4, approximately 18% of the participants' Kaiser questionnaires had not been scanned into the chart, making retrieval of data on certain variables impossible. For many variables, this author retrieved the necessary information from the associated visit chart note but some variables (such as the depression screening tool) were frequently not documented in the chart note. Relying on busy clinic staff who did not foresee the use of those questionnaires for research in the future was a significant limitation of using a retrospective chart review. Although many of the variables of interest were present on the questionnaire, the use of an existing questionnaire limited the number and types of variables collected at the baseline. Potential variables of interest that were not included in the Kaiser questionnaire consisted mainly of psychosocial factors that have previously been associated with the development of WSP and syndromes of altered pain sensitivity. Had this been a prospective study, the baseline questionnaire would have included measures of the participants' anxiety, health worry preoccupation, pain catastrophizing, and fatigue. A prospective study would have also allowed the study team to test aspects of the participants' pain processing such as temporal summation and pain thresholds prior to any transition to WSP or FM.

Another limitation of using retrospectively collected data is the inability for this study to determine a causal relationship between the risk factors and the development of WSP and/or FM. Although this study was able to establish temporal precedence by demonstrating that exposure to certain risk factors preceded the development of WSP and FM, inability to manipulate the variables of interest leaves the researchers unable to state that exposure to these variables caused the development of WSP and FM.

As discussed in Chapters 4 and 5, a significant limitation to the analysis of Aim 3 was the low number of individuals with WSP who were willing to be examined for FM. As indicated by the power analysis, the limited number of participants available for analysis limited the power associated with this aim. The limited power available to detect significant risk factors makes this author unable to confidently identify all relevant variables involved in the transition from CRSP to FM. Through a modified analysis using 40 participants with FM and 40 participants without WSP or FM and an associated power analysis, an attempt was made to describe the pertinent risk factors associated with the development of FM from CRSP. While one must take account of the limitations of this current analysis, the results provide the pain management community with some indication of the clinical features involved in the transition from CRSP to WSP and FM.

As with all epidemiological studies, the potential for misclassification must be considered (Holm, et al., 2007). Such misclassification had the potential to occur at two points in this study, although several steps were taken at each point to minimize this risk. First, the potential exists that participants were misclassified when determining whether or not they presented with WSP on their 2007 study questionnaire. As discussed in a previous discussion in this chapter, stringent criteria were used to assess for the presence of WSP. If any misclassification occurred it would likely have been to err on the side of caution and not deem a person's pain as widespread. In order to minimize the chance of misclassification, any questionable body drawings were also reviewed by two

researchers, Drs. Bennett and Jones, who have extensive experience in diagnosing WSP and FM. This author is confident that all steps were taken in order to maximize the validity of classifying WSP.

Identifying those individuals who met the diagnostic criteria for FM represents another possible point for misclassification. While the possibility for mis-diagnosis regularly exists, the study team followed diagnostic criteria, were trained by the same experts who regularly diagnose FM, and had the time and resources necessary to carry out a careful tender point exam. Again, any questionable cases were referred to Dr. Bennett, who has long been an authority on FM and the diagnosis of this condition.

Strengths of design

A significant strength of this study was the ability to follow up on participants after a six year time period without having to use a costly and time intensive prospective design. While this design carried some limitations (outlined previously), having 2001/2002 data on pertinent variables allowed this author to determine a temporal relationship between exposure to several variables and the transition to WSP and FM. Utilizing this design allowed the author to examine a transition to WSP and FM over a six year time period. Due to time constraints, many prospective designs have to follow up within one to two years, a significant limitation when observing a time intensive process such as the development of widespread sensitization. Using previously collected participant information allowed this group of researchers to utilize the ideal time period for which to follow up and investigate this transition. The unique availability of the 2001/2002 information regarding pertinent risk factors made this study possible and provided valuable information that will lead to future prospective and interventional studies.

This study also benefitted from a relatively large sample size for the first two aims. Other studies investigating the transition to WSP and/or FM in patients with regional pain disorders (not the general population) had sample sizes in the one to two hundred range

(Andersson, 2004; Buskila, 1997; Forseth, et al., 1999; Lapossy, et al., 1995). A larger sample size allowed for more variability among responses and hopefully, an accurate representation of the population of patients with CRSP. The sample size of 512 participants led to 114 who developed WSP, allowing for adequate statistical power to detect relationships among certain predictor variables and the development of WSP.

Using a well defined cohort of individuals already prone to the development of WSP (Flor, et al., 1997; Natvig, et al., 2001) allowed this author to achieve greater power for detecting pertinent risk factors by attaining an increased rate of transition to WSP as compared to what is found in the general population. Not only did this allow for a greater detection of risk factors associated with a transition to WSP, this study confirmed that individuals with CRSP develop WSP at a higher frequency than those individuals in the population (23% of CRSP participants developed WSP as compared to 10-11% in the general population) (Macfarlane, 1999). The downside of using a group of patients with an increased risk of developing the outcome variable is the limited generalizability of the findings. One cannot extrapolate these results to individuals in the general population who do not have a history of chronic spinal pain.

Future directions

While the design of this study and the utilization of information collected in 2001/2002 allowed for the prospective collection of some variables, this study carried many of the limitations of retrospective research. Specifically, this design of this study did not allow for the collection of biological information that could be important in the development of WSP and FM. Investigating these factors prospectively is essential to determine whether or not changes in pain processing precede (and can therefore predict) the onset of specific chronic pain syndromes. Several studies have documented alterations in the nervous system of patients with chronic pain but without identifying these abnormalities prior to the onset of chronic pain one has no way of knowing whether these factors are a

cause or result of the pain syndrome. Future, prospective research into the development of WSP, FM, and other disorders of pain processing will provide concrete and reliable insights into the most relevant biological and psychosocial risk factors. Other prospective studies have been most successful in identifying psychosocial risk factors for the development of WSP but conclusions based on this information remain limited without a better understanding of the biological variables preceding the development of WSP and FM (Smith, Macfarlane, & Torrance, 2007). There exists the strong likelihood that biological variables interact with psychosocial variables to create the development of disorders of pain processing. For instance, one prospective study investigated just such an interaction between the HPA axis and psychosocial risk factors (McBeth, et al., 2007). The researchers took a group from the general population who did not have WSP but were at future risk for the development of WSP based on their psychosocial profile. They prospectively assessed the HPA function of these individuals then followed them to determine which participants developed WSP. They discovered that individuals with altered HPA function did indeed more frequently develop WSP. The authors propose that psychosocial factors associated with the onset of WSP are moderated by the presence of HPA axis dysfunction. This study not only demonstrates the importance of investigating the interaction between biological and psychosocial risk factors but also presents one methodological option for future prospective studies. Namely, the benefit of using a population who may be more likely to develop the syndrome of interest due to the presence of already-identified risk factors. While the current study utilized this approach by investigating participants with a regional pain disorder, future studies could build on this by choosing participants with other established risk factors. For instance a prospective study could utilize a sample of relatives of patients with FM. Siblings or children of patients with FM could be gathered for testing of genetic markers, sensitivity to pain, neuroimaging, and psychosocial variables and then followed over time to

determine the development of FM. This method would enhance research by oversampling individuals most likely to develop the syndrome of interest and perhaps shortening the time period needed to follow the participants.

Researchers have recently begun another prospective study that answers the call for further investigation of biological, genetic, and psychosocial risk factors and their interactions into the development of disorders of pain sensitivity. Again, this study can serve as a model for future prospective investigations of WSP and FM. Four research sites are undergoing a seven-year prospective study of 3200 TMD-free females (Diatchenko, et al., 2006). At baseline, prior to the development of the pain syndrome of interest, the researchers have gathered genetic information based on previously identified genes associated with pain sensitivity, psychological measurements, and numerous assessments of pain perception. This study, the first of its kind to investigate the risk factors for a syndrome of pain perception on this scale, will establish a model for future investigations. One primary goal of this research is to investigate the genetic polymorphisms that influence pain sensitivity and amplification. While several individual studies have provided clues into the genes associated with pain processing, this study operationalizes this information to see the effect of these genetic influences as a whole and in combination with other biological and psychosocial factors. This step is necessary as studies only looking at family aggregation are prone to confounding factors such as the social, psychological, and behavioral factors within a particular family.

The research study previously outlined by Diatchenko et. al (2006) is an example of an investigation into one particular central sensitization syndrome. More prospective studies such as this are needed to understand who is at risk for the development of central sensitization disorders and to gain insight into the mechanisms that cause the central nervous system to become hypersensitive in the first place. Researchers are beginning to understand that altered pain processing in the nervous system underlies

these disorders but the next step must be increasing our understanding of how and why this occurs. Had this author had more foresight, all suspected central sensitization syndromes would have been included in the current study. This would have led to the determination of whether syndromes including TMD, chronic fatigue syndrome, vulvar vestibulitis, post traumatic stress disorder, primary dysmenorrhea, in addition to the four that were included, do increase the risk of developing whole body central sensitization such as WSP and FM. Future research into these syndromes could further establish the pathophysiological mechanisms initiating and maintaining central sensitization, confirm the existence of central sensitization in all these disorders, and clarify the physical and psychosocial risk factors for the development and progression of these disorders.

Along with prospective studies to establish a more firm causal relationship among risk factors, there is also a need for interventional studies to investigate the impact of modifying suspected predictor variables. Several studies, along with this study, agree that the presence of pain and the severity of that pain is the most important clinical risk factor for the development of various chronic pain syndromes (Smith, et al., 2007). This finding highlights the need to intervene to mitigate pain severity in an attempt to alter the course of chronic pain. Individuals with especially severe pain and/or multiple pain sites should be identified as at-risk individuals and treated aggressively in an attempt to modify a negative clinical outcome. Similarly, clinicians and researchers alike should recognize psychological distress as a potential risk factor and appropriately intervene, not passing this off as an inevitable consequence of chronic pain. Finally, while weight alone does not cause the onset of chronic pain, evidence demonstrates that significantly obese individuals follow a downward clinical trajectory. Clinicians should use this point as a source of education and work to assist patients in finding the most appropriate avenues to weight loss.

Several risk factors identified likely represent more complex underlying processes leading to the development of altered pain processing. For instance, being of female gender could point to genetic and endocrine influences yet to be elucidated (Smith, et al., 2007). These types of underlying mechanisms need further research to help the pain community full understand the biological underpinnings of pain processing disorders. One such factor is a history of abuse or traumatic childhood experiences. As discussed previously, many researchers, including this one, have identified a relationship between abuse and the development of chronic pain but most researchers recognize this represents a more complex relationship than findings initially suggest. Two prominent researchers in this area propose that, in those individuals with a history of childhood maltreatment, pain in adulthood is moderated by post traumatic stress disorder (PTSD) (Raphael & Widom, 2008). Specifically, a prospective study they conducted demonstrated participants who experienced childhood maltreatment had high rates of pain in adulthood only if they also had a history of PTSD. They propose that these individuals represent a stress vulnerable population and may be at an increased risk for the development of FM. It is studies like these that will help the pain community identify the underlying mechanisms behind knowingly complex risk factors.

Clinical implications

Demonstrating that nearly a quarter of patients with CRSP develop WSP has significant implications for the care of patients with chronic spinal disorders. Knowing that WSP and FM are associated with more impaired quality of life (Bergman, 2005; Burckhardt, et al., 1993) and greater cost to society through missed work and disability (Boonen, et al., 2005) as compared to CRSP reinforces the need to prevent this downward clinical trajectory. This study identified modifiable risk factors such as BMI and pain intensity that could readily be addressed through encouragement and education by clinical practitioners. While other identified risk factors cannot be easily

modified, knowledge of exposure to these variables can inform a practitioner to who might be at greatest risk for developing WSP and FM. For instance, recognizing that CRSP patients with other central sensitivity syndromes are at greater risk should persuade clinicians to utilize aggressive pain management modalities that seek to address the underlying mechanisms of each syndrome.

Summary

This study advances the understanding of the relationship between CRSP, WSP, and FM in several ways. Findings from this research demonstrate that a subset of patients with CRSP develop WSP and/or FM over time, document that this transition is associated with a more detrimental clinical impact, and identifies the factors that place a person with CRSP at an increased risk for this downward clinical trajectory. The discovery of risk factors associated with a transition to WSP and FM contributes insights into the mechanism underlying the development of these disorders. Establishing that these risk factors impact the development of WSP and FM should inform future prospective studies aimed at further exploration into the complex cause of these disorders.

References

Aaron, L. A., & Buchwald, D. (2001). A review of the evidence for overlap among unexplained clinical conditions. *Annals of Internal Medicine, 134*(9 Pt 2), 868-881.

Aggarwal, V. R., McBeth, J., Zakrzewska, J. M., Lunt, M., & Macfarlane, G. J. (2006). The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? *International Journal of Epidemiology, 35*(2), 468-476.

Almeida, T. F., Roizenblatt, S., & Tufik, S. (2004). Afferent pain pathways: A neuroanatomical review. *Brain Research, 1000,* 40-56.

Andersson, G. B. J. (1999). Epidemiological features of chronic low-back pain. *Lancet, 354*(9178), 581-585.

Andersson, H. I. (2004). The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. *European Journal Of Pain, 8*(1), 47-53.

Arendt-Nielsen, L., & Graven-Nielsen, T. (2003). Central sensitization in fibromyalgia and other musculoskeletal disorders. *Current Pain & Headache Reports, 7*(5), 355-361.

Banic, B., Petersen-Felix, S., Andersen, O. K., Radanov, B. P., Villiger, P. M., Arendt-Nielsen, L., et al. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain, 107*(1-2), 7-15.

Bennett, R. (2005). Fibromyalgia: From present to future. *Current Rheumatology Reports, 7*(5), 371-376.

Bennett, R., Jones, J., Turk, D. C., Russell, I. J., & Matallana, L. (2006). An internet survey of 2,596 people with fibromyalgia. *BioMed Central, in press*.

Bennett, R. M. (1996). Review: Fibromyalgia and the Disability Dilemma: A New Era in Understanding a Complex, Multidimensional Pain Syndrome. .*Arthritis & Rheumatism, 39*(10), 1627-1634.

Bennett, R. M. (1999). Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc, 74*(4), 385-398.

Bergman, S. (2005). Psychosocial aspects of chronic widespread pain and fibromyalgia. *Disability & Rehabilitation, 27*(12), 675-683.

Bergman, S., Herrstrom, P., Jacobsson, L. T. H., & Petersson, I. F. (2002). Chronic widespread pain: A three year followup of pain distribution and risk factors. *Journal Of Rheumatology, 29*(4), 818-825.

Bonafede, R. P., Downey, D. C., & Bennett, R. M. (1995). An association of fibromyalgia with primary Sjogren's syndrome: a prospective study of 72 patients. *Journal of Rheumatology, 22*(1), 133-136.

Boonen, A., van den Heuvel, R., van Tubergen, A., Goossens, M., Severens, J. L., van der Heijde, D., et al. (2005). Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Annals of the Rheumatic Diseases, 64*(3), 396-402.

Bradley, L. A. (2008). Pathophysiologic mechanisms of fibromyalgia and its related disorders. *Journal of Clinical Psychiatry, 69 Suppl 2*, 6-13.

Burckhardt, C. S., Clark, S. R., & Bennett, R. M. (1993). Fibromyalgia and quality of life: A comparitive analysis. *Journal of Rheumatology 20*, 475-479.

Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Wessoleck, E., Heuft, G., Pfleiderer, B., et al. (2009). Altered brain activity during pain processing in fibromyalgia. *Neuroimage, 44*(2), 502-508.

Buskila, D., Neumann, L., Vaisberg, G., Alkalay, D., & Wolfe, F. (1997). Increased rates of fibromyalgia following cervical spine injury: A controlled study of 161 cases of traumatic injury. . *Arthritis and Rheumatism, 40*(3), 446-452.

Buskila, D., Press, J., & Abu-Shakra, M. (2003). Fibromyalgia in systemic lupus erythamatosus. *Clinical Reviews in Allergy and Immunology*, *25*, 25-28.

Buskila, D., & Sarzi-Puttini, P. (2006). Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome. *Arthritis Research & Therapy, 8*(5), 218.

Buskila, D., Shnaider, A., Neumann, L., Zilberman, D., Hilzenrat, N., & Sikuler, E. (1997). Fibromyalgia in hepatitis C virus infection: Another infectious disease relationship. *Archives of Internal Medicine, 157*(21), 2497-2500.

Chou, R., Ballantyne, J. C., Fanciullo, G. J., Fine, P. G., & Miaskowski, C. (2009). Research Gaps on Use of Opioids for Chronic Noncancer Pain: Findings From a Review of the Evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. *The Journal of Pain, 10*(2), 147-159.e115.

Ciccone, D. S. P., Elliott, D. K. B. S., Chandler, H. K. P., Nayak, S. P., & Raphael, K. G. P. (2005). Sexual and Physical Abuse in Women With Fibromyalgia Syndrome: A Test of the Trauma Hypothesis. *Clinical Journal of Pain 21*(5), 378-386.

Clauw, D. (2002). Fibromyalgia associated syndromes. *Journal Of Musculoskeletal Pain, 10*(1-2), 201-214.

Clauw, D. J., & Crofford, L. J. (2003). Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Best Practice & Research In Clinical Rheumatology, 17*(4), 685-701.

Clauw, D. J., Williams, D., Lauerman, W., Dahlman, M., Aslami, A., Nachemson, A. L., et al. (1999). Pain sensitivity as a correlate of clinical status in individuals with chronic low back pain. *Spine, 24*(19), 2035-2041.

Coaccioli, S., Varrassi, G., Sabatini, C., Marinangeli, F., Giuliani, M., & Puxeddu, A. (Writer) (2008). Fibromyalgia: Nosography and Therapeutic Perspectives. *Pain Practice*.

Coderre, T. J., Katz, J., Vaccarino, A. L., & Melzack, R. (1993). Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain, 52*, 259-285.

Colloca, L., & Benedetti, F. (2007). Nocebo hyperalgesia: how anxiety is turned into pain. *Current Opinion in Anaesthesiology, 20*(5), 435-439.

Cook, D. B., Lange, G., Ciccone, D. S., Liu, W. C., Steffener, J., & Natelson, B. H. (2004). Functional imaging of pain in patients with primary fibromyalgia. *Journal of Rheumatology, 31*(2), 364-378.

Coster, L., Kendall, S., Gerdle, B., Henriksson, C., Henriksson, K. G., Bengtsson, A., et al. (2008). Chronic widespread musculoskeletal pain - a comparison of those who meet criteria for fibromyalgia and those who do not. *European Journal of Pain: Ejp, 12*(5), 600-610.

Croft, P., Rigby, A. S., Boswell, R., Schollum, J., & Silman, A. (1993). The prevalence of chronic widespread pain in the general population. *Journal of Rheumatology, 20*(4), 710-713.

Curatolo, M., Arendt-Nielsen, L., & Petersen-Felix, S. (2004). Evidence, mechanisms, and clinical implications of central hypersensitivity in chronic pain after whiplash. . *Clinical Journal of Pain, 20*(6), 469-476.

Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L., Giani, C., Zbinden, A. M., & Radanov, B. P. (2001). Central hypersensitivity in chronic pain after whiplash injury. *Clinical Journal of Pain, 17*(4), 306-315.

Dadabhoy, D., Crofford, L. J., Spaeth, M., Russell, I. J., Clauw, D. J., Dadabhoy, D., et al. (2008). Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. *Arthritis Research & Therapy, 10*(4), 211.

Davis, D. A. M. A., Luecken, L. J. P., & Zautra, A. J. P. (2005). Are Reports of Childhood Abuse Related to the Experience of Chronic Pain in Adulthood?: A Meta-analytic Review of the Literature. *Clinical Journal of Pain, 21*(5), 398-405.

Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., et al. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism, 48*(5), 1420-1429.

Dessein, P. H., Shipton, E. A., & Budd, K. (2000). Nociceptive and non-nociceptive rheumatological pain: recent developments in the understanding of pathophysiology and management in rheumatoid arthritis and fibromyalgia. *Pain Reviews, 7*(2), 67-79.

Diatchenko, L., Nackley, A. G., Slade, G. D., Fillingim, R. B., Maixner, W., Diatchenko, L., et al. (2006). Idiopathic pain disorders--pathways of vulnerability. *Pain, 123*(3), 226-230.

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., et al. (2005). Genetic basis for individual variations in pain perception and the developmehtof a chronic pain condition. *Hum Omol Genet, 14*(1), 135-143.

Edwards, R. R. (2005). Individual differences in endogenous pain modulation as a risk factor for chronic pain. *Neurology, 65*(3), 437-443.

Eide, P. K. (2000). Wind-up and the NMDA receptor complex from a clinical perspective. *European Journal Of Pain, 4*, 5-17.

Fillingim, R. B., Wallace, M. R., Herbstman, D. M., Ribeiro-Dasilva, M., & Staud, R. (2008). Genetic contributions to pain: a review of findings in humans. *Oral Diseases, 14*(8), 673-682.

Flor, H. (2003). Cortical reorganisation and chronic pain: implications for rehabilitation. *Journal of Rehabilitation Medicine* (41 Suppl), 66-72.

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neuroscience Letters, 224*(1), 5-8.

Flor, H., Diers, M., & Birbaumer, N. (2004). Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. *Neuroscience Letters, 361*(1-3), 147-150.

Forseth, K. O., Husby, G., Gran, J. T., & Forre, O. (1999). Prognostic factors for the development of fibromyalgia in women with self-reported musculoskeletal pain. A prospective study. *Journal Of Rheumatology, 26*(11), 2458-2467.

Geisser, M. E., Glass, J. M., Rajcevska, L. D., Clauw, D. J., Williams, D. A., Kileny, P. R., et al. (2008). A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. *Journal of Pain, 9*(5), 417-422.

Giesecke, T., Gracely, R. H., Grant, M. A., Nachemson, A., Petzke, F., Williams, D. A., et al. (2004). Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis & Rheumatism, 50*(2), 613-623.

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry, 7*(3), 254-275.

Goldberg, M. S., Scott, S. C., & Mayo, N. E. (2000). A review of the association between cigarette smoking and the development of nonspecific back pain and related outcomes. *Spine, 25*(8), 995-1014.

Gracely, R. H., Petzke, F., Wolf, J. M., & Clauw, D. J. (2002). Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis & Rheumatism, 46*(5), 1333-1343.

Graven-Nielsen, T., & Arendt-Nielsen, L. (2002). Peripheral and central sensitization in musculoskeletal pain disorders: An experimental approach *Current Rheumatology Reports, 4*(4), 313-321.

Greenspan, J. D., Craft, R. M., LeResche, L., Arendt-Nielsen, L., Berkley, K. J., Fillingim, R. B., et al. (2007). Studying sex and gender differences in pain and analgesia: A consensus report. *Pain, 132*, S26-S45.

Gupta, A., Silman, A. J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G. J., et al. (2007). The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology, 46*(4), 666-671.

Henriksson, C. M. (1995). Living with continuous muscular pain - patient persepctives. Part I: Encounters and consequences. *Scandinavian Journal of Caring Science, 9*, 67-76.

Herren-Gerber, R., Weiss, S., Arendt-Nielsen, L., Petersen-Felix, S., Di Stefano, G., Radanov, B. P., et al. (2004). Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. *Pain Medicine, 5*(4), 366-376.

Holm, L. W., Carroll, L. J., Cassidy, J. D., Skillgate, E., & Ahlbom, A. (2007). Widespread pain following whiplash-associated disorders: incidence, course, and risk factors. *Journal of Rheumatology, 34*(1), 193-200.

Hooper, M. M., Stellato, T. A., Hallowell, P. T., Seitz, B. A., & Moskowitz, R. W. (2007). Musculoskeletal findings in obese subjects before and after weight loss following bariatric surgery. *International Journal of Obesity, 31*(1), 114-120.

Huppe, A., Brockow, T., & Raspe, H. (2004). [Chronic widespread pain and tender points in low back pain: a population-based study]. *Zeitschrift fur Rheumatologie, 63*(1), 76-83.

Johnston, V., Jimmieson, N. L., Jull, G., Souvlis, T., Johnston, V., Jimmieson, N. L., et al. (2008). Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. *Pain, 137*(2), 257-265.

Jones, G. T., Silman, A. J., Power, C., & Macfarlane, G. J. (2007). Are common symptoms in childhood associated with chronic widespread body pain in adulthood? Results from the 1958 British birth cohort study. *Arthritis and Rheumatism, 56*(5), 1669-1675.

Jones, K. D., Adams, D., Ross, R., & Bennett, R. (2006). Fibromyalgia: A rational guide to management in primary care. *Clinician Reviews, 16*(5), 3-13t.

Julien, N., Goffaux, P., Arsenault, P., & Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain 114*, 295-302.

Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2006). Chronic widespread pain and its comorbidities: a population-based study. *Archives of Internal Medicine, 166*(15), 1649-1654.

Kato, K., Sullivan, P. F., Evengard, B., Pedersen, N. L., Kato, K., Sullivan, P. F., et al. (2006). Importance of genetic influences on chronic widespread pain. *Arthritis & Rheumatism, 54*(5), 1682-1686.

Katz, W. A., & Rothenberg, R. (2005). The nature of pain: Pathophysiology. *Jcr-Journal Of Clinical Rheumatology, 11*(2), S11-S15.

Kleinbohl, D., Holzl, R., Moltner, A., Rommel, C., Weber, C., & Osswald, P. M. (1999). Psychophysical measures of sensitization to tonic heat discriminate chronic pain patients. *Pain, 81*(1-2), 35-43.

Koelbaek Johansen, M., Graven-Nielsen, T., Schou Olesen, A., & Arendt-Nielsen, L. (1999). Generalised muscular hyperalgesia in chronic whiplash syndrome. *Pain, 83*(2), 229-234.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*(9), 606-613.

Lapossy, E., Maleitzke, R., Hrycaj, P., Mennet, W., & Muller, W. (1995). The frequency of transition of chronic low back pain to fibromyalgia. *Scandinavian Journal of Rheumatology, 24*(1), 29-33.

Larson, A. A., Giovengo, S. L., Russell, I. J., & Michalek, J. E. (2000). Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. *Pain, 87*(2), 201-211.

Laursen, B. S., Bajaj, P., Olesen, A. S., Delmar, C., & Arendt-Nielsen, L. (2005). Health related quality of life and quantitative pain measurement in females with chronic non-malignant pain. *European Journal of Pain: Ejp, 9*(3), 267-275.

Lawrence, R. C., Helmick, C. G., Arnett, F. C., Deyo, R. A., Felson, D. T., Giannini, E. H., et al. (1998). Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis & Rheumatism, 41*(5), 778-799.

Lidbeck, J. (2002). Central hyperexcitability in chronic musculoskeletal pain: a conceptual breakthrough with multiple clinical implications. *Pain Research & Management, 7*(2), 81-92.

Limer, K. L., Nicholl, B. I., Thomson, W., & McBeth, J. (2008). Exploring the genetic susceptibility of chronic widespread pain: the tender points in genetic association studies. *Rheumatology, 47*(5), 572-577.

Littlejohn, G. O., & Guymer, E. K. (2006). Fibromyalgia syndrome: which antidepressant drug should we choose? *Curr Pharm Des, 12*(1), 3-9.

Lovick, T. A. (2008). Pro-nociceptive action of cholecystokinin in the periaqueductal grey: a role in neuropathic and anxiety-induced hyperalgesic states. *Neuroscience & Biobehavioral Reviews, 32*(4), 852-862.

Luo, X., Peittrobon, R., Sun, S. X., Liu, G. G., & Hey, L. (2003). Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. *Spine, 29*(1), 79-86.

Macfarlane, G. J. (1999). Generalized pain, fibromyalgia and regional pain: an epidemiological view. *Best Practice & Research in Clinical Rheumatology, 13*(3), 403-414.

Macfarlane, T. V., Blinkhorn, A., Worthington, H. V., Davies, R. M., & Macfarlane, G. J. (2002). Sex hormonal factors and chronic widespread pain: a population study among women. *Rheumatology, 41*(4), 454-457.

Marchand, S. (2008). The physiology of pain mechanisms: from the periphery to the brain. *Rheumatic Diseases Clinics of North America, 34*(2), 285-309.

Mayer, T. G., Towns, B. L., Neblett, R., Theodore, B. R., Gatchel, R. J., Mayer, T. G., et al. (2008). Chronic widespread pain in patients with occupational spinal disorders: prevalence, psychiatric comorbidity, and association with outcomes. *Spine, 33*(17), 1889-1897.

McBeth, J., Macfarlane, G. J., Benjamin, S., Morris, S., & Silman, A. J. (1999). The association between tender points, psychological distress, and adverse childhood experiences: a community-based study. *Arthritis & Rheumatism, 42*(7), 1397-1404.

McBeth, J., Macfarlane, G. J., Benjamin, S., & Silman, A. J. (2001). Features of somatization predict the onset of chronic widespread pain: results of a large population-based study. *Arthritis & Rheumatism, 44*(4), 940-946.

McBeth, J., Macfarlane, G. J., Hunt, I. M., & Silman, A. J. (2001). Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology, 40*(1), 95-101.

McBeth, J., Morris, S., Benjamin, S., Silman, A. J., & Macfarlane, G. J. (2001). Associations between adverse events in childhood and chronic widespread pain in adulthood: are they explained by differential recall? *Journal of Rheumatology, 28*(10), 2305-2309.

McBeth, J., & Silman, A. J. (1999). Editorial. *Journal of Psychosomatic Research, 47*(2), 109-114.

McBeth, J., Silman, A. J., Gupta, A., Chiu, Y. H., Ray, D., Morriss, R., et al. (2007). Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. *Arthritis & Rheumatism, 56*(1), 360-371.

Meeus, M., Nijs, J., Meeus, M., & Nijs, J. (2007). Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with

fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology, 26*(4), 465-473.

Mendell, L. M. (1966). Physiological properties of unmyelinated fiber projection to the spinal cord. *Experimental Neurology, 16,* 316-332.

Mendell, L. M., & Wall, P. D. (1965). Response of singe dorsal cord cells to peripheral cutaneous unmyelinated fibers. *Nature, 206,* 97-99.

Mikkelsson, M., El-Metwally, A., Kautiainen, H., Auvinen, A., Macfarlane, G. J., & Salminen, J. J. (2008). Onset, prognosis and risk factors for widespread pain in schoolchildren: A prospective 4-year follow-up study. *Pain, 138*(3), 681-687.

Mountz, J. M., Bradley, L. A., & Alarcon, G. S. (1998). Abnormal functional activity of the central nervous system in fibromyalgia syndrome. *American Journal of the Medical Sciences, 315*(6), 385-396.

Natvig, B., Bruusgaard, D., & Eriksen, W. (2001). Localized low back pain and low back pain as part of widespread musculoskeletal pain: Two different disorders? A cross-sectional population study. *Journal Of Rehabilitation Medicine, 33*(1), 21-25.

Nielsen, L. A., & Henriksson, K. G. (2007). Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. *Best Practice & Research in Clinical Rheumatology, 21*(3), 465-480.

O'Neill, S., Manniche, C., Graven-Nielsen, T., & Arendt-Nielsen, L. (2006). Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *European Journal Of Pain, 10*.

O'Neill, S., Manniche, C., Graven-Nielsen, T., & Arendt-Nielsen, L. (2007). Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *European Journal of Pain: Ejp, 11*(4), 415-420.

Pampel, F. C. (2000). *Logistic Regression: A Primer*. Thousand Oaks: Sage Publications.

Pamuk, O. N., Yesil, Y., Cakir, N., Pamuk, O. N., Yesil, Y., & Cakir, N. (2006). Factors that affect the number of tender points in fibromyalgia and chronic widespread pain patients who did not meet the ACR 1990 criteria for fibromyalgia: are tender points a reflection of neuropathic pain? *Seminars in Arthritis & Rheumatism, 36*(2), 130-134.

Papageorgiou, A. C., Silman, A. J., & Macfarlane, G. J. (2002). Chronic widespread pain in the population: a seven year follow up study. *Annals of the Rheumatic Diseases, 61*(12), 1071-1074.

Peng, C. Y. J., Lee, K. L., & Ingersoll, G. M. (2002). An introduction to logistic regression analysis and reporting. *The Journal of Educational Research, 96*(1), 3-14.

Peolsson, M., Borsbo, B., Gerdle, B., Peolsson, M., Borsbo, B., & Gerdle, B. (2007). Generalized pain is associated with more negative consequences than local or regional pain: a study of chronic whiplash-associated disorders. *Journal of Rehabilitation Medicine, 39*(3), 260-268.

Perrot, S., Dickenson, A. H., Bennett, R. M., Perrot, S., Dickenson, A. H., & Bennett, R. M. (2008). Fibromyalgia: harmonizing science with clinical practice considerations. *Pain Practice, 8*(3), 177-189.

Price, D. D., & Staud, R. (2005). Neurobiology of fibromyalgia syndrome. *Journal of Rheumatology - Supplement, 75*, 22-28.

Raphael, K. G., & Widom, C. S. (2008). *A prospective investigation of childhood victimization and pain in middle adulthood.* Paper presented at the International Association for the Study of Pain, Glasgow, Scotland.

Raphael, K. G. P. (2005). Childhood Abuse and Pain in Adulthood: More Than a Modest Relationship? *Clinical Journal of Pain, 21*(5), 371-373.

Russell, I. J. (1998). Advances in fibromyalgia: possible role for central neurochemicals. *American Journal of the Medical Sciences, 315*(6), 377-384.

Russell, I. J., & Bieber, C. S. (2006). Myofascial pain and fibromyalgia syndrome. In S. B. McMahon & M. Koltzenburg (Eds.), *Wall and Melzack's Textbook of Pain* (5th ed.). Philadelphia: Elsevier Churchill Livingstone.

Russell, I. J., Vaeroy, H., Javors, M., & Nyberg, F. (1992). Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis & Rheumatism, 35*, 550-556.

Scott, D., Jull, G., & Sterling, M. (2005). Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. *Clinical Journal of Pain, 21*(2), 175-181.

Shapiro, J. R., Anderson, D. A., & Danoff-Burg, S. (2005). A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. *Journal of Psychosomatic Research, 59*(5), 275-282.

Sheather-Reid, R. B., & Cohen, M. L. (1998). Psychophysical evidence for a neuropathic component of chronic neck pain. *Pain, 75*(2-3), 341-347.

Sidney Benjamin, S. M., John McBeth, Gary J. Macfarlane, Alan J. Silman, (2000). The association between chronic widespread pain and mental disorder: A population-based study. *Arthritis & Rheumatism, 43*(3), 561-567.

Slade, G. D., Diatchenko, L., Bhalang, K., Sigurdsson, A., Fillingim, R. B., Belfer, I., et al. (2007). Influence of psychological factors on risk of temporomandibular disorders. *Journal of Dental Research, 86*(11), 1120-1125.

Smith, B. H., Macfarlane, G. J., & Torrance, N. (2007). Epidemiology of chronic pain, from the laboratory to the bus stop: time to add understanding of biological mechanisms to the study of risk factors in population-based research? *Pain, 127*(1-2), 5-10.

Stahl, S., & Briley, M. (2004). Understanding pain in depression. *Human Psychopharmacology, 19 Suppl 1*, S9-S13.

Staud, R. (2002). Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Current Rheumatology Reports, 4*(4), 299-305.

Staud, R. (2004). Fibromyalgia pain: do we know the source? *Current Opinion in Rheumatology, 16*(2), 157-163.

Staud, R. (2006). Are patients with systemic lupus erythematosus at increased risk for fibromyalgia? *Current Rheumatology Reports, 8*(6), 430-435.

Staud, R. (2007). Future perspectives: pathogenesis of chronic muscle pain. *Best Practice & Research in Clinical Rheumatology, 21*(3), 581-596.

Staud, R., & Domingo, M. (2001). Evidence for abnormal pain processing in fibromyalgia syndrome. *Pain Medicine, 2*(3), 208-215.

Staud, R., Price, D. D., Robinson, M. E., Mauderli, A. P., & Vierck, C. J. (2004). Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. *Pain, 110*(3), 689-696.

Staud, R., Robinson, M. E., Vierck, C. J., Jr., & Price, D. D. (2003). Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain, 101*(1-2), 167-174.

Staud, R., & Rodriguez, M. E. (2006). Mechanisms of disease: Pain in fibromyalgia syndrome. *Nature Clinical Practice Rheumatology, 2*(2), 90-98.

Staud, R., Vierck, C. J., Robinson, M. E., & Price, D. D. (2006). Overall fibromyalgia pain is predicted by ratings of local pain and pain-related negative affect-possible role of peripheral tissues. *Rheumatology, Rheumatology Advance Access published on April 18, 2006, DOI 10.1093/rheumatology/kel121*.

Tabachnick, B. G., & Fidell, L. S. (2001). *Using Mutlivariate Statistics* (4th ed.). Needham Heights, MA: Allyn and Bacon.

Tan, G., Jensen, M. P., Thornby, J. I., & Shanti, B. F. (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *Journal of Pain, 5*(2), 133-137.

Tishler, M., Barak, Y., Paran, D., & Yaron, M. (1997). Sleep disturbances, fibromyalgia and primary Sjogren's syndrome. *Clinical & Experimental Rheumatology, 15*(1), 71-74.

Urban, M. O., & Gebhart, G. F. (1999). Central mechanisms in pain. *Medical Clinics of North America, 83*(3), 585-596.

Visscher, C., Hofman, N., Mes, C., Lousberg, R., & Naeije, M. (2005). Is temporomandibular pain in chronic whiplash-associated disorders part of a more widespread pain syndrome? *Clinical Journal of Pain, 21*(4), 353-357.

Walker-Bone, K., Reading, I., Coggon, D., Cooper, C., & Palmer, K. T. (2004). The anatomical pattern and determinants of pain in the neck and upper limbs: an epidemiologic study. *Pain, 109*(1-2), 45-51.

Webb, R., Brammah, T., Lunt, M., Urwin, M., Allison, T., & Symmons, D. (2003). Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. *Spine, 28*(11), 1195-1202.

Weir, P. T., Harlan, G. A., Nkoy, F. L., Jones, S. S., Hegmann, K. T., Gren, L. H., et al. (2006). The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *JCR: Journal of Clinical Rheumatology, 12*(3), 124-128.

White, K. P., & Harth, M. (1999). The occurrence and impact of generalized pain. *Best Practice & Research in Clinical Rheumatology, 13*(3), 379-389.

White, K. P., Speechley, M., Harth, M., & Ostbye, T. (1999). Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: The London Fibromyalgia Epidemiology Study. *Arthritis & Rheumatism, 42*(1), 76-83.

Wiesenfeld-Hallin, Z., Hao, J. X., Xu, X. J., Aldskogius, H., & Seiger, A. (1993). Genetic factors influence the development of mechanical hypersensitivity, motor deficits

and morphological damage after transient spinal cord ischemia in the rat.[erratum appears in Pain 1994 Apr;57(1):135]. *Pain, 55*(2), 235-241.

Wiesenfeld-Hallin, Z., Xu, X. J., & Hokfelt, T. (2002). The role of spinal cholecystokinin in chronic pain states. [Review]. *Pharmacology & Toxicology, 91*(6), 398-403.

Wilder-Smith, O. H., Tassonyi, E., & Arendt-Nielsen, L. (2002). Preoperative back pain is associated with diverse manifestations of central neuroplasticity. *Pain, 97*(3), 189-194.

Wolfe, F., Anderson, J., Harkness, D., Bennett, R. M., Caro, X. J., Goldenberg, D. L., et al. (1997). Work and disability status of persons with fibromyalgia. *Journal of Rheumatology, 24*(6), 1171-1178.

Wolfe, F., Cathey, M. A., & Kleinheksel, S. M. (1984). Fibrositis (Fibromyalgia) in rheumatoid arthritis. *Journal of Rheumatology, 11*(6), 814-818.

Wolfe, F., Ross, K., Anderson, J., Russell, I. J., & Hebert, L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis & Rheumatism, 38*(1), 19-28.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., et al. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis & Rheumatism, 33*(2), 160-172.

Wood, P. B. (2005). Neuroimaging in functional somatic syndromes. *International Review of Neurobiology, 67*, 119 - 163.

Woolf, C. J., & Thompson, S. W. N. (1991). The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation;

implications for the treatment of post-injury pain hypersensitivity states. *Pain 44*, 293-299.

Wynne-Jones, G., Jones, G. T., Wiles, N. J., Silman, A. J., & MacFarlane, G. J. (2006). Predicting new onset of widespread pain following a motor vehicle collision. *Journal Of Rheumatology, 33*(5), 968-974.

Yunus, M. B. (1994). Psychological aspects of fibromyalgia syndrome: A component of the dysfunctional spectrum syndrome. *Baillieres Clinical Rheumatology, 8*, 811-837.

Yunus, M. B. (2007). Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Practice & Research in Clinical Rheumatology, 21*(3), 481-497.

Yunus, M. B. (2008). Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Seminars in Arthritis & Rheumatism, 37*(6), 339-352.

Yunus, M. B., Arslan, S., & Aldag, J. C. (2002). Relationship between body mass index and fibromyalgia features. *Scandinavian Journal of Rheumatology, 31*(1), 27-31.

Zhang, J., & Yu, K. F. (1998). What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA, 280*(19), 1690-1691.

Zubieta, J. K., Heitzey, M. M., Smith, Y. R., Bueller, J. A., Xu, K., Xu, Y., et al. (2003). COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science, 299*(5610), 1240-1243.

Zusman, M. (2002). Forebrain-mediated sensitization of central pain pathways: 'non-specific' pain and a new image for MT. *Manual Therapy, 7*(2), 80-88.