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SAN DIEGO STATE UNIVERSITY

Biopsychosocial pathways of pain in patients with systemic sclerosis

A dissertation proposal submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Erin Lynn Merz

Committee in charge:

University of California, San Diego
- Professor Paul J. Mills
- Professor Thomas L. Patterson

San Diego State University
- Professor Vanessa L. Malcarne, Chair
- Professor Linda C. Gallo
- Professor Scott C. Roesch

2014

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The Dissertation of Erin Lynn Merz is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

San Diego State University

2014

DEDICATION

I dedicate this dissertation to my grandmother Helen Kelly, who, at 93 years-old, continues to teach me about kindness, grace, and optimism. I am so lucky to be her granddaughter. I also dedicate this project to the memory of my grandparents Charles Kelly, and Margaret and Herman Merz. My grandfather Kelly taught me to be adventurous, curious, and active. My grandmother Merz taught me about resilience, generosity, and forgiveness. And my grandfather Merz taught me about hard work and the great privilege of education.

I also dedicate this project to the orthopedic surgeons Dr. Douglas Gula and Dr. David Watt, the nursing staff at McCullough-Hyde Memorial Hospital, an unnamed team of field paramedics in Hamilton, Ohio, and everyone at McCullough-Hyde Physical Therapy, especially Tim and Joe. I cannot adequately express my gratitude for the incalculable care that you all provided me. Your expertise and bedside manner enabled my recovery and the ability to live an active and healthy life. Thank you for accidentally inspiring my interest in health psychology.

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ACKNOWLEDGMENTS

I frequently reflect on the fact that I have not arrived to the end of my graduate education alone. It has been my good fortune to study under great teachers who gave their time to challenge me, often beyond my own level of comfort, in order to promote my growth. I have been provided with many tools, from language and mathematics, to science and philosophy. I use all of these on a daily basis, usually in concert – Psychology is not a one-trick-pony.

All of my teachers have made a difference in my life, and it is my great privilege to acknowledge a handful of special people who prepared me for this project. I thank my high school teacher Amy Haga and my college professor Steven Bauer for teaching me to write effectively and to use language to articulate my ideas. I express deep and lasting gratitude to my high school teacher Donald Pankuch, and my college professors Tim Dowd and Arthur Miller for providing a thought-provoking introduction to my studies in psychology. I thank my graduate school professors, Scott Roesch and Linda Gallo for sharing their knowledge with me. They have also been major influences on my personal philosophy and career. I would particularly like to acknowledge my mentor, Vanessa Malcarne, whose guidance has been invaluable over the last several years. Vanessa's high standards, discerning eye, and red pen have advanced my academic development in infinite ways. She also seems to find my antics amusing, which I appreciate.

I am grateful to Shervin Assassi, Maureen Mayes, all of my co-authors from the *Genetics versus ENvironment In Scleroderma Outcome Study* for the opportunity to collaborate on this project. I thank my committee members Paul Mills and Thomas Patterson for offering their encouragment and expertise. I thank Georgia Sadler and my

labmates for their support over the years. I am grateful to Jim Sallis and everyone at *Active Living Research* for providing me with my first research experiences in behavioral medicine. I thank my JDP cohort for being bright, hilarious, insightful, supportive, and (oddly) musical. I thank my friends, family, and especially Kevin Dooley for their support throughout graduate school. Finally, I thank the patients who have participated in the *Genetics versus ENvironment In Scleroderma Outcome Study*. Their generous contributions of time and information have not only helped form the basis of this dissertation and other projects, but have provided important insight about how to improve the lives of patients with systemic sclerosis.

Chapter 2, in full, is a reprint of the material as it appears in Arthritis Care and Research 2013. Merz, Erin L.; Malcarne, Vanessa L.; Roesch, Scott C.; Sharif, Roozbeh; Harper, Brock E.; Draeger, Hilda T.; Gonzalez, Emilio B.; Nair, Deepthi K.; McNearney, Terry A; Assassi, Shervin; Mayes, Maureen D., American College of Rheumatology, 2013. The dissertation author was the primary investigator and author of this paper.

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Chapter 4, in part is currently being prepared for submission for publication of the material. Merz, Erin L.; Malcarne, Vanessa L.; Roesch, Scott C.; Nair, Deepthi K.; Salazar, Gloria; Assassi, Shervin; Mayes, Maureen D. The dissertation author was the primary investigator and author of this paper.

VITA

EDUCATION

2014	Ph.D.	San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology Behavioral Medicine Track
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PEER REVIEWED JOURNAL ARTICLES

Merz, E. L., Fox, R. S., & Malcarne, V. L. (in press). Expressive writing interventions in cancer patients: A systematic review. *Health Psychology Review, doi: 10.1080/17437199.2014.882007*

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McNally, R. J., Malcarne, V. L., Najmi, S., Hansdottir, I., Reese, H. E., & Merz, E. L. (2010). Vulnerability to anxiety disorders across the lifespan. In R. E. Ingram & J. M. Price (Eds.), *Vulnerability to Psychopathology: Risk across the Lifespan, 2nd edition*. New York: Guilford.

PRESENTATIONS

Malcarne, V. L., Fox, R. S., Mills, S. D., Gholizadeh, S., Merz, E. L., Clements, P. J., Kafaja, S., Khanna, D., & Furst, D. E. (2014, February). *Prevalence and correlates of body image dissatisfaction in patients with limited and diffuse systemic sclerosis*. Poster presentation at the annual meeting of the Systemic Sclerosis World Congress, Rome, Italy.

Fox, R. S., Mills, S. D., Pan, T. M., Merz, E. L., & Malcarne, V. L. (2014, February). *Interventions targeting psychosocial and process-related outcomes following an abnormal breast cancer screening test: A systematic review.* Poster presentation at the annual meeting of the American Psychosocial Oncology Society, Tampa, FL.

Fox, R. S., Gholizadeh, S., Mills, S. D., Merz, E. L., Clements, P. J., Kafaja, S., Malcarne, V. L., Fust, D. E., & Khanna, D. (2013, October).*The validity of the Satisfaction with Appearance scale and the Brief Satisfaction with Appearance scale for patients with limited and diffuse systemic sclerosis.* Oral presentation at the annual meeting of the American College of Rheumatology/ Association of Rheumatology Health Professionals, San Diego, CA.

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Mills, S. D., Fox, R. S., Malcarne, V. L., Merz, E. L., Clements, P. J., Khanna, D., Kafaja, S., & Furst, D. E. (2013, August). *A psychometric evaluation of the Satisfaction with Appearance Scale (SWAP) and Brief-SWAP in systemic sclerosis patients*. Poster presentation at the annual meeting of the American Psychological Association, Honolulu, HI. (Selected for a Certificate of Merit from the Association of Test Publishers).

Riley, N., Merz, E. L., Malcarne, V. L., & Sadler, G. R. (2013, May). *The Breast Cancer Clinical Trials Education Program*. Poster presentation at the California Breast Cancer Research Program Symposium, Costa Mesa, CA.

Riley, N., Merz, E. L., Malcarne, V. L., & Sadler, G. R. (2012, September). *Clinical trials knowledge, attitudes, and research participation among African American and Hispanic American women as a result of a breast cancer clinical trials education program.* Podium presentation at the annual meeting of the American Association for Cancer Education, Ann Arbor, MI.

Merz, E. L., Malcarne, V. L., Roesch, S. C., Sharif, R., Harper, B. E., Draeger, H., Gonzalez, E. B., McNearney, T. A., Assassi, S., & Mayes, M. D. (2012, August). *Measuring illness behavior in patients with systemic sclerosis*. Poster presentation at the annual meeting of the American Psychological Association, Orlando, FL.

Harry, K. M., Merz, E. L., Malcarne, V. L., Furst, D. E., Clements, P. J. & Weisman, M. H. (2012, April). *God locus of control and coping strategies on disease-related distress in patients with systemic sclerosis*. Poster presentation at the annual meeting of the Society of Behavioral Medicine, New Orleans, LA.

Bess, C., Merz, E. L., Malcarne, V. L., Riley, N., & Sadler, G. R. (2012, April). *Acculturation, age, level of education, religiosity, subjective social status as predictors of cancer fatalism*. Poster presentation at the annual meeting of the Society of Behavioral Medicine, New Orleans, LA.

Riley, N., Merz, E. L., Malcarne, V. L., & Sadler, G. R. (2011, September). *The influence of perceived community support on African American women's response to a program promoting clinical trials participation*. Poster presentation at the annual meeting of the American Association for Cancer Education, Buffalo, NY. (Selected for Best Research Poster Award).

Merz, E. L., Malcarne, V. L., Riley, N., & Sadler, G. R. (2011, April). *Stress, racism, and health among African American and Hispanic American women*. Poster presentation at the annual meeting of the Society of Behavioral medicine, Washington, DC.

Sobel, R. M., Merz, E. L., Malcarne, V. L., Riley, N., & Sadler, G. R. (2011, April). *Religiosity, fatalism and acculturation in Hispanic American women*. Poster presentation at the annual meeting of the Society of Behavioral medicine, Washington, DC.

Merz, E. L., Malcarne, V. L., Roberson, C. K., Varni, J. W., & Sadler, G. R. (2011, February). *Problem orientation and mood disturbance among spouses of men with prostate cancer*. Poster presentation at the annual meeting of the American Psychological Oncology Society, Anaheim, CA.

Sobel, R. M., Merz, E. L., Malcarne, V. L., Ko, C. M., Varni, J. W., & Sadler, G. R. (2011, February). *Distress levels of prostate cancer patients' spousal caregivers*. Poster presentation at the annual meeting of the American Psychological Oncology Society, Anaheim, CA.

Merz, E. L., Malcarne, V. L., Roesch, S. C., Riley, N., & Sadler, G. R. (2010, October). *Measuring depression with the PHQ-9 among English- and Spanish-speaking Latinas*. Podium presentation at the annual meeting of the American Association for Cancer Education, San Diego, CA.

Riley, N., Merz, E. L., Malcarne, V. L., Sadler, G. R., & Sosa, E. (2010, October). *Language preference as a determinant of Hispanic American women's clinical trials knowledge, attitudes, and behaviors*. Podium presentation at the annual meeting of the American Association for Cancer Education, San Diego, CA.

Merz, E. L., Malcarne, V. L., Hansdottir, I., Furst, D. E., Clements, P. J. & Weisman, M. H. (2010, April). *Psychosocial predictors of fatigue in systemic sclerosis*. Poster presentation at the annual meeting of the Society of Behavioral Medicine, Seattle, WA.

Marin, A. M., Merz, E. L., Malcarne, V. L., Riley, N., & Sadler, G. R. (2010, April). *Efficacy of a new breast cancer clinical trials education program for African American and Hispanic American women*. Poster presentation at the annual meeting of the Society of Behavioral Medicine, Seattle, WA.

Cain, K., Merz, E., Franklin, C., & Dumbauld, J. (2009, February). *Using accelerometers and GPS in neighborhood research: Practical issues*. Podium presentation at the annual meeting for Active Living Research, San Diego, CA.

Merz, E. L., Kwack, L., Roberson, C. K., Malcarne, V. L., Varni, J. W., & Sadler, G. R. (2007, October). *Concordance among prostate cancer patients and their spouses: Does it matter?* Poster presentation at the annual meeting of the American Association for Cancer Education, Birmingham, AL.

ABSTRACT OF THE DISSERTATION

Biopsychosocial pathways of pain in patients with systemic sclerosis

by

Erin Lynn Merz

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014
San Diego State University, 2014

Professor Vanessa L. Malcarne, Chair

Systemic Sclerosis (SSc) is a rheumatic disease characterized by fibrosis of the skin and internal organs. Patients are at risk for poor quality of life, including significant pain. This dissertation evaluated a biopsychosocial model of pain-related quality of life in SSc. Data from the *Genetics versus ENvironment In Scleroderma Outcome Study* (GENISOS), a prospective cohort study of patients with SSc were used to test the study aims.

Study 1 used baseline data to evaluate the factor structure of the Illness Behavior Questionnaire. Four previously derived solutions were tested but none were sufficiently valid or reliable. Exploratory analysis suggested that there were five factors that were relevant to SSc patients: Symptom Bother, Health Worry, Interpersonal Functioning,

Other Life Worries, and Affective Inhibition. These indices were related to fatigue, pain, disability, social support, and mental health but not disease severity. Study 2 utilized baseline data to derive biopsychosocial profiles of SSc patients based on indicators of disease severity, perceived physical health, health worry, mental health, and social support. Three classes, which were distinguished by different trait patterns, were termed *Managing, Resilient,* and *Distressed*. Results suggested that the *Distressed* group, which represented individuals with less severe disease but poor psychosocial functioning had the highest pain and analgesic usage. Study 3 evaluated pain over time with regard to medical, psychological, and social characteristics. Pain generally improved for all patients. Individuals with diffuse disease reported worse initial pain, although both classifications had same rate of change. However, when psychosocial characteristics were added to the model, disease classification was no longer a significant predictor. Individuals with better mental health and perceived physical health reported better pain at disease onset. Change in pain over time was moderated by perceived physical health and social support.

Overall, the findings suggest that, even in the context of a disease which is characterized by significant damage of bodily tissue, the overall experience of pain was best explained by psychological and social phenomena. Emotional and social functioning, which are potentially modifiable risk factors, may be important targets for comprehensive pain management in this population.

CHAPTER 1: INTRODUCTION

Systemic Sclerosis

Systemic Sclerosis (SSc) is a chronic, debilitating, multisystem, rheumatic disease characterized by the thickening of skin and fibrosis of internal organs due to a buildup of collagen (Medsger, 2004). Patterns of symptoms include dermatologic, vascular, pulmonary, cardiac, gastrointestinal, neurological, musculoskeletal, and renal problems. Symptoms of SSc include epithelial calcium deposits, rigid fingers and toes that become fixed in position, tendon friction rubs, itching, inflamed blood vessels, lower esophogeal dysfunction, acid reflux, heart burn, and Raynaud's phenomenon (Medsger, 2004). Raynaud's phenomenon is a vascular problem resulting from a reduction in the number and size of blood vessels wherein the small blood vessels of the fingers and toes narrow, causing hypersensitivity to cold temperatures (Medsger, 2004). When exposed to cold stimuli, blood circulation becomes dangerously inadequate, which can result in symptoms ranging from skin discoloration to digital ulcers. Because Raynaud's phenomenon can be idiopathic, the first non-Raynaud's symptoms mark the beginning of the SSc disease process (Medsger, 2004).

Individuals with SSc generally deteriorate over time, similar to other chronic diseases; however, the disease trajectory can be uncertain and unpredictable, with periods of improvement and decline (Medsger, 2004). Although SSc is relatively heterogeneous, given that patients present with many permutations of symptoms, there are two general classifications. Limited cutaneous SSc is milder and is characterized by slow fibrosis, and mainly affects the skin and limbs (LeRoy et al., 1988; Medsger, 2003). For limited SSc patients, skin thickening increases slowly during early disease (within five years of onset)

and plateaus thereafter, with minimal organ involvement until late in the disease process (Medsger, 2003). In later-stage limited disease, patients may have problems with pulmonary arterial hypertension and esophageal reflux and stricture (Medsger, 2003). Diffuse cutaneous SSc, which has a worse prognosis, is characterized by rapidly progressing fibrosis, and more extensive skin and joint damage with trunk involvement and organ damage (LeRoy et al., 1988; Medsger, 2003). During the first five years, patients often have puffy fingers, swollen legs and feet, tendon friction rubs, finger joint contractures, gastrointestinal involvement, and visceral organ dysfunction (Medsger, 2003). However, as patients transition to the intermediate and late phases of the disease, skin thickening improves somewhat, although there can be spontaneous exacerbations (Medsger, 2003).

SSc can be fatal in severe cases, with restrictive lung disease, pulmonary arterial hypertension, and pulmonary fibrosis being the most common causes of SSc-related death (Assassi et al., 2009; Barnes & Mayes, 2012; Ostojić & Damjanov, 2006; Steen & Medsger, 2007). Mortality rates have declined in recent years, in part due to lead time bias (i.e., patients are being diagnosed earlier), but also improvements in treating renal failure and lung disease (Barnes & Mayes, 2012; Medsger, 2004). Current estimates of standardized all-cause mortality ratios range widely (Ioannidis et al., 2005). The risk of death for patients with SSc is estimated to be between 1.5 and 7.2 times higher than would otherwise be expected in the general population (Ioannidis et al., 2005).

Because the pathophysiology of SSc is not well understood and there is no known cure, care is palliative. The primary goals of treatment are to preserve functioning and improve quality of life. Significant improvements in symptom management via

medications and other therapies have helped to slow disease progression, relieve symptoms, and increase patient well-being (Charles, Clements, & Furst, 2006; Medsger, 2004). Given the multitude of problems associated with SSc, a multidisciplinary approach including rheumatology, dentistry, physical and occupational therapy, and psychology may be needed to improve patient functioning and quality of life.

Epidemiology and risk factors

SSc is a relatively rare disease, although with a prevalence of 150 to 300 cases per million (Barnes & Mayes, 2012; Mayes et al., 2003; Nikpour et al., 2010), it is more common than most of the more than100 rheumatic diseases[1]. The overall incidence rate of SSc is 21 per million each year (Barnes & Mayes, 2012; Mayes et al., 2003; Nikpour et al., 2010). Although SSc occurs over the lifespan, the majority of patients have a disease onset between the ages of 30 and 50 (Mayes et al., 2003; Mayes & Reveille, 2004). Both genders are affected; however, women are at a 4 to 7 times greater risk (Mayes & Reveille, 2004; Nikpour et al., 2010). African Americans and the Choctaw Native American tribe, who reside predominantly in Oklahoma, have a greater burden of disease, but SSc does affect all racial and ethnic groups (Mayes, 2003; Nikpour et al., 2010).

The etiology of SSc is currently unknown. A number of studies have suggested that SSc may be partially influenced by genetics (Assassi et al., 2009; Mayes, 2003; Mayes & Reveille, 2004; Nikpour et al., 2010). Although specific risk factors have not

[1] Rheumatic diseases which are more common include osteoarthritis, rheumatoid arthritis, systemic lupus, Sjögrens syndrome, and spondylarthritides (Helmick et al., 2008).

yet been identified, it is suspected that environmental or occupational exposures also play a role in disease development (Barnes & Mayes, 2012; Oliver & Silman, 2009). Estrogen and reproductive history have also been proposed as risk factors of SSc, although there are no strong and consistent links (Mayes, 2003; Mayes & Reveille, 2004).

Disease severity and health-related quality of life

Because SSc is a disease of multiple bodily systems, there is no single diagnostic test nor a global indicator of disease severity (Hudson, Steele, Canadian Scleroderma Research Group, & Baron, 2007; Medsger, 2003). Physician assessments of clinical variables such as forced vital lung capacity and skin thickness have been widely used as measures of disease damage and severity (Hudson et al., 2007). Diffuse or limited disease classification can also be considered a proxy for disease severity, given that the diagnostic classification system by Leroy et al. (1988) is defined primarily by patterns and severity of skin thickening.

Other indices such as the *Valentini Disease Activity Index* and *Medsger Disease Severity Score* which combine clinical, laboratory, and patient reported variables have been proposed, with scores ranging from mild to end-stage disease (Hudson et al., 2007; Medsger, 2003). The *Valentini Disease Activity Index* includes three patient assessments (perception of change in skin, vascular, and cardiopulmonary symptoms), whereas all ratings of the *Medsger Disease Severity Score* are clinician administered (Hudson et al., 2007). Although these indices offer a snapshot understanding of overall severity, the total scores collapse information on the clinical characteristics such as skin sclerosis and lung

disease, and thus the overall score may be less precise than each of these components individually.

The complications of SSc are associated with consequences in mental and physical health-related quality of life. An in-depth qualitative study of 19 patients with SSc suggested that pain, coping, social issues, appearance, and communication with one's physician are a patient's primary disease-related concerns (Suarez-Almazor, Kallen, Roundtree, & Mayes, 2007). Individuals with SSc report problems in multiple domains (Malcarne, Fox, Mills & Gholizadeh, 2013; Thombs et al., 2010) including anxiety and depression (Benrud-Larson et al., 2002; Hyphantis et al., 2007; Legendre, Allanore, Ferrand, & Kahan, 2005; Richards, Herrick, Griffin, Gwilliam, & Fortune, 2004), body dissatisfaction/low appearance self-esteem (Benrud-Larson et al., 2003; Malcarne, Hansdottir, Greenbergs, Clements, & Weisman, 1999; Van Lankveld, Vonk, Teunissen, & van den Hoogen, 2007), sleep (Bassel et al., 2011; Frech et al., 2011; Milette et al., 2011; Prado, Allen, Trevisani, Toscano, & Earley, 2002), fatigue (Assassi et al., 2011; Thombs et al., 2008; Yacoub, Bensabbah, & Hahhah-Hassouni, 2012), poor interpersonal functioning (Benrud-Larson et al., 2002; Kwakkenbos et al., 2012), sexual difficulties (Knafo, Haythornthwaite, Heinberg, Wigley, & Thombs, 2011; Schouffoer et al., 2009), disability (Hudson et al., 2008; Malcarne et al., 2007; Müller, Rehberger, Günther, & Schmitt, 2012; Sharif et al., 2011), and pain (Benrud-Larson et al., 2002; Del Rosso et al., 2004; Malcarne et al., 2007; Richards et al., 2003; Schieir et al., 2010).

Indicators of disease status (e.g., forced vital lung capacity, skin thickness) can be helpful in understanding a patient's perception of their health and, relatedly, quality of life; however, the explanatory value of medical variables is limited (Malcarne, 2004;

Malcarne et al., 2007). Researchers and clinicians have become increasingly aware that disease severity is inadequate for differentiating between patients who are at risk for poor quality of life in SSc (Malcarne, 2004; Malcarne et al., 2007). Correspondingly, the focus has turned to psychosocial models for understanding health-related quality of life difficulties (Malcarne et al., 2013; Richards et al., 2004).

Pain

A significant quality of life issue in SSc is chronic pain. Pain is a virtually ubiquitous problem in SSc and, like other rheumatic conditions, is a complex process with nociceptive (acute mechanical damage/inflammation), neuropathic (peripheral nerve damage/dysfunction), and central (central nervous system processing dysfunction) pain syndrome properties (Borenstein, 2010). Early in the disease process, patients generally report nonspecific muscle pain, stiffness, and digital discomfort and puffiness (Medsger, 2003). Rheumatologists observe that there is substantial variability in the progression of pain. As the disease progresses, patients report gastrointestinal and esophageal pain (Franck-Larsson, Graf, & Rönnblom, 2009), and clinically, there appears to be periods of worsening and improvement (Medsger, 2003), although the natural history of SSc pain has not been documented empirically.

Assessments of pain rely on self-report, given that pain is a subjective, even private, experience. In a recent, cross-sectional study (N = 585, with 61% being limited and 39% being diffuse) from the Canadian Scleroderma Research Group Registry, Schieir and colleagues (2010) found that 83% of all SSc patients experience some level of pain. This is similar to pain prevalence reported in other studies of SSc patients

(Benrud-Larson et al., 2002; Richards et al., 2004; Edwards, Goble et al., 2006). Patients report a wide range of experiences from mild discomfort to incapacitating pain. In general, the majority of patients report mild pain (Benrud-Larson et al., 2002; Georges et al., 2006; Haythornthwaite, Heinberg, & McGuire, 2003; Malcarne & Greenbergs, 1996; Malcarne et al., 2007; Schieir et al., 2010). However, within the Canadian registry 37% had moderate or severe levels of pain (Schieir et al., 2010). A number of studies suggest that patients with the limited subtype report lower levels of pain than patients with the diffuse subtype (Benrud-Larson et al., 2002; Georges et al., 2006; Malcarne et al., 2007; Richards et al., 2003). However, the differences are generally small, if statistically significant, suggesting that there may not be major between-group clinical implications regarding pain (Del Rosso et al., 2004; Schieir et al., 2010).

There is wide recognition that, even at mild levels, pain is implicated in disability, work ability/employment status, excessive physician visits, high costs, and more generally, decreased quality of life (Bassel et al., 2011; Carreira, 2006; Edwards et al., 2011; Georges et al., 2006; Haythornthwaite et al., 2003; Hudson et al., 2008; Knafo et al., 2011; Milette, et al., 2011; Sandqvist, Scheja, & Hesselstrand, 2010; Wilson, 1997; Yacoub, Amine, Bensabbah, & Hajjaj-Hassouni, 2012). These personal, social, and financial expenses highlight the importance of better understanding the nature of SSc. Indeed, pain-related quality of life has been recognized as “the most important patient-reported outcome in rheumatology” by the 2010 Report of the American College of Rheumatology Pain Management Task Force (Borenstein et al., 2010)

Historically, rheumatologic pain has been considered a symptom secondary to a pathological process (i.e., the reductionistic biomedical model of pain). In SSc, pain is

thought to be a result of disease activity and previously sustained damage (Carreira, 2006). Clinical variables that have been have been indicated with pain in SSc include Raynaud's phenomenon, nerve damage, arthritis, digital ulcers, swollen joints, skin thickening, inflammatory myopathy, and gastrointestinal and esophageal symptoms (Johnson, Gladman, Schentag, & Lee, 2006; Haythornthwaite, Heinberg, & McGuire, 2003; Malcarne et al., 2007; Merkel et al., 2002; Schieir et al., 2010; Toffolo, Furtado, Klein, Watanabe, Andrade, & Natour, 2008). Given the diversity of pain sites, and that the level of pain one experiences is not always relative to clinical variables and tissue damage (Benrud-Larson et al., 2002; Edwards, Calahan, Mensing, Smith, & Haythornthwaite, 2011), pain has been difficult to characterize in SSc. This underscores the potential importance of patient-level psychosocial variables in SSc-related pain.

The Biopsychosocial model of pain in SSc

A more holistic conceptualization, the biopsychosocial model of pain, is a widely accepted framework that takes biological, psychological, and social perspectives into account (Fava & Sonino, 2008; Gatchel, Peng, Peters, Fuchs, & Turk, 2007). This model suggests that pain is not a purely physical phenomenon. Instead, it highlights the interconnections among the disease, person, and environment, and more specifically, it postulates that none of these factors can explain pain in isolation. Accumulated evidence from observational studies from samples with pain-related disorders suggests that pain is related to mood and affect, pain behavior, pain cognitions, communication of pain, social support, and demographic characteristics (Gatchel et al., 2007). Although these relationships are often studied in a bivariate manner, the various factors are better

understood synergistically, as they work together in complex ways to shape perceptions of pain (Gatchel et al., 2007).

Surprisingly, the majority of studies of pain in SSc have focused solely on its medical correlates, although several have evaluated psychosocial predictors as well. There have also been a number of biopsychosocial pain investigations across other rheumatic diseases (Edwards et al., 2011). Findings from diseases such as rheumatoid arthritis, osteoarthritis, lupus, fibromyalgia, and others can help inform understanding about pain in SSc until more disease-specific studies are carried out. Together, the findings from these studies provide a framework of potentially important biopsychosocial aspects of pain in SSc, which are detailed below.

Emotional Health

Depression is common in rheumatic disease (Dickens, McGowan, Clark-Carter, & Creed, 2002), and especially for patients with SSc, who report higher levels of depressive symptoms than patients with rheumatoid arthritis (Danieli et al., 2005). In SSc, the estimated rates of depression are between 36% and 65% (Thombs et al., 2007). Anxiety is also prevalent, with rates that have been shown to exceed depression in rheumatoid arthritis (Ødegård, Finset, Mowinckel, Kvien, & Uhlig, 2007) and SSc (Legendre et al., 2005; Ostojic, Zivojinovic, Reza, & Damjanov, 2010). Emotional health problems are commonly implicated in pain, with up to half of people in chronic pain also reporting clinically significant depression and/or anxiety (Gatchel et al., 2007). Poor emotional health may be a result of being in pain, pain may be exacerbated by poor mood, or it is possible that the two occur in conjunction. Similar patterns occur in the rheumatic

diseases, as patients with fibromyalgia, osteoarthritis, and rheumatoid arthritis who experience pain are at a 2 to 8 times greater risk for clinically significant depression (Edwards et al., 2011; Goldenberg, 2010). In a large, cross-sectional analysis of 22,131 rheumatoid arthritis patients derived from the National Bank for Rheumatic Diseases, pain was the third most important correlate of depression, following symptom intensity, and the number of reported comorbidities, such as cardiovascular and gastrointestinal disorders (Wolfe & Michaud, 2009).

Mental health constructs including negative affect, mood, anxiety, and depression have been linked with pain in a number of cross-sectional studies in SSc (Benrud-Larson et al., 2002; Georges et al., 2006; Hansdottir, Malcarne, Furst, Weisman, & Clements, 2004; Hyphantis et al., 2007; Kwakkenbos et al., 2012; Milette, Hudson, Baron, Thombs & the Canadian Scleroderma Research Group, 2010; Richards et al., 2004; Schieir et al., 2010; Wafki et al., 2012). In one of the first such studies of 142 SSc patients, Benrud-Larson and colleagues (2002) found that pain was a strong predictor of depression ($\beta = .43$, $p \leq .01$) in a model that also included employment, education, and disability. Similarly, Kwakkenbos and colleagues (2012) found a smaller link between pain and depression ($\beta = .11$, $p = .05$) in SSc patients ($N = 215$), after adjusting for 19 other variables including demographics, disease severity, and psychosocial concerns such as coping, appearance self-esteem, and social support. A number of other studies have demonstrated the mood-pain relationship in SSc, with the largest study to date ($N = 585$), showing a modest link ($b = .08$, $p < .05$, 95% CI: .06-.10) after accounting for a number of relevant medical variables (Schieir et al., 2010). Pain has also been linked with anxiety ($\beta = .31$, $p = .009$) in a model with demographics, personality, and other clinical variables

in a smaller sample (N = 56) of SSc patients (Hyphantis et al., 2007). These studies provide convincing evidence that pain and emotional health are associated; however, the strength of the unique relationship appears to be somewhat dependent on the other variables that are simultaneously considered. Additionally, all these analyses were cross-sectional, precluding conclusions about causality and how pain and emotional health may fluctuate over time.

Although there have been no studies that have addressed the longitudinal relationship between emotional health and pain in SSc, several longitudinal studies have been conducted in other rheumatic disorders. To date, the findings have been mixed, suggesting that pain may affect emotional health, and that poor emotional health may exacerbate pain. In an early investigation, Brown (1990) found a consistent correlation between depression and pain over 7 points of data collection that took place every 6 months, in a sample of patients with rheumatoid arthritis (N = 243). However, causality between the two was precarious; increased pain preceded depression only during the final 12 months of the study, and thus there was not adequate evidence that pain led to increased depression (Brown, 1990). Another study of rheumatoid arthritis patients (N = 238) demonstrated that anxiety was predictive of pain over 10 years (b = 0.33, se = 0.04, p < .0001; Ødegård et al., 2007). Wolfe and Michaud (2009) found that pain lead to depression in a cohort of rheumatoid arthritis patients from the National Data Bank for Rheumatic Diseases, as pain was shown to continually predict depression over 9 years. In a separate analysis which contained some subjects from this cohort, and others from a Swiss cohort (N = 15,282), pain predicted both the stable and fluctuating components of emotional health over 4 time-points in 4 years (Courvoisier et al., 2012). Additionally,

Hawker and colleagues (2011) found that pain was linked with increased depressive symptoms over time, in a sample of 529 patients with osteoarthritis; however, disability and fatigue fully mediated this relationship. Conversely, depression has also been shown to be predictive of pain. For instance, depression was the best predictor of pain at 1- and 2-year follow-ups among 3,407 osteoarthritis patients (Riddle, Kong, & Fitzgerald, 2011).

Illness Behaviors and Cognitions

Maladaptive illness behaviors, defined as extreme cognitive, emotional and behavioral reactions to illness (Mechanic & Volkart, 1961), may be of interest in understanding pain in SSc. Illness behaviors include a range of reactions from active behavior, such as overusing the healthcare system, to mental behavior (i.e., cognitions), such as rumination and worry (Pilowsky & Spence, 1975). Of particular interest, with regard to pain, are cognitive and affective responses to SSc, which can range from general concerns, to preoccupation with pain, to feeling helpless or fearful. The severe responses are sometimes termed worry or catastrophizing, and have been linked with increased pain in many clinical populations (Gatchel et al., 2007). Extreme and negative cognitions have also been reliably associated with pain in rheumatic diseases (Edwards, Bingham et al., 2006; Edwards et al., 2011). For example, in a sample of 29 fibromyalgia patients, catastrophizing was correlated with self-reported pain ratings ($r = .41$, $p < .05$; Gracely et al., 2004). Pain cognitions were similarly predictive of pain ($\beta = 0.35$, $p = 0.002$) among 106 osteoarthritis patients (Somers et al., 2009). Additionally, Edwards and colleagues (2010) found that catastrophizing and pain severity were associated in 185

patients with rheumatoid arthritis. More specifically, catastrophizing interacted with educational attainment and social status such that catastrophizers with good social support and higher education reported lower pain (Edwards et al., 2010), highlighting the importance of examining the components of the biopsychosocial model conjointly.

The relationship between pain and extreme cognitive and emotional responses has also been demonstrated in SSc. Richards and colleagues (2003) found that patients (N = 49) who reported higher levels of pain also reported more consistently thinking about the serious consequences of SSc (r = .38, p < .05). Maladaptive disease cognitions showed partial correlations with pain (rs = |.31-.40|, ps < .01) controlling for marital status, disease symptoms, and physical functioning among 123 SSc patients (van Lankveld, Teunissen, Näring, Vonk, & van den Hoogen, 2008). In another study of 190 patients, Edwards, Goble, and colleagues (2006) assessed the link between catastrophizing and affective and sensory pain. In this sample, catastrophizing was independently linked with sensory pain (β = .24, p = .001) after adjusting for demographic covariates, disability, and depression (Edwards, Goble et al., 2006). A significant interaction also emerged, accounting for 4% of the variance in affective pain (Edwards, Goble et al., 2006). Specifically, educational attainment and social support moderated the relationship between cognitions and pain affect; patients who engaged in catastrophic cognitions, had little education, and poor social support also reported worse pain affect (Edwards, Goble et al., 2006).

Although there have been no prospective studies of pain-related cognitions in SSc, there have been several investigations in rheumatoid arthritis. Covic, Adamson, Spencer, and Howe (2003) found that feeling helpless was predictive of pain 1 year later

in a sample of 157 patients, and that pain, was predictive of depression. Similarly, Lefebvre and Keefe (2002) found that patients (N = 45) who engaged in extreme pain cognitions also reported greater pain in a daily diary study over 30 days. Thus, there does appear to be some evidence that pain cognitions can influence pain directly, but that the inclusion of emotional health is imperative to better understand this relationship.

Social Resources

Social support, a multidimensional construct comprised of interpersonal empathy, companionship, and aid, is thought to affect pain perceptions directly, or by enhancing psychological well-being and mood, and promoting health behavior such as participating in activities and adhering to medical regimens (Uchino, 2006). Cumulative evidence suggests that low levels of social support are associated with greater pain in many populations (Gatchel et al., 2007), including those with rheumatic disease (Edwards et al., 2011); although many studies have focused on the indirect relationship between social support and pain via mood or coping. Pain may restrict one's ability to participate in their typical social activities, paradoxically decreasing support at a time when it would be particularly beneficial.

Research in the rheumatic diseases has shown that pain and social support are associated. In a large, cross-sectional study (N = 628) of patients with different rheumatic diseases, pain was significantly correlated with satisfaction with social support (r = -.29, p < .001; Savelkoul et al., 2000). Social support may be of particular importance in SSc, as evidence suggests that patients may avoid socializing due to appearance concerns (Haythornthwaite, Heinberg, & McGuire, 2003), and over 50% of patients with

rheumatic disorders report moderate to high levels of loneliness (Kool & Geenen, 2012). Benrud-Larson and colleagues (2002) found that limited and diffuse cutaneous SSc patients did not generally differ on social adjustment to their diseases, although limited patients did report a slightly larger social network (12.56 social contacts *vs*. 10.00 social contacts; $p < .05$). Additionally, pain and social adjustment were significantly related, although this relationship was accounted for by depression (Benrud-Larson et al., 2002).

A number of studies have noted a connection between social resources and depression, which is of importance, given that depression may mediate the social support-pain relationship (Uchino, 2008). Significant relationships have been found between depression and the unavailability of social support (Coty & Wallston, 2010), poor quality of social support (Kwakkenbos et al., 2012), low satisfaction with emotional support (Roca, Wigley, & White, 1996), potential for social support (van Lankveld et al, 2008) and social network size (Sandusky, McGuire, Smith, Wigley, & Haythornthwaite, 2009). However, Doeglas and colleagues (2004) did not find a social support-depression relationship in rheumatoid arthritis. The findings between social support and depression, and depression and pain (as described in the *Emotional Health* section, above) underscore the importance of looking at these variables together in a single model.

Several prospective analyses across rheumatic diseases have suggested that social support affects pain perceptions both directly and indirectly. Waltz, Kriegel, and van't Pad Bosch (1998) found that lower perceived spousal emotional support at baseline was predictive of greater pain at 1 year later. Similarly, Zautra and Smith (2001) found that greater interpersonal stress preceded higher pain ratings each week, in a longitudinal study spanning 12-20 weeks among 188 women with rheumatoid arthritis and

osteoarthritis. In a longitudinal study of 78 patients with rheumatoid arthritis, a lack of social support was related to greater levels of pain three and five years later, even after accounting for baseline levels of pain, demographics, and disability (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003). Interestingly, social support did not interact with personality or disease status, suggesting that it was an independent predictor of pain (Evers et al., 2003). In a one-week daily diary study, Holtzman, Newth, and Delongis (2004) did not find a direct relationship between satisfaction with social support and pain severity among 73 patients with rheumatoid arthritis; however, social support indirectly influenced pain via the use of adaptive coping strategies. Notably, this study was of a much shorter duration than the other studies that ranged from 12 weeks to 5 years of follow-up. Perhaps moment-to-moment changes in social support are more important in predicting patient behavior, rather than pain directly, while the cumulative effects of poor social support over long periods of time serve as a direct connection to pain.

Longitudinal Pain Research in SSc

There is a clear need for additional study of pain in SSc, particularly investigations that consider the collective influence of medical, affective, cognitive, and social variables. Considering the chronic, long-term nature of SSc, it is surprising that the majority of studies about pain have been cross-sectional. Longitudinal research studies in osteoarthritis (Zhang et al., 2009), rheumatoid arthritis (Covic et al., 2003; Courvoisier et al., 2012; Keefe, Brown, Wallston, & Caldwell, 1989), fibromyalgia (Dobkin, DeCivita, Abrahamowicz, Baron, & Bernatsky, 2006), and lupus (Gilboe, Kvien, & Husby, 2001),

have facilitated a better understanding of pain processes, and related biopsychosocial predictors, in these other rheumatic diseases.

There has been one study that evaluated SSc pain prospectively (Sekhon, Pope, the Canadian Scleroderma Research Group, & Baron, 2010). Patients in this study (N = 109) reported an overall slight increase in pain between consecutive physician visits, ranging from 8-18 months apart (Sekhon et al., 2010). Of these patients, 10.1% rated their overall health status, including pain, as having improved over the past year, whereas 37.6% reported a decline (Sekhon et al., 2010). This study is an important, first investigation in the longitudinal nature of SSc-related pain. However very little is known about the (in)stability of pain, and the patterns of biopsychosocial influence on pain in SSc. Prospective studies are needed to describe pain trajectories and to provide a more insightful understanding of biopsychosocial correlates of pain over time.

Studies

There is a clear need for research aimed at understanding potentially modifiable predictors and corollaries of disease-related pain, particularly in the integration of medical, emotional, cognitive, and social variables. Because there have been few studies examining pain, and even less attention with regard to these variables, a sequence of studies were designed to expand understanding of pain in SSc by applying the biopsychosocial model.

For all studies, data was derived from the *Genetics versus ENvironment In Scleroderma Outcome Study* (GENISOS), a prospective cohort study of patients with SSc (Reveille et al., 2001). The GENISOS represents a collaboration among the University of

Texas-Houston Health Center, the University of Texas Medical Branch at Galveston, and the University of Texas-San Antonio Health Science Center. Potential participants were recruited from the private practices of the faculty rheumatologists, outpatient clinics of the county hospital rheumatology clinics, and via advertisements through local chapters of the Scleroderma Foundation and local television. Enrollment has been ongoing since 1998. Therefore the sample sizes for each of the three studies differs somewhat given the date of data extraction for each. To participate, patients had to be at least 18 years old, diagnosed by a physician with SSc as defined by the 1980 American Rheumatism Association criteria (Masi et al., 1980), within 5 years of their disease onset (defined as the first non-Raynaud's symptom), a defined ethnicity (i.e., all four grandparents from the same ethnic group), and a resident within the geographic catchment area of one of the participating centers.

After agreeing to participate and giving informed consent, each patient was interviewed over the phone to determine their language of preference, and each patient's medical record was reviewed for sociodemographic and clinical information. Participants were later mailed a survey packet to be completed and brought to their first study visit. The study packet contained demographics questions, health care access/utilization questions, and psychosocial measures. The comprehensive baseline/enrollment visits were conducted as regular outpatient visits and intermittently inpatient services (as needed) at the hospitals staffed by the clinician-investigators. During this visit, data from the medical records were corroborated and clarified. Patients also received comprehensive clinical examinations including evaluations of clinical manifestations (e.g., muscle weakness, sclerodactyly, modified Rodnan skin score, Raynaud's

phenomenon, gastrointestinal involvement), comorbidities, tests of pulmonary function, an electrocardiogram, a chest radiograph, and blood samples. Translators were used for participants who did not speak English.

The aim of the first study (Merz et al., 2013) was to evaluate the psychometric properties of a commonly used measure of illness behavior (i.e., the Illness Behavior Questionnaire; Pilowsky & Spence, 1983) for use in the two succeeding studies. Illness behaviors, especially affective and cognitive responses such as excessive and anxious health-related concerns, have been shown to be an important component of the biopsychosocial model. Data from the baseline assessment of the GENISOS were utilized. Four previously derived factor structures, which were obtained from predominantly psychiatric samples were tested using confirmatory factor analysis. Next exploratory factor analyses were conducted to uncover a plausible factor structure relevant to patients with SSc. Convergent and divergent validity was tested by evaluating the relationships between each factor and measures of disease severity, fatigue, pain, disability, social support, and mental health. It was hypothesized that higher scores (i.e., greater endorsement of different illness behaviors) would be related to worse fatigue, pain, disability, social support, and mental health.

The aim of the second study (Merz et al., 2014) was to examine interactions among medical, psychological and social characteristics of SSc patients and determine the extent to which classes of patients, based on these characteristics, differed with regard to pain and analgesic use. Data from the baseline assessment of the GENISOS were utilized. Indicators of disease severity, perceived physical health, health worry, mental health, and social support were analyzed using a type of finite mixture modeling (i.e.,

latent profile analysis) to derive homogenous classes with similar biopsychosocial trait profiles. The resultant profiles were then compared using ANOVA and chi-square analyses. The first hypothesis was that at least two classes describing distinct biopsychosocial profiles would emerge. It was also hypothesized that profiles characterized by poorer subjective ratings of perceived physical health, health worry, mental health, and social support would be related to pain and medication, whereas skin thickening and percent predicted forced vital lung capacity within the profiles would be less relevant.

The aim of the third study (Merz et al., in preparation) was describe the course of pain over three measurement observations and to determine the biopsychosocial correlates related to pain over time. Data from the first three measurement observations of the GENISOS were utilized. Repeated measures of the pain measure were modeled as a time-varying outcome using multilevel modeling. Disease classification, baseline values of mental health, perceived physical health, health worry, and social support were included as time-invariant predictors in conditional models. It was hypothesized that pain would become more severe over time, given the degenerative nature of SSc. Based on the biopsychosocial theory of pain and the aforementioned empirical findings, it was hypothesized that the more severe diffuse cutaneous disease classification, poorer mental health, poorer perceived physical health, greater health worry, and lower social support would be associated with more severe pain and a poorer pain prognosis. The final hypothesis for the third study was that the psychosocial variables would be more important than disease type in understanding longitudinal pain.

CHAPTER 2: MEASURING ILLNESS BEHAVIOR IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Running title: Validity of the IBQ in SSc Patients

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ABSTRACT

Illness behaviors (cognitive, affective, and behavioral reactions) among individuals with systemic sclerosis (SSc) are of clinical concern due to relationships between these behaviors and physical and mental-health quality of life such as pain and symptoms of depression. Self-report measures with good psychometric properties can aid in the accurate assessment of illness behavior. The Illness Behavior Questionnaire (IBQ) was designed to measure abnormal illness behaviors; however, despite its long-standing use, there is disagreement regarding its subscales. The goal of the present study was to evaluate the validity of the IBQ in a cohort of patients with SSc. Patients with SSc (*N* = 278) completed the IBQ at enrollment to the *Genetics versus ENvironment In Scleroderma Outcome Study* (GENISOS). Structural validity of previously derived factor solutions was investigated using confirmatory factor analysis. Exploratory factor analysis was utilized to derive SSc-specific subscales. None of the previously derived structural models were supported for SSc patients. Exploratory factor analysis supported a SSc-specific factor structure with 5 subscales. Validity analyses suggested that the subscales were generally independent of disease severity, but were correlated with other health outcomes (i.e., fatigue, pain, disability, social support, mental health). The proposed subscales are recommended for use in SSc, and can be utilized to capture illness behavior that may be of clinical concern.

Introduction

Systemic sclerosis (SSc) is a chronic, rheumatic condition characterized by the thickening of skin and fibrosis of internal organs. It is most common among women between ages 30 and 50 but is relatively rare, with an overall prevalence of 150 to 300 cases per million (Barnes & Mayes, 2012; Mayes et al., 2003). There are two subtypes; limited cutaneous SSc is milder and has less severe organ involvement, diffuse cutaneous SSc is characterized by more extensive skin and organ involvement and worse prognosis (Medsger, 2004). Individuals with SSc report problems across multiple domains including fatigue (Assassi et al., 2011), pain (Schieir et al., 2010), disability (Malcarne et al., 2007), sleep (Frech, Hays, Maranian, Clements, Furst, & Khanna, 2011), interpersonal functioning (Suarez-Almazor, Kallen, Roundtree, & Mayes, 2007), anxiety, depression (Legendre, Allanore, Ferrand, & Kahan, 2005), and more generally, physical and mental-health related quality of life (Hudson et al., 2009). There is also an increasing awareness that disease severity is inadequate for discriminating patients who are at risk for poor adjustment, suggesting a need to also emphasize psychosocial variables (Malcarne et al., 2007).

Illness behaviors, defined as cognitive, emotional and behavioral reactions (Mechanic & Volkart, 1961), can occur in response to chronic diseases such as SSc. Although illness behavior is neutral by definition, some behaviors are more adaptive than others (Pilowsky & Spence, 1975). For example, concerns about health may encourage a patient with SSc to seek necessary medical help, or could lead to excessive doctor's visits and anxiety. It may be helpful to divulge one's feelings about their disease to others, but excessive disclosure may lead to social network problems. Such extreme responses,

termed *abnormal illness behavior*, also include actions to maintain the sick role, or a level of disability that exceeds the given pathology (Pilowsky & Spence, 1975).

The Illness Behavior Questionnaire (IBQ) is a widely used tool that was developed to measure these reactions (Pilowsky & Spence, 1983). The IBQ contains 62 yes/no items, including all 14 items of the Whiteley Index (Pilowsky, 1967). The history and development of the IBQ have been discussed elsewhere (Prior & Bond, 2008). The IBQ was developed in a relatively small sample (N = 100) of pain clinic patients using principal components analysis with varimax rotation, which yielded 7 subscales[2]: *General Hypochondriasis* (anxious health-related concern), *Disease Conviction* (belief that a "real" disease is present), *Psychological vs. Somatic Functioning* (tendency to somaticize), *Denial* (tendency to attribute life stress to physical problems), *Affective Inhibition* (inability to express personal feelings to others), *Affective Disturbance* (anxiety, depression), and *Irritability* (anger, friction).

The IBQ has been associated with physical and psychological quality of life across a variety of conditions such as healthcare utilization and disability (Clark & Smith, 1997), post-operative outcomes (Hayden, Myers, & Jamieson, 2006), health-related quality of life (Sanchez et al., 2009), psychopathology (Hobbis, Turpin, & Read, 2003), anxiety (Joyce, Bushnell, Walshe, & Morton, 1986), depression (Fava, Pilowsky, Pierfederici, Bernardi, & Pathak, 1982), fatigue (Assasi et al., 2011, Burgos, Alarcón, McGwin, Crews, Reveille, & Vilá, 2009), pain (Keefe, Crisson, Maltbie, Bradley, & Gil,

[2] Pilowsky and Spence (1983) initially used items 1-52 in their analysis and removed 22 items due to poor loadings. Items 53-62 were written afterwards based on face validity and added to the subscales to improve internal consistency reliability. Thus, only 40 of the 62 items were ultimately used in the original 7 subscales.

1986), and social support (Grassi & Rosti, 1996). Unfortunately the psychometric properties of the IBQ have not been well-established.

The original factor structure (Pilowsky & Spence, 1983) has been shown to be unstable across studies. Although internal structure is only one consideration when evaluating a measure's overall performance (Hopwood & Donnellan, 2010), this does suggest that the interpretability of the IBQ for other disease groups may be uncertain. Several alternate structures have been proposed (Main & Waddell, 1987; Prior & Bond, 2010; Zonderman, Heft, & Costa, 1985), although most researchers utilize the original subscales. The original subscales have been used in patients with cancer (Tulipani, Morelli, Spedicato, Maiello, Todarello, & Porcelli, 2010), gastroesophogeal reflux disease (Hayden et al., 2006), myocardial infarction (Byrne, 1982), stroke (Clark & Smith, 1997), lupus (Alarcón et al., 2004), fibromyalgia (Huber, Suman, Biasi, & Carli, 2009), osteoarthritis, rheumatoid arthritis (Ahern, McFarlane, Leslie, Eden, & Roberts-Thomson, 1995), chronic fatigue syndrome, multiple sclerosis (Trigwell, Hatcher, Johnson, Stanley, & House, 1995), and back pain (Keefe et al., 1986; Waddell, Pilowsky, & Bond, 1989).

There are several possibilities as to why the IBQ has not been well-replicated in different populations and diseases. The IBQ may have been overfactored (Main & Waddell, 1987), which can lead to unreliable or split factors (Fava & Velicer, 1992). Because IBQ items are binary, poor factor specification is especially problematic given the high influence of item-level error on a factor (Main & Waddell, 1987). It is also plausible that previous samples were not large enough to reproduce the IBQ's structure. The original subscales were developed using data from 100 patients, although the

structure did later replicate in 1,578 pain and psychiatric patients (Pilowsky, 1993). Another study (Main & Waddell, 1987) also used a relatively small sample (N = 200), but others reported findings from large (N = 675-1,061) samples (Prior & Bond, 2010; Zonderman et al., 1985).

Another consideration is that the factorial instability is due to a disconnect between methodological and practical considerations, and the challenges inherent to measuring complex psychological constructs (Hopwood & Donnellan, 2010). Alternately, it has been suggested that the IBQ's inconsistent factor structure is due to disease-specific illness behaviors unique to the physical process, treatment, and functional and social implications (Prior & Bond, 2008). Accordingly, some items may be more or less relevant for a given disease. For example, the *Disease Conviction* subscale may not apply to individuals with an identified pathology; it is reasonable that a person with a diagnosed disease would indeed have a strong belief that they have a disease. Thus, a new research agenda has been proposed (Prior & Bond 2008; 2010), which entails investigating the need for disease-specific subscales to best capture the experiential, cognitive, and behavioral aspects of a given illness. Because understanding illness behavior may aid in providing total clinical care, so that patients with maladaptive illness behaviors may be identified and offered additional intervention or referral, it would be beneficial to determine whether the IBQ can be used in patients with SSc.

The study's first aim was to evaluate the various IBQ factor structures. If the internal structure is not upheld, which could suggest problems with previously derived solutions for patients with SSc, the second aim of the study was to uncover a plausible factor structure specifically for SSc. The third aim was to establish convergent and

divergent validity of the subscales derived from the best fitting model, via correlations of derived subscales with disease severity, and other quality of life variables. We predicted that the dimensions of the IBQ would have little to no correlation with disease severity, as has been shown with other psychosocial variables (Malcarne et al., 2007). We also predicted that greater endorsement of illness behaviors would be related to worse fatigue, pain, disability, social support, and mental health, as has been previously demonstrated (Assassi et al., 2011; Clark & Smith, 1997; Joyce et al., 1986; Fava et al., 1982; Burgos et al., 2009; Keefe et al., 1986; Grassi & Rosti, 1996).

Method

Subjects

This investigation utilized data provided by participants from the *G*enetics versus *EN*vironment *I*n Scleroderma *O*utcome *S*tudy (GENISOS), a prospective early-disease (within 5 years of onset) cohort study that represents collaboration among the University of Texas Health Science Center at Houston, the University of Texas Medical Branch at Galveston, and the University of Texas-Health Science Center at San Antonio. Enrollment is ongoing. Data are collected annually via a clinical exam and survey packet during regular outpatient visits, and intermittently as inpatient services (as needed) at the hospitals staffed by the clinician-investigators. Patients with SSc who lived within the geographic catchment area of one of the three centers were recruited from the rheumatology faculty clinics, the county hospital, and chapters of the Scleroderma Foundation (Reveille et al., 2011). Participants had to be at least 18 years old.

Procedure

Baseline data from the GENISOS study were used (Reveille et al., 2011). IRB approval was obtained at all participating institutions, including San Diego State University and University of California, San Diego for analysis of archival data. All participants gave written informed consent. Participants received clinical examinations by the physician investigators including evaluations of clinical manifestations (e.g., sclerodactyly, skin thickening, Raynaud's phenomenon, gastrointestinal involvement), comorbidities, an electrocardiogram, a chest radiograph, and blood samples and completed a packet of psychosocial measures.

Measures

Illness Behavior Questionnaire (IBQ; Pilowsky & Spence, 1983). The IBQ is a 62-item self-report measure designed to measure illness behavior (see the supplementary appendix for basic item data). Using a yes/no format, respondents indicate whether an item describes them, with 'abnormal' behaviors being scored 1 point.

Modified Rodnan Skin Score (mRSS; Clements et al., 2000). The mRSS total score is an established indicator of skin disease severity in SSc calculated by measuring the extent and severity of skin thickening on 17 body surfaces by palpation on a 4-point scale (0 = uninvolved to 3 = severe thickening). Higher scores indicate greater severity.

Forced Vital Lung Capacity (% predicted FVC). Percent predicted FVC is a validated measure for severity of SSc-related interstitial lung disease (Furst et al., 2007). It indicates the ratio of the volume of air that the study subject can forcibly exhale after a maximum inspiration to the same volume in age, gender, weight, height, and ethnicity

matched unaffected controls. All pulmonary measurements met criteria outlined by the American Thoracic Society/European Respiratory Society, and were reviewed by a pulmonologist. Lower scores indicate greater severity of SSc-related interstitial lung disease.

Fatigue Severity Scale (FSS; Schwartz, Jandorf, & Krupp, 1993). The FSS is a widely used 29-item self-report questionnaire wherein respondents rate the extent of their agreement with statements regarding their level of fatigue on a Likert scale (1 = completely disagree to 7 = completely agree). It has demonstrated adequate test-retest reliability, discriminant validity, and convergent validity (Schwartz et al., 1993). The FSS yields an overall score and 4 factor-analytically derived subscales. The total score, in which higher total scores represent more severe global fatigue, was used in the current study. Internal consistency ($\alpha = .90$) was good.

Medical Outcomes Study Short-Form 36 (SF-36; Ware & Sherbourne, 1992). The SF-36 is a 36-item self-report health-related quality of life measure that yields 8 factor-analytically derived subscales and 2 composite scores of physical and mental health. The questions follow a variety of response formats, scoring algorithms are required for generating the subscales. It is reliable and valid for SSc (Danieli et al., 2005). The Bodily Pain ($\alpha = .87$) and Mental Health ($\alpha = .79$) subscales were utilized. Higher scores indicate better domain-related quality of life.

Modified Health Assessment Questionnaire (mHAQ; Poole, Williams, Bloch, Hollak, & Spitz, 1995). The mHAQ is a 8-item self-report index of overall disability. Respondents rate their functional ability to perform tasks on a 4-point scale (0 = without any disability to 3 = unable to do). It has been validated for use in SSc (Poole & Steen,

1991; Poole et al., 1995), and shown to have a one-factor structure (Cole, Motivala, Khanna, Lee, Paulus, & Irwin, 2005). Internal consistency (α = .91) was good in the current sample. Higher scores reflect greater disability.

Interpersonal Support Evaluation List (ISEL; Cohen, Mermelstein, Kamarck, & Hoberman, 1985). The ISEL is a widely-used 40-item self-report measure of perceived social support wherein respondents rate whether a statement is "probably true" or "probably false" based on their experience. The ISEL yields four subscales and a total score of overall support which has been supported using confirmatory factor analysis (Brookings & Bolton, 1988). The total score was used for the current study and demonstrated good internal consistency (α = .87). Higher scores indicate better social support.

Data Analysis

Factor analysis was conducted to achieve aims one and two. Theory-driven confirmatory factor analysis (CFA) was utilized to evaluate previously derived IBQ factor structures. If CFA models do not provide sufficient fit, it is reasonable to follow up with exploratory factor analysis (EFA; Schmitt, 2011). Data-driven EFA was conducted to explore alternate structures by estimating the number of underlying latent variables within the data and thus identifying SSc-specific subscales.

Because the IBQ contains binary data, traditional factor analytic techniques are inappropriate, as the assumptions of linearity and normality are violated (Woods, 2002). A tetrachoric correlation matrix, wherein it is assumed that a normally distributed continuous latent variable underlies the "truncated" binary items should therefore be used

(Woods, 2002). Moreover, ordinary least-squares and maximum likelihood estimation approaches are not recommended due to dependencies and systematic residuals among observed variables (Muthén & Satorra, 1995). Consequently, a tetrachoric correlation matrix with a weighted least-squares means and variance adjusted (WLSMV) estimation procedure in MPlus 6.1 (Muthén & Muthén, 1998-2010) that is robust to non-normal and non-independent data was used. Internal consistency for all factors in all models was evaluating using the Kuder-Richardson-20 formula.

Evaluation of model fit.

For CFA and EFA, it is recommended that samples are at least 200 (Schumacker & Lomax, 2004), although samples greater than 250 are preferred for binary data (Yu, 2002). The current sample is near the low end of this desired range, but does meet these recommendations. Because χ^2 tests may not be suitable to determine model fit, descriptive fit indices were also calculated (Millsap & Kwok, 2004). The Comparative Fit Index (CFI; Bentler, 1990) and Root Mean Square Error of Approximation (RMSEA; Steiger, 1990) were used, as other descriptors (e.g., Root Mean Square Residual; Hu & Bentler, 1999) are unfit for binary data (Yu, 2002). A model fit well if CFI values were $\geq$ .95 and RMSEA values were $\leq$ .05 based on widely accepted guidelines (Yu, 2002).

Previous researchers have used different combinations of items in their exploratory factor analyses of the IBQ. In the original study, items 1-52 were included in the analysis, and items 53-62 were added afterwards to increase the number of items per subscale and to improve internal consistency (Pilowsky & Spence, 1983). Prior and Bond (2010) used a similar strategy by including items 1-52 in their analysis, and later adding

items 54 and 59, based on face validity and internal consistency. Zonderman, Heft and Costa (1985) found that the solutions for two analyses (the first on items 1-52, the second on items 1-63) were identical and reported the latter solution. Main and Waddell (1987) removed 25 items due to poor reliability and/or incidence, leaving 37 items for the analyses. Given the heterogeneity of approaches, and Pilowsky's (1993) suggestion that the IBQ may be particularly useful as an item pool, all 62 items were analyzed in the EFA so that results were not reliant on face validity. Models with 1-7 factors were tested to reflect the various numbers of dimensions found in previous studies. A factor needed at least 3 items (preferably 4) to reduce the likelihood of over-factoring (Main & Waddell, 1987). In EFA, items with loadings of the strict criterion of >.40 was used to inhibit errors in factor estimation. Cross-loadings were determined as loadings greater than half of the primary loading. Although underfactoring (i.e., including too few factors in a model) has not typically been a criticism of the IBQ, it can lead to problems, such as the combination of multiple factors (Fava & Velicer, 1992); therefore, the pattern matrix was also inspected for interpretability. Items derived from the factor analysis were further evaluated for their contribution to the internal consistency of their subscale. Based on recommendations for decreasing redundancy among subscale items, items were retained if their removal from a subscale resulted in decreased internal consistency, and eliminated if internal consistency was unchanged upon removal (Devillis, 2012). Subscale intercorrelations were then evaluated; models with intercorrelations with high multicollinearity (r >.7) were considered unsuitable.

Results

Descriptive characteristics are available in Table 2.1. Skin thickening (t [274] = -13.79; diffuse M = 22.03 [11.10]; limited M = 6.74 [5.39]) and forced vital lung capacity (t [262] = 2.65; diffuse M = 80.09 [20.71]; limited M = 87.16 [22.36]) indicated greater disease severity in the diffuse subtype (ps < .001 and <.01, respectively).

CFAs of original and alternate models

First, CFA was used to examine the model fit of the 7 dimensions comprised of 40 items, as suggested by Pilowsky and Spence (1983). Internal consistencies were poor (.200 - .697); only *Affective Disturbance* (.759) was reliable. Model fit was poor statistically, χ^2 (719, N = 278) = 1048.04, p < .001, and descriptively, CFI = .893, RMSEA = .041. Interfactor correlations ranged from |.20–1.06[3]|, suggesting high redundancy among factors. Because internal consistency and solution were both poor, most dimensions were inadmissible, thus alternate structures were considered.

The 6 dimensions comprised of 47 IBQ items as suggested by Zonderman and colleagues (1985) were tested first. Internal consistency was better (.632 - .796). Model fit was poor statistically, χ^2 (1019, N = 278) = 1538.46, p < .001, and descriptively, CFI = .871, RMSEA = .043. Interfactor correlations ranged from |.21 – .81|.

The 6 dimensions comprised of 33 IBQ items as suggested by Main and Waddell (1987) were tested next. Internal consistencies ranged from .566 to .814. Model fit was

[3] Correlation coefficients among factors that are > 1 indicate that the factors are indistinguishable; therefore, model fit is unacceptable.

poor statistically, χ^2 (492, N = 278) = 1093.12, p < .001, and descriptively, CFI = .782, RMSEA = .066. Interfactor correlations ranged from |.32 – .72|.

Finally, the 3 dimensions comprised of 31 IBQ items as suggested by Prior and Bond (2010) were tested. Internal consistency was good (.733 - .805); however, model fit was poor statistically, χ^2 (431, N = 278) = 804.70, p < .001, and descriptively, CFI = .893, RMSEA = .056. Interfactor correlations ranged from |.69 – .74|.

Exploratory analysis of IBQ items[4]

Because none of the models fit adequately, EFA was utilized to determine if a better model could be derived (Table 2.2). The 4-factor model was the first to meet the descriptive fit criteria, therefore models 4-7 were evaluated for interpretability. Inspection of the simple structure of these models showed an adequate number of items on the 4- and 5-factor models. For the 6- and 7-factor models, several dimensions yielded only 2 to 3 items. Given the issues of over-factoring (Main & Waddell, 1987), these models were not evaluated further.

Both the 4- and 5-factor models were reviewed on the basis of simple structure and interpretability. Both contained 3 identical factors. However, the largest factor from the 4-factor model was split into 2 meaningful factors in the 5-factor model, suggesting that the 4-factor model was underfactored. At this point, 33 items were removed due to insufficient loadings or cross-loadings. Each factor was then further refined based on

[4] In the exploratory analysis, raw data (not reverse scored) were analyzed.

internal consistency, as described above. The final solution used 23 items. The factor loadings are shown in Table 2.3.

SSc-specific subscales of the IBQ

Table 2.4 describes the subscales, and items shared with subscales from previous solutions. Intercorrelations among the SSc subscales (*r*s = .00 to .38) were reasonable.

Symptom Bother. Three items that loaded onto this subscale were removed as they did not improve internal consistency. Thus, the first subscale retained the 5 best items out of the 8 that met the interpretability criteria. Higher scores indicate greater intensity and life interference of disease-related symptoms. Internal consistency (.778) was adequate.

Health Worry. One item that loaded onto the second subscale was removed as it did not improve internal consistency. Thus, the second subscale retained the 5 best items out of the 6 that met interpretability criteria. Higher scores indicate that a respondent is more preoccupied with health in general. Internal consistency (.725) was adequate.

Interpersonal Functioning. Two items that loaded onto the third subscale were removed as they did not improve internal consistency. Thus, the third subscale retained the 5 best items out of the 7 that met interpretability criteria. Higher scores indicate more interpersonal problems. Internal consistency (.720) was adequate.

Other Life Worries. Four items loaded onto the fourth subscale. Higher scores indicate a greater number of non-illness problems. Internal consistency (.715) was adequate.

Affective Inhibition. Four items loaded onto the fifth subscale. Higher scores reflect greater difficulty expressing emotion to others. Internal consistency (.662) for this subscale was weaker.

Relationships of subscales to quality of life outcomes

Correlations between the subscales and other measures were performed to establish convergent and divergent validity (Table 2.5). As predicted, the proposed subscales were not generally associated with disease severity. As predicted, the subscales were related to fatigue, pain, disability, social support, and mental health in the expected directions. Higher scores on the subscales were associated with worse outcomes, with stronger relationships among related domains (e.g., relationships between symptom bother and pain, or between affective inhibition and social support).

Discussion

The current study expands on efforts to create a useful measure that characterizes illness behaviors by examining the psychometric properties of the IBQ (Pilowsky & Spence, 1983) in patients with SSc. None of the previous solutions adequately fit data from patients with SSc. Failing to replicate the factor structure of a measure is one element that may call its performance into question, thus, the approach became exploratory. The physiological and psychological aspects of specific diseases vary widely, thus it is reasonable for different diseases to have different factor structures and resultant subscales for the IBQ (Prior & Bond, 2008). Thus, only items that were meaningful for SSc patients were included to ensure sharper measurement of the relevant

aspects of illness behavior for SSc. On the basis of a number of statistical and theoretical decisions, a SSc-specific structure was derived. The proposed subscales comprised illness-related (Symptom Bother, Health Worry), social (Interpersonal Functioning), and affective (Other Life Worries, Affective Inhibition) domains.

Internal consistency of the subscales was acceptable; although *Affective Inhibition* was lower but satisfactory, given the small number of items and exploratory nature of the study (Robinson, Shaver, & Wrightsman, 1991). Although higher internal consistencies have been reported for longer subscales (Prior & Bond, 2010), this is unsurprising given that items were added after factor analysis based on face validity, with the specific intention of increasing internal reliability. Shorter forms that are sufficiently valid and reliable to achieve measurement objectives are generally preferable in clinical contexts.

The validity analyses suggested that SSc-specific subscale scores were generally unrelated to skin thickness and pulmonary function. This suggests that disease severity only partially explains illness behavior. Fatigue, pain, disability, social support, and mental health were generally associated with the subscales, such that greater endorsement of the illness behavior domains was predictive of poorer outcomes. Taken together, these findings suggest that these subscales provide an acceptable assessment of illness behavior in SSc. However, score interpretation should be considered in the larger context of a patient's current physical status and psychological comorbidities.

Given the rarity of SSc, a notable strength of the current study is the large, representative sample of patients. However, there were some limitations. Only cross-sectional data were utilized. The sample size was on the low end of recommendations for latent variable analyses. Despite these limitations, this study provides preliminary support

for the utility of the IBQ for patients with SSc. Future work should focus on confirming this factor structure in a different sample of patients with SSc, and on comparing the measurement model between diffuse and limited subtypes. Additionally, researchers and clinicians should begin building more integrative models of illness behavior, with attention to the physical, psychological and social aspects of SSc to enhance total patient care. Within such a framework, clinicians will be better equipped to identify at-risk patients to implement appropriate interventions to target problematic illness behaviors (Kirmayer & Looper, 2006), underscoring the need for a reliable and valid screening tool.

In sum, this study evaluated the factorial validity of the IBQ in a sample of patients with SSc derived from the GENISOS cohort. The original factor structure of the IBQ was not supported among, providing one piece of evidence that may call the factor structure into question. Therefore, a SSc-specific factor structure was uncovered, which demonstrated convergent and divergent validity. These subscales offer clinicians a relatively concise way to identify patients who may benefit from additional intervention.

Chapter 2, in full, is a reprint of the material as it appears in Arthritis Care and Research 2013. Merz, Erin L.; Malcarne, Vanessa L.; Roesch, Scott C.; Sharif, Roozbeh; Harper, Brock E.; Draeger, Hilda T.; Gonzalez, Emilio B.; Nair, Deepthi K.; McNearney, Terry A; Assassi, Shervin; Mayes, Maureen D., American College of Rheumatology, 2013. The dissertation author was the primary investigator and author of this paper.

Table 2.1: Sample characteristics.

Variable		*n*	percent
Sex	Women	233	83.8%
	Men	45	16.2%
Ethnicity	White	135	48.6%
	Hispanic	82	29.5%
	Black	53	19.1%
	Asian	7	2.5%
	American Indian	1	0.3%
Marital status	Married/Partnered	159	58.2%
	Never married	30	11.0%
	Divorced/Separated	72	26.4%
	Widowed	12	4.4%
Education	Less than high school	44	16.1%
	High school diploma	143	52.4%
	Associate's degree	26	9.5%
	Bachelor's degree	38	13.9%
	Post-graduate	22	8.1%
Family income	< $14,999	67	24.1%
	$15,000 - $29,999	65	23.4%
	$30,000-$49,999	56	20.1%
	$50,000-$99,999	51	18.3%
	≥ $100,000	29	10.4%
Disease subtype	Diffuse	160	57.6%
	Limited	118	42.4%
		M	*SD*
Age (years)		49.05	12.92
Age of disease onset (years)		46.42	13.03
Modified Rodnan Skin Score		15.49	11.84
Forced Vital Lung Capacity		83.06	21.66

Table 2.2: Weighted least-squares means and variance adjusted (WLMSV) exploratory factor analysis on 62 items of the IBQ

Model	RMSEA	CFI	WLMSV χ^2	*df*	*p*
1-factor	.041	.815	2695.99	1829	<.001
2-factor	.031	.897	2250.30	1768	<.001
3-factor	.026	.930	2033.10	1708	<.001
4- factor	.022	.955	1860.94	1649	<.001
5- factor	.018	.970	1732.58	1591	.007
6- factor	.014	.983	1614.28	1534	.075
7- factor	.012	.987	1536.84	1478	.140

Table 2.3: Summary of loadings for 5 rotated factors

	1	2	3	4	5
IBQ3	**.632**	.159	-.017	.192	.038
IBQ16	**.988**	-.295	.016	-.003	.077
IBQ26	**.970**	-.270	-.011	-.020	-.076
IBQ41	**.727**	.036	.068	.114	-.100
IBQ50	**.613**	.014	.068	.053	-.074
IBQ1	.180	**.796**	-.129	-.083	-.040
IBQ8	.036	**-.647**	-.110	.042	-.114
IBQ21	.040	**.613**	.012	-.007	.088
IBQ24	.128	**.533**	.130	-.008	-.071
IBQ34	.267	**.745**	-.179	-.076	.033
IBQ4	-.152	.077	**-.647**	.038	.145
IBQ48	.154	.051	**.534**	.205	.030
IBQ51	-.196	.200	**.729**	.043	-.082
IBQ56	.001	-.021	**.743**	.044	-.019
IBQ61	-.128	.096	**.730**	.129	-.035
IBQ27	.083	-.122	.032	**.875**	-.011
IBQ43	-.017	-.217	.099	**.735**	.045
IBQ55	.408	.146	.086	**-.705**	.059
IBQ60	.072	.018	-.008	**.790**	-.004
IBQ22	-.024	.110	-.197	.038	**-.785**
IBQ36	.143	-.016	-.011	.214	**.551**
IBQ53	.137	.046	-.191	.229	**.650**
IBQ62	-.105	.041	.006	.165	**.768**

Table 2.4: SSc-specific subscales and membership in previous scales

Subscale	IBQ Item		Other Scale Memberships			
			Pilowsky & Spence	Zonderman, Heft, & Costa	Main & Waddell	Prior & Bond
Symptom Bother	IBQ3	Does your illness interfere with your life a great deal?	DC	ID	LD	AI
	IBQ16	Are you bothered by many pains and aches?	PS(R)	ID	LD	AI
	IBQ26	Do you experience a lot of pain with your illness?		ID		AI
	IBQ41	Do you find that you are bothered by many different symptoms?	DC		AHD	AI
	IBQ50	Do you often have the symptoms of a very serious disease?				AI
Health Worry	IBQ1	Do you worry a lot about your health?		HW		CH
	IBQ8	Is it easy for you to forget about yourself and think about other things? (R)		ID(R)	AHD(R)	
	IBQ21	Are you afraid of illness?	GH	HW		CH
	IBQ24	Do you think that you worry about health more than other people?	GH	HW		CH
	IBQ34	Do you often worry about the possibility that you have got a serious illness?		HW	AHD	CH
Interpersonal Functioning	IBQ4	Are you easy to get along with when you are ill?	I(R)	I(R)	AHD(R)	
	IBQ48	Do you worry or fuss over small details that seem unimportant to others?		I	AHD	GAS

Table 2.4*:* SSc-specific subscales and membership in previous scales, Continued

Subscale	IBQ Item		Other Scale Memberships			
			Pilowsky & Spence	Zonderman, Heft, & Costa	Main & Waddell	Prior & Bond
	IBQ51	Do you find that you get angry easily?	I	I	AHD	GAS
	IBQ56	Are you more irritable towards other people?	I	I	AHD	
	IBQ61	Do you often find that you lose patience with other people?	I	I	AHD	
Other Life Worries	IBQ27	Except for your illness, do you have any problems in your life?	D(R)	ALP	LD(R)	GAS
	IBQ43	Do you have any family problems?	D(R)	ALP	LD(R)	GAS
	IBQ55	Would all your worries be over if you were physically healthy?	D	ALP(R)	LD	
	IBQ60	Do you have personal worries which are not caused by physical illness?	D(R)	ALP	LD(R)	
Affective Inhibition	IBQ22	Can you express your personal feelings easily to other people?	AIN(R)	AIN(R)	SI(R)	
	IBQ36	When you are angry, do you tend to bottle up your feelings?	AIN	AIN	SI	
	IBQ53	Do you prefer to keep your feelings to yourself?	AIN	AIN	SI	
	IBQ62	Is it hard for you to show people your personal feelings?	AIN	AIN	SI	

Note. (R): reverse-scored; AHD: Affective, Hypochondriacal Disturbance; AI: Affirmation of Illness; AIN: Affective Inhibition; ALP: Absence of Life Problems; CH: Concern for Health; DC: Disease Conviction; D: Denial; GAS: General Affective State; GH: General Hypochondriasis; HW: Health Worry I: Irritability; ID: Illness Disruption; LD: Life Disruption; PS: Psychological vs. Somatic; SI: Social Inhibition

Table 2.5: Associations between IBQ scales for SSc and disease-related outcomes

IBQ Scale	Modified Rodnan Skin Score	Forced Vital Lung Capacity	Fatigue	Pain	Disability	Social support	Mental health
Symptom Bother	.14*	-.05	.42***	-.57***	.42***	-.15*	-.31***
Health Worry	.11	-.01	.10	-.17**	.21**	-.25***	-.42***
Interpersonal Functioning	-.05	.06	.22***	-.14*	.16**	-.19**	-.33***
Other Life Worries	-.09	.00	.08	-.00	.00	-.13*	-.21**
Affective Inhibition	.05	-.14*	.09	-.15*	.15*	-.32***	-.30***

Note. *** $p < .001$; ** $p < .01$; * $p < .05$

CHAPTER 3: BIOPSYCHOSOCIAL TYPOLOGIES OF PAIN IN A COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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ABSTRACT

Despite being a common problem in Systemic Sclerosis (SSc), the extant literature on pain has primarily focused on biomedical correlates, or bivariate relationships with a few psychological characteristics. There is a need to investigate the more heuristic biopsychosocial model, which incorporates the simultaneous contributions of medical, psychological, and social variables in understanding pain. Patients with SSc (N = 333) received clinical exams and completed self-report surveys at enrollment to the *Genetics versus ENvironment In Scleroderma Outcome Study* (GENISOS). Latent profile analysis was used to derive biopsychosocial profiles of patients using skin thickening, percent predicted forced vital lung capacity, perceived physical health, health worry, mental health, and social support. The profiles were examined in relation to pain and pain medication usage. A 3-profile solution provided the best fit to the data. Based on the biopsychosocial indicators, the profiles were characterized as *Managing* (n = 217), *Resilient* (n = 86), and *Distressed* (n = 30). Between-group differences for pain emerged, with the *Distressed* group, whose disease was less severe than the *Resilient* group, reporting the highest pain and the greatest utilization of pain medication. Clinicians should consider biopsychosocial characteristics as contributing factors to the experience of pain in patients with SSc. Patients who are similar to those in the *Distressed* profile may be at an increased risk for pain and would likely benefit from a referral to a behavioral health or other ancillary service provider for pain management, rather than relying solely on pharmacological therapies.

Introduction

Systemic Sclerosis (SSc) is a rheumatic disease characterized by skin thickening and fibrosis of internal organs due to a buildup of collagen and other extracellular matrix proteins (Medsger, 2003). There are two general classifications: limited cutaneous SSc (lcSSc), which has skin involvement only distal to the elbows and knees and is characterized by slow fibrosis and milder internal organ involvement (Leroy et al., 1988; Medsger, 2003), and diffuse cutaneous SSc (dcSSc), which has a worse prognosis, extensively affects the skin and internal organs, and is characterized by rapidly progressing fibrosis (Leroy et al., 1988; Medsger, 2003). Clinical care for SSc is complicated by a lack of effective treatments for many manifestations of disease. Therefore, the primary goals of care are to preserve functioning, relieve symptoms, and improve quality of life.

Pain is a virtually ubiquitous problem in SSc. Indeed, 83% of patients in a large, recent sample reported significant pain (Schieir et al., 2010), which is similar to previous rates (Edwards, Goble et al., 2006; Benrud-Larson et al., 2002; Richards, Herrick, Griffin, Gwilliam, & Fortune, 2004). Early in the disease process, patients report nonspecific muscle pain and stiffness (Medsger, 2003), while other symptoms (e.g., difficulty swallowing, gastrointestinal discomfort) emerge as the disease progresses (Franck-Larsson, Graf, & Rönnblom, 2009). In SSc, pain has been typically conceptualized according to the biomedical model, which suggests that pain is a symptom secondary to disease activity and previously sustained tissue damage (Carreira, 2006). However, the level of pain one experiences is not always relative to disease severity (Benrud-Larson et al., 2002; Edwards, Cahalan, Mensing, Smith, &

Haythornthwaite, 2011). For example, although lcSSc patients typically report less pain than dcSSc patients, the differences are generally small and not clinically meaningful (Benrud-Larson et al., 2002; Georges et al., 2006; Malcarne et al., 2007; Richards, Herrick, Griffin, Gwilliam, Loukes, & Fortune, 2003; Schieir et al., 2010). Alternatively, a biopsychosocial framework for understanding pain, which has been widely accepted across disciplines and diseases, suggests that pain is not a purely physical phenomenon (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). This model highlights interconnections among the disease, person, and environment, and postulates that none of these factors can independently explain pain. Instead, biological, psychological, and social factors work together in complex ways to shape pain perceptions (Garchel et al., 2007).

At the broadest level, emotional health and pain share a significant connection, with up to half of chronic pain patients also reporting depression and/or anxiety (Garchel et al., 2007). Symptoms of depression (Thombs, Taillefer, Hudson, & Baron, 2007) and anxiety (Legendre, Allanore, Ferrand, & Kahan, 2005) are common in SSc, and psychological health has been broadly linked with pain in this population (Benrud-Larson et al., 2002; Georges et al., 2006; Hyphantis et al., 2007; Kwakkenbos, van Lankveld, Vonk, Becker, van den Hoogen, & van den Ende, 2012; Richards et al., 2004; Schieir et al., 2010). For example, depressive (Schieir et al., 2010) and anxious (Hyphantis et al., 2007) symptomatology, and mental health-related quality of life (Georges et al., 2006) have demonstrated relationships with pain, even after accounting for other disease and psychosocial variables.

The way a person thinks about his/her health has also been linked with pain in clinical (Garchel et al., 2007) and rheumatic (Edwards, Bingham, Bathon, &

Haythornthwaite, 2006; Edwards et al., 2011) populations. Illness cognitions can range from general concerns to more severe responses and preoccupation, with more extreme responses being of the greatest significance to pain. Research suggests that thinking about the serious consequences of SSc (Richards et al., 2003), castastrophizing thoughts (Edwards, Bingham et al., 2006), and maladaptive disease cognitions (van Lankveld, Teunissen, Näring, Vonk, & van den Hoogen, 2008) are all associated with greater pain. Other variables have also been shown to influence the cognition-pain relationship; patients with less education and social support who engage in catastrophic cognitions report greater pain (Edwards, Goble et al., 2006).

A great deal of research has supported a link between social support and pain both directly, and via mood (Garchel et al., 2007). Research in the rheumatic diseases has also largely supported this connection (Edwards, Calahan et al., 2011; Savelkoul, Post, de Witte, & van den Borne, 2000). For example, in a study of patients with rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis, lower satisfaction with social support was correlated with greater pain (Savelkoul et al., 2000). To date, only one study of SSc patients has evaluated the social support-pain relationship. In this study, patients with poor social adjustment reported worse pain; although this relationship was accounted for by depression, suggesting that emotional health was the conduit for this association (Benrud-Larson et al., 2002).

There is a growing appreciation for the biopsychosocial model of pain in SSc, however, a better understanding of how these factors interact is needed. A number of the reviewed studies included biopsychosocial variables, but these constructs were typically included in adjusted models, rather than considering heterogeneity among them.

Alternatively, these variables may be modeled as multiplicative (combined) effects to understand general patterns at the level of the person. Although no analysis can capture all individual differences, the goal of this study was to determine whether general typologies that incorporate biological, psychological, and social characteristics could be identified to enhance understanding of SSc-related pain. The first aim was to evaluate the interrelationships of these factors by deriving homogeneous biopsychosocial trait profiles of SSc patients, and to interpret the response patterns that cluster together. The indicator variables (skin thickening, percent predicted forced vital lung capacity, perceived physical health, health worry, mental health, social support) were selected given the substantive reasoning that they may conjointly relate to pain. The second aim was to evaluate the predictive utility of each profile with respect to pain ratings and pain medication utilization. It was hypothesized that profiles characterized by poorer subjective ratings of perceived physical health, health worry, mental health, and social support would be related to pain and medication, whereas skin thickening and percent predicted forced vital lung capacity within the profiles would be less relevant.

Method

Participants and Procedures

The sample (N = 333) was comprised of individuals who completed the baseline examination of the *G*enetics versus *EN*vironment *I*n Scleroderma *O*utcome *S*tudy (GENISOS), an ongoing, prospective, early-disease (within 5 years of onset) cohort study aimed at understanding morbidity and mortality in SSc. Patients with SSc who lived within the geographic catchment area of one of the three centers (University of Texas

Health Science Center at Houston, University of Texas Medical Branch at Galveston, University of Texas-Health Science Center at San Antonio) were recruited from the rheumatology faculty clinics, the county hospital, and chapters of the Scleroderma Foundation (Reveille et al., 2001).

Baseline visits were conducted during outpatient appointments and inpatient services at facilities staffed by the clinician-investigators. During this visit, data from medical records were clarified. Patients received a standardized clinical exam which included an evaluation of skin thickening and pulmonary function and were administered a packet of psychosocial measures. All participants gave written informed consent. Institutional Review Board approval was obtained at all participating institutions.

Variables

*Skin Thickening***.** The modified Rodnan Skin Score (mRSS; Kahaleh, Sultany, Smith, Huffstutter, Loadholt, & LeRoy, 1986), an objective indicator of skin disease severity, is calculated by measuring the extent and severity of skin thickening on 17 body surfaces by palpation on a 4-point scale (0 = uninvolved to 3 = severe thickening). Scores range from 0-51.

*Forced Vital Lung Capacity***.** Percent predicted forced vital lung capacity (%FVC) is an objective, validated measure for severity of SSc-related interstitial lung disease (Furst et al., 2007) indicating the ratio of the volume of air that the subject can forcibly exhale after a maximum inspiration to the same volume in age, gender, weight, height, and ethnicity matched unaffected controls. All pulmonary measurements met criteria outlined by the American Thoracic Society/European Respiratory Society, and were

reviewed by a pulmonologist. Lower scores indicate greater severity of SSc-related interstitial lung disease.

Perceived Physical Health[5]. The Physical Functioning subscale from the Medical Outcomes Study Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992) was used to evaluate self-reported overall physical health. Scores are transformed into a 0-100 scale; lower scores indicate greater difficulties performing activities due to physical functioning. Internal consistency was $\alpha = .920$.

Health Worry. Five items from the Illness Behavior Questionnaire (IBQ; Pilowsky & Spence, 1983) were used to generate the Health Worry scale for SSc (Merz et al., 2013). An example item is, "Do you worry a lot about your health?" Scores range from 0-5; higher scores indicate greater worry and concern regarding one's health. Internal consistency was $\alpha = .721$.

Mental Health. The SF-36 (Ware & Sherbourne, 1992) Mental Health Component Summary Score measures global emotional health and related functional impairment. It is comprised of four subscales (Mental Health, Role Limitations Due To Emotional Problems, Social Functioning, Vitality) which are transformed into a 0-100 scale; lower scores indicate greater psychological distress and more limitations due to emotional problems. Internal consistency was $\alpha = .807$.

Social Support. The 40-item Interpersonal Support Evaluation List (ISEL; Cohen, Mermelstein, Kamarck, & Hoberman, 1985) was used to derive a measure of perceived social support. Respondents rate whether a statement is "probably true" or "probably

[5] The Physical Functioning scale score was used instead of the Physical Component score because the Component score includes an indicator of pain.

false" based on their experience. An example item is, "There is at least one person I know whose advice I really trust." The ISEL yields four subscales and an overall support score that is calculated by averaging the 4 subscales. Overall support scores range from 0-10; higher scores indicate better social support. Internal consistency was $\alpha = .870$.

Pain. The Pain subscale from the SF-36 (Ware & Sherbourne, 1992) was used to evaluate self-reported severity and impact of pain. Scores are transformed into a 0-100 scale; lower scores indicate greater pain severity and interference. Internal consistency was $\alpha = .884$.

Pain Medication. Participants were asked whether they had taken acetominophen, non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, and narcotics over the past month[6]. A variable with four categories (*No medication*, *Acetaminophen/NSAIDs*, *Tramadol*, *Narcotics*) was created to represent typical pain medication usage. Respondents taking multiple medications (11.1% of the sample; two medications: $n = 34$; three medications: $n = 3$) were coded with the strongest drug being taken (i.e., an individual taking both acetaminophen and tramadol was coded as *Tramadol*; an individual taking both tramadol and narcotics was coded as *Narcotics*).

Data Analysis

Latent Profile Analysis (LPA; Lanza, Flaherty, & Collins, 2003), an empirically driven statistical technique that defines taxonomies (classes) of people based on common

[6] Participants were also asked about aspirin and muscle relaxers, but these were not included in the pain medication variable given that aspirin is usually taken as an anti-platelet agent, and muscle relaxers ($n = 4$) are typically taken for fibromyalgia and are not considered pain medication. The 4 individuals taking muscle relaxers were also taking narcotics and were coded as such.

characteristics, was used to derive categorical latent variables representing classes of SSc patients with similar biopsychosocial profiles. Because it is difficult to interpret interactions with more than three variables, and because traditional analytic methods are at the level of the variable, not the person, LPA is a preferred technique for making inferences about individuals. This method summarizes complicated relationships among variables, similar to the way in which symptom clusters are categorized in medical settings to help inform diagnosis and treatment, and to make predictions about an individual. LPA uses all observations of the continuous indicator variables to define these classes via maximum likelihood estimation (Little & Rubin, 1987). The probability that an individual was properly classified, which enables each person to be categorized into the best-fitting class, is estimated simultaneously with the overall model (Hill, Degnan, Calkins, & Keane, 2006). Models are estimated with classes added iteratively to determine which model is the best fit. It is recommended that the sample size for LPA be large because class solutions produced from smaller samples may be unstable (Roesch, Villodas, & Villodas, 2010). Recommendations mirror that of Structural Equation Modeling, with sample sizes of 200 being adequate (Schumacker & Lomax, 2004).

To achieve the first aim, LPA was conducted using MPlus 6.1 (Muthén & Muthén, 1998-2010). Models were evaluated using the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LMRT; Lo, Mendell, & Rubin, 2001), the Bootstrapped Likelihood Ratio Test (BLRT; McLachlan & Peel, 2000), Akaike information criteria (AIC; Akaike, 1974), sample size-adjusted Bayesian information criteria (sBIC; Schwarz, 1978), and Entropy (Ramaswamy, Desarbo, Reibstein, & Robinson, 1993) to determine the optimal number of classes. The LMRT and the BLRT compare the fit of a target

model (e.g., 2-class model) to a comparison model specifying one less class (e.g., 1-class model). The *p*-value generated for the LMRT and BLRT indicates whether the solution with more ($p < .05$) or fewer ($p > .05$) classes fits better. The AIC and sBIC are descriptive fit indices wherein smaller values indicate better model fit. Entropy describes the accuracy of classification of individuals into a class; bigger values (i.e., closer to 1) indicate greater accuracy. Models were also evaluated on interpretability to determine whether the classes truly represented different categories, rather than being an artifact of a nonnormal distribution (Muthén, 2006). Given that small classes (i.e., those with less than 5% of the sample) are typically considered spurious, a condition often associated with extracting too many classes/profiles (Hipp & Bauer, 2006), the number of patients categorized into each class was also considered. The overall sample means (and SDs) and conditional response means (and SDs) of each indicator variable from the best-fitting solution were compared for interpretation. The classes were then related to disease and demographic characteristics. For the second aim, ANOVA and chi-square tests were conducted to evaluate potential differences in pain and pain medication usage as a function of class. To identify between-class differences, Bonferroni post-hoc tests were conducted and adjusted standardized residuals were examined using a familywise error rate of .05.

Results

Sample characteristics are described in Table 3.1. Most participants were women, married, and had at least a high school diploma or General Education Development certificate. Ages ranged from 16 to 86. Age of disease onset ranged from 14 to 84.

Disease duration ranged from 0 to 5 years. Individuals with dcSSc had greater skin thickening (t [330] = -15.22, $p < .001$; dcSSc = 21.98 ± 10.95; lcSSc = 6.82 ± 5.10) and lower forced vital lung capacity (t [309] = 2.54, $p = .011$; dcSSc = 80.07 ± 20.74; lcSSc = 86.33 ± 22.37).

Development of Biopsychosocial Classes Using Latent Profile Analysis

Intercorrelations among the indicator variables were nonsignificant or small/moderate in size which allowed for more differentiation between classes[7]. Latent profile models containing 1-4 classes were fit to the data. Fit indices for each LPA are presented in Table 3.2. The LMRT and BLRT indicated that the 2-class solution fit better than the 1-class solution ($p = .005$). The 3-class solution was superior to the 2-class solution according to the LMRT ($p = .05$) and BLRT values ($p < .0001$), and lower AIC and sBIC values. Although the 4-class solution revealed slightly lower AIC and sBIC values, and a statistically significant BLRT value ($p < .0001$), Entropy was lower, and the LMRT indicated that it was not statistically different from the 3-class solution ($p = .32$). Therefore, the 3-class solution was considered the best fit to the data.

The overall sample means and conditional response means used to substantively interpret each class are available in Table 3.3. Figure 3.1 presents the *z*-transformed conditional response means (Ms = 0, SDs = 1) for the purposes of illustration. To facilitate interpretation of the profiles, the *z* scores for the figure were set such that higher scores represented better functioning. Class 1 is comprised of 65.2% of the sample and represents individuals with relatively less severe skin thickening and forced vital lung

[7] A table of these relationships is available from the study authors upon request.

capacity, better perceived physical health, fewer health worries, better mental health, and more social support. Accordingly, this profile was referred to as *Managing*. Class 2 is comprised of 25.8% of the sample and was termed *Resilient* because it represents individuals with relatively more severe skin thickening and forced vital lung capacity and poorer perceived physical health, but fewer health worries, better mental health, and more social support. Class 3, labeled *Distressed*, is comprised of 9.0% of the sample and is characterized by individuals with relatively less severe skin thickening and forced vital lung capacity, but poorer perceived physical health, more health worries, poorer mental health, and lower social support.

In sum, the *Managing* and *Distressed* classes were similar with regard to skin thickening and percent predicted forced vital lung capacity; however, they differed on their perceived physical health and their psychosocial characteristics. Specifically, the *Distressed* class had the poorest psychosocial functioning of the three groups. *Resilient* patients had more severe skin thickening and percent predicted forced vital lung capacity than the other groups, and accordingly, their perceived physical health was poorer. However, the *Resilient* class reported better psychosocial functioning, with scores equivalent to the healthier *Managing* patients. The profiles differed somewhat on how much they worried about their health: *Distressed* patients reported the most worry, *Managing* patients reported the least worry, and the *Resilient* class, which was the sickest class, reported moderate worry.

Disease Characteristic and Sociodemographic Group Differences

Follow-up analyses suggested that the classes differed by disease type, χ^2 (2) =

75.77, $p < .0001$. The proportions of lcSSc and dcSSc patients were similar to the overall sample for the *Distressed* class (60.0% lcSSc, 40.0% dcSSc) and the *Managing* class (55.6% lcSSc, 44.4% dcSSc). However, the *Resilient* class had more dcSSc (97.7%) than lcSSc (2.3%) patients than would be expected due to chance. There was a significant difference for income (χ^2 [8] = 21.44, p =.006), with *Distressed* patients reporting a higher proportion of lower income than would be expected by chance (51.9% reported an annual income lower than $14,999). The classes did not differ on history of digital ulcers, arthritis, disease duration, age, gender, race/ethnicity, or education (ps > .05).

Association of Biopsychosocial Profiles with Pain and Pain Medication

Figure 3.2 provides a graphic depiction of pain and medication use between the classes. ANOVA results suggested overall group differences in pain, F (2, 290) = 16.47, $p < .001$, partial η^2 = .102. Post-hoc comparisons revealed a large difference (d = 1.00, $p < .001$) between the *Managing* (54.91 ± 26.26) and *Distressed* classes (29.48 ± 24.38), such that *Distressed* patients reported greater pain[8]. A moderate significant difference (d = .52, $p < .001$) suggested that *Resilient* patients **(**41.44 ± 25.36**)** reported more pain than *Managing* patients. Although the difference between the *Distressed* and *Resilient* classes was not statistically significant, there was a trend and medium-sized effect suggesting that *Distressed* patients had greater pain than *Resilient* patients (d = .48, p = .103).

Chi-square test results suggested that pain medication usage was not equal among the classes, χ^2 (6) = 14.88, p = .021. These relationships are described in Table 3.4.

[8] Note that on the SF-36, lower scores indicate greater pain severity and interference, whereas higher scores indicate less pain severity and interference.

Inspection of the standardized residuals for each class by pain medication category revealed that the *Managing* class (62.67%) was significantly more likely to *not* be taking pain medication whereas the *Distressed* class (36.67%) was significantly less likely to *not* be taking pain medication than would be expected based on the total sample. Additionally, the *Managing* class (2.76%) was significantly less likely to be taking tramadol, whereas the *Distressed* class (13.33%) was significantly more likely to be taking tramadol.

Discussion

Skin thickening, percent predicted forced vital lung capacity, perceived physical health, health worry, mental health, and social support were used to identify biopsychosocial profiles of patients with SSc. Three classes emerged and were termed *Managing*, *Resilient*, and *Distressed*. One remarkable finding was that while the *Managing* and *Distressed* groups were similar with regard to skin thickening and percent predicted forced vital lung capacity, they differed on perceived physical health, mental health, and social support. Specifically, the *Managing* group was functioning well psychosocially; the *Distressed* group was not. The *Resilient* group had a much more severe disease manifestation; however, *Resilient* patients mirrored the *Managing* group psychosocially.

When the groups were evaluated in relation to other clinical variables that cause persistent pain (i.e., digital ulcers, arthritis), there were no differences. Moreover, it is significant that the proportion of lcSSc and dcSSc patients in the *Managing* and *Distressed* typologies was roughly equivalent to the overall sample, but that the *Resilient*

typology was predominantly comprised of dcSSc patients. This suggests that disease severity is not the key factor for differentiating between patients who are at risk for decreased quality of life, consistent with previous findings (Malcarne et al., 2007; Richards et al., 2004). Indeed, when the classes were evaluated in relation to pain and medication, the *Distressed* group, which was less severely affected, reported greater pain and medication usage.

One interesting finding from this study was that social support in the *Distressed* group was approximately two standard deviations lower than the other profiles. The health benefits of social support from family, friends and other informal groups (as opposed to health professional or therapeutic support), have been recognized across disease populations (Barth, Schneider, & von Känel, 2010; Garchel et al., 2007), including rheumatic diseases (Edwards, Calahan et al., 2003; Mazzoni & Cicognani, 2011). The current findings suggest that social support is of great interest in understanding the experience of SSc patients, particularly given that SSc patients may avoid socializing due to appearance concerns (Haythornthwaite, Heinberg, & McGuire, 2003), and that over half of patients with rheumatic disorders report moderate to high levels of loneliness (Kool & Geenen, 2012). It is also worth mentioning that, social support is not characterized by the number of relationships one has, but rather the perceived availability and quality of support (Cohen et al., 1985). A person may have many social contacts but not feel supported by them, or, conversely, a person may derive adequate support from just one relationship.

Effective pain management is a primary goal of patient care, although it has not been well investigated in SSc (Giuggioli, Manfredi, Colaci, & Ferri, 2010). Because not

all patients respond well to pharmacological pain management (Lundborg, Nitescu, Appelgren, & Curelaru, 1999), other methods that target modifiable psychosocial factors (i.e., emotional health, cognitions, social support) should be considered. Approaches such as cognitive-behavioral therapy (which involves skill building in areas such as mindfulness, relaxation, coping, social support, changing maladaptive beliefs), have already been identified and used in other pain populations (Edwards et al., 2011; Gatchel et al., 2007; Hassett & Williams, 2011; Kerns, Sellinger, & Goodin, 2011). While outcomes to these treatments are less straightforward (e.g., successful treatment may mean that pain is partially ameliorated, a patient is experiencing their pain differently, healthcare costs have decreased), they may be promising as an adjunct for patients who are not benefiting from pharmacological therapy.

However, prior to implementing and evaluating interventions for individuals with characteristics similar to the *Distressed* profile, it is important to determine whether such patients can be feasibly identified within clinical settings. To this end, researchers and clinicians are encouraged to assess for perceived physical health, health worry, mental health, and social support in addition to disease severity of the skin and lungs, which are routinely evaluated.

Limitations of this study include limited generalizability to late-stage patients, who typically experience greater pain. Also, because the data were cross sectional, it is not possible to know whether *Distressed* patients were functioning poorly prior to their diagnosis, or these characteristics emerged during the disease process. Because the medication question did not specify that the medication must be for SSc discomfort, it is possible that acetaminophen/NSAIDs taken for other pain (e.g., headaches) may have

been erroneously captured in that response category. It is also important to note that other variables likely relate to SSc pain, and the six indicators selected for the current study are not exhaustive. Rather, the choices were guided by theoretical rationale, as the goal of the current study was not to investigate all potential corollaries of pain, but to evaluate whether biopsychosocial variables could be modeled synergistically. This study was the first to use a person-centered approach to model biopsychosocial traits in relation to pain in SSc. The results suggest that psychosocial functioning is fundamental to understanding pain in this population. Clinicians are encouraged to take a holistic approach in assessments and to make referrals for ancillary pain management services when indicated.

Chapter 3, in full, is a reprint of the material as it appears in Arthritis Care and Research 2014. Merz, Erin L.; Malcarne, Vanessa L.; Assassi, Shervin; Nair, Deepthi K.; Graham, Tiffany A.; Yellman, Brayden P.; Estrada-Y-Martin, Rosa M.; Mayes, Maureen D., American College of Rheumatology, 2014. The dissertation author was the primary investigator and author of the paper.

Table 3.1: Sample characteristics

Variable		*n*	percent
Sex	Women	278	83.5%
	Men	55	16.5%
Race/Ethnicity	White	157	47.2%
	Hispanic	97	29.1%
	Black	68	20.4%
	Asian	10	3.0%
	American Indian	1	0.3%
Marital status	Married/Partnered	180	56.6%
	Not Married/Partnered	138	43.4%
Education	Less than high school	49	15.3%
	High school diploma/GED	166	51.7%
	Associate's degree	32	10.0%
	Bachelor's degree	47	14.6%
	Post-graduate	27	8.4%
Family income	< $29,999	149	47.8%
	$30,000-$49,999	64	20.5%
	$50,000-$99,999	60	19.2%
	≥ $100,000	39	12.5%
Disease subtype	Diffuse cutaneous	192	57.8%
	Limited cutaneous	140	42.2%
Pain medication use	Not taking pain medication	190	57.1%
	Acetaminophen/NSAIDs	66	19.8%
	Tramadol	18	5.41%
	Narcotics	59	17.7%
History of digital ulcers		200	60.1%
Arthritis		101	30.3%
		M	*SD*
Age		48.00	13.04
Age of disease onset		46.02	13.20
Disease duration (years)		1.20	1.40
Skin thickening (MRSS)		15.62	11.67
Forced Vital Lung Capacity		82.70	21.63
IBQ	Health Worry Scale	2.19	1.63
ISEL	Total Social Support Scale	8.20	1.63
SF-36	Mental Health Component Score	45.51	12.91
	Physical Functioning Scale	43.32	28.66
	Pain Scale	48.81	27.18

Table 3.2: Model fit indices for skin thickening, forced vital lung capacity, perceived physical health, health worry, mental health, total social support

Solution	LMRT (*p*)	BLRT (*p*)	AIC	sBIC	Entropy
1 class			12802.40	12810.04	
2 class	118.590 (.005)	121.507 (<.0001)	12694.90	12706.98	.806
3 class	95.834 (.05)	98.191 (<.0001)	12610.71	12627.24	.799
4 class	35.530 (.32)	35.530 (<.0001)	12589.18	12610.17	.695

Note. LMRT = Lo-Mendell-Rubin Test, BLRT = Bootstrapped Lo-Mendell Rubin Test, AIC = Akaike Information Criterion, sBIC = sample size-adjusted Bayesian Information Criterion

Table 3.3: Overall sample means ± SD and Biopsychosocial profile conditional response means ± SD

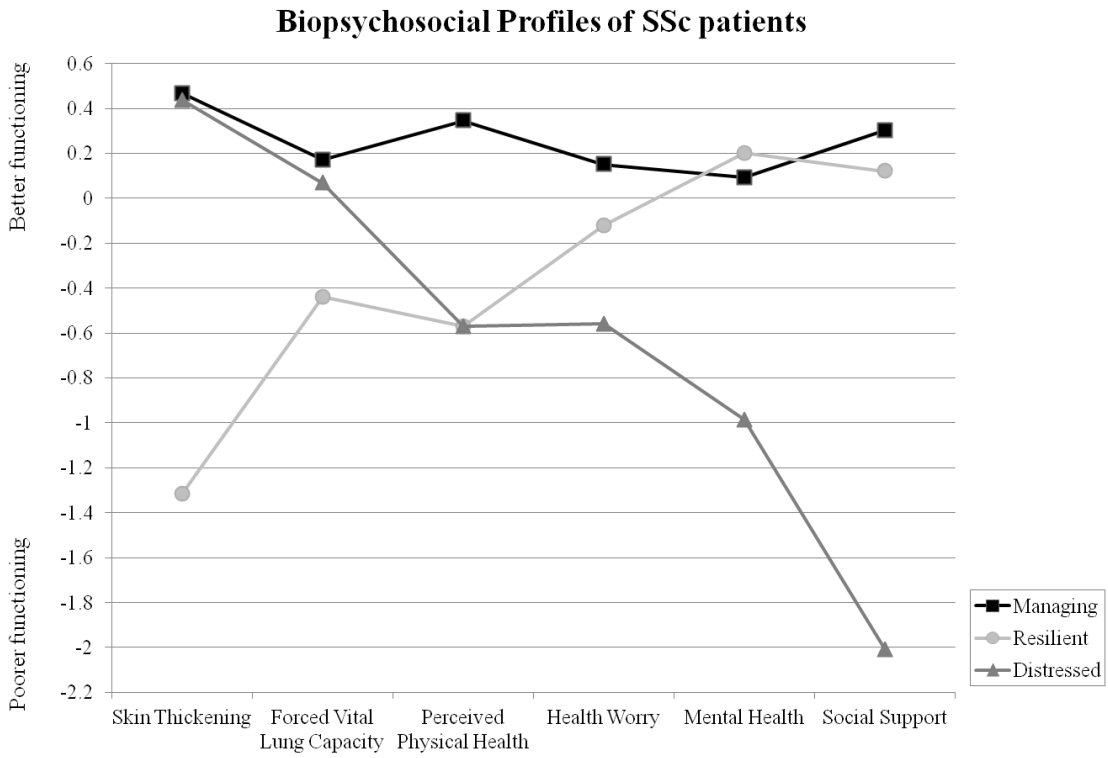
	n	Skin‡	Lung†	Physical†	Worry‡	Mental†	Social†
Sample	333	15.62 ± 11.67	82.70 ± 21.63	43.32 ± 28.66	2.19 ± 1.63	45.51 ± 12.91	8.20 ± 1.63
3-class solution							
Class 1 (*Managing*)	217	10.17 ± 20.08	86.38 ± 23.63	53.22 ± 31.54	1.94 ± 1.97	46.72 ± 15.36	8.70 ± 1.92
Class 2 (*Resilient*)	86	30.96 ± 13.20	73.19 ± 33.22	26.95 ± 51.30	2.38 ± 2.64	48.10 ± 15.17	8.40 ± 2.32
Class 3 (*Distressed*)	30	10.53 ± 12.25	84.17 ± 28.11	26.94 ± 35.78	3.10 ± 1.81	32.78 ± 16.60	4.92 ± 1.75

Note. †higher scores indicate better functioning; ‡lower scores indicate better functioning

Table 3.4: Percentage of patients within each biopsychosocial group regularly taking pain medication

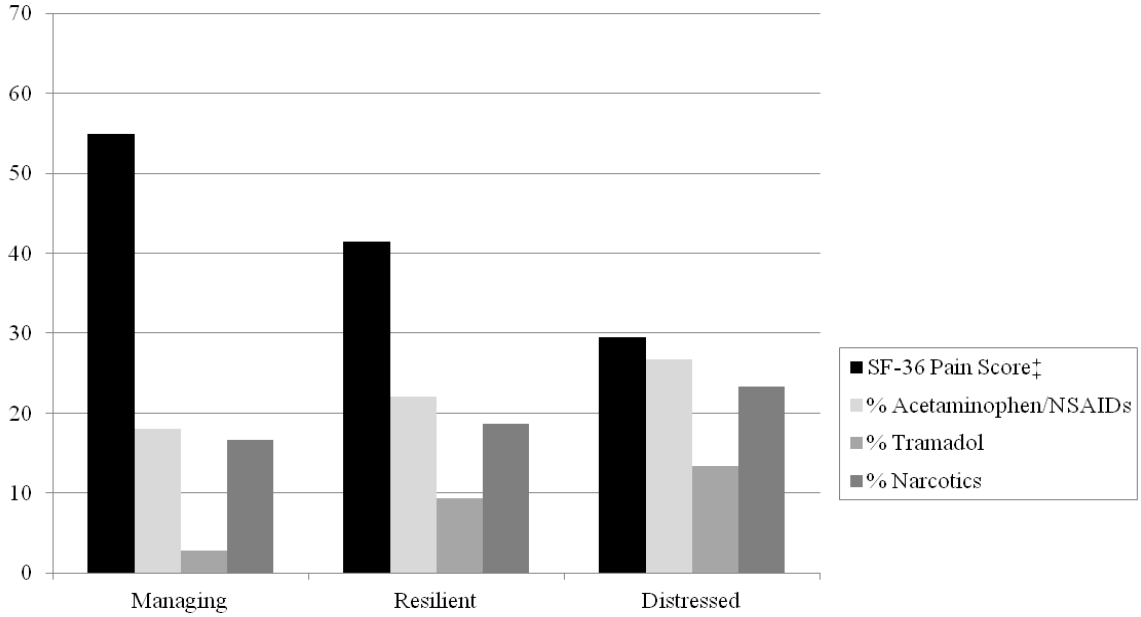
	Not taking pain medication	Acetaminophen/ NSAIDS	Tramadol	Narcotics
Managing (*n* = 217)	62.67%*	17.97%	2.76%**	16.59%
Resilient (*n* = 86)	50.00%	22.09%	9.30%	18.60%
Distressed (*n* = 30)	36.67%*	26.67%	13.33%*	23.33%

Note. Overall model, χ^2 (6) = 14.88, $p = .021$; * $p < .05$; ** $p < .01$



Note. For illustrative purposes, *z* scores were set so that higher scores represented better functioning

Figure 3.1: *Z* transformed conditional response means of the 3-class solution



Note. ‡higher scores on the SF-36 indicate better functioning (i.e., less pain); Significant between-group differences were observed for pain, F (2, 290) = 16.47, $p < .001$, and pain medication usage, χ^2 (6) = 14.88, $p = .021$.

Figure 3.2: Self-reported pain (SF-36) and pain medication usage for each biopsychosocial class

CHAPTER 4: LONGITUDINAL PATTERNS OF PAIN IN PATIENTS WITH DIFFUSE AND LIMITED SYSTEMIC SCLEROSIS: INTEGRATING MEDICAL, PSYCHOLOGICAL, AND SOCIAL CHARACTERISTICS

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Running title: Prospective course of SSc pain

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ABSTRACT

Pain is a common quality of life concern in systemic sclerosis (SSc) but has been understudied. This investigation sought to describe the nature of longitudinal pain during the early phase of the disease and to examine variables that may predict pain over time. A prospective cohort (N = 316) of patients with early disease SSc were followed for three years. Multilevel modeling was used to describe longitudinal changes in pain and also the extent to which pain variance was explained by diagnostic classification, mental health, perceived physical health, health worry, and social support. Pain remained relatively stable, with a small amount of improvement over time. When diagnostic classification was entered as the only predictor of pain, the diffuse disease type, which is more severe, was associated with worse pain. However, this association was reduced to nonsignificance after accounting for the psychosocial variables. Clinically relevant effects for mental health and social support emerged. Better emotional health was associated with lower levels of initial pain, although the trajectories of change in pain were similar irrespective of mental health status. However, the level of social support impacted the speed of pain recovery, with the highest level of support demonstrating the fastest improvements in pain. These data provide evidence that mental health and social support may be more important than diagnostic classification in understanding SSc pain. Researchers and rheumatology health professionals may want to consider these factors in comprehensive pain models and pain management protocols.

Introduction

Systemic Sclerosis (SSc) is a chronic connective tissue disease characterized by fibrosis of the skin and internal organs, which leads to skin thickening and decreased organ function (Medsger, 2003). The symptomatology of SSc is complex and involves multiple body systems, leading to dermatologic, vascular, pulmonary, cardiac, gastrointestinal, neurological, musculoskeletal, and renal complications. The course of SSc is highly variable. Patients go through periods of improvement and decline, with a general pattern of deterioration over time. SSc is more common in women and disease onset is typically between ages 40 and 50.

There are two clinical types of the disease which are distinguished primarily by the patterns and severity of skin and organ involvement. Diffuse cutaneous SSc is the more severe disease type, with rapidly progressing fibrosis in the trunk and internal organs during early disease (LeRoy et al., 1988; Medsger, 2003). During the first five years, patients often have puffy fingers, swollen legs and feet, tendon friction rubs, finger joint contractures, gastrointestinal involvement, and visceral organ dysfunction (Medsger, 2003). However, as patients transition to the intermediate and late phases of the disease, skin thickening improves somewhat, although there can be spontaneous exacerbations (Medsger, 2003). Limited cutaneous SSc is characterized by slower fibrosis distal to the elbows and knees (Medsger, 2003). For these patients, skin thickening increases slowly during early disease (within five years of onset) and plateaus thereafter, with minimal organ involvement until late in the disease process (Medsger, 2003). In later-stage limited disease, patients may have problems with pulmonary arterial hypertension and esophageal reflux and stricture (Medsger, 2003).

Although there are no curative treatments for SSc, there are a number of therapies that target specific disease manifestations (e.g., renal failure, Raynaud's phenomenon). Clinical care focuses on preserving functioning and improving quality of life. One significant quality of life issue in SSc is disease-related pain (Benrud-Larson et al., 2002; Richards et al., 2004; Edwards et al., 2006; Schieir et al., 2010; Suarez-Almazor, Kallen, Roundtree, & Mayes, 2007). There are numerous personal and financial costs to SSc pain such as frequently seeking medical consultation, employment difficulties, and challenges with maintaining life roles (Carreira, 2006). The prevalence of SSc pain ranges from 62% (Benrud-Larson et al., 2002) to 83% (Schieier et al., 2010), with a wide range of pain severities reported. For example, in a large (N = 585) descriptive study of SSc pain, 46% of patients described their pain as mild, 27% as moderate, and 10% as severe (Schieir et al., 2010). However, the factors that differentiate risk of SSc pain are not well understood.

Several studies have implicated disease activity and clinical manifestations SSc pain (Johnson, Gladman, Schentag, & Lee, 2006; Malcarne et al., 2007; Merkel et al., 2002; Schieier et al., 2010; Toffolo, Furtado, Klein, Watanabe, Andrade, & Natour, 2008). However, severity of disease does not adequately explain between-person variability in pain (Carreira, 2006). Indeed, patients with limited disease typically report having less pain than individuals with diffuse disease; but the differences are generally quite small and not clinically meaningful (Del Rosso et al., 2004; Schieir et al., 2010). This is unsurprising, given a substantial body of literature suggesting that the subjective experience of pain is greatly impacted by psychological and social phenomena (Fava & Sonino, 2008; Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

Several studies of SSc patients have explored the notion that psychosocial characteristics may also explain the prevalence and severity of SSc pain. Poor emotional well-being (Kwakkenbos et al., 2012; Schieir et al., 2010), negative cognitions (Edwards et al., 2006; Richards et al., 2003; van Lankveld, Teunissen, Näring, Vonk, & van den Hoogen, 2008), low social support (Savelkoul et al., 2000), and combinations of these variables (Merz et al., 2014), have all been implicated in worse pain cross-sectionally. This suggests that SSc pain is influenced by psychosocial factors and it should not be conceptualized from a reductionistic biomedical conceptualization.

Despite a growing research focus on the prevalence and correlates of pain in SSc, little is known about whether pain worsens, improves, or remains stable over time. To date, there has only been one longitudinal investigation of SSc pain (Sekhon, Pope, Canadian Scleroderma Research Group, & Baron, 2010). In this study, 109 SSc patients (limited vs. diffuse classification unknown) with an average disease duration of 9.18 years (*SD* = 6.60) provided data at two time-points ranging from 8-18 months apart. On average, pain did not change between observations. Additionally, there were not significant differences in pain when the sample was stratified by self-reported change in overall health status (10.1% reported an improvement, 37.6% reported a decline, 52.3% reported no change). This suggests that, over a short time span, health status and pain may be unrelated. However, because this sample was predominantly comprised of patients with intermediate stage disease, the results may not be applicable to patients with a more recent disease onset. It may be particularly important to understand pain in early SSc given that the majority of degenerative disease activity takes place during this phase, and also because this is a critical period of psychosocial adjustment to the disease.

Additionally, a better understanding of the course of pain earlier in the disease process may help inform intervention opportunities to improve patient quality of life in the long term.

There is a clear need to better understand (in)stability of SSc pain at an earlier point in the disease process. Therefore, the aims of the current study were to: (1) describe pain in early-disease SSc patients over three years, and (2) determine the role of medical, psychological, and social variables in pain over time. For the second aim, disease type (diffuse, limited) was chosen to represent disease severity, and the characteristics of mental health, perceived physical health, health worry, social support were chosen to represent emotional, cognitive, and social functioning. Given the degenerative nature of SSc, it was hypothesized that, overall, pain would become more severe over time. Based on the biopsychosocial theory of pain and the aforementioned empirical findings, it was also hypothesized that the more severe diffuse cutaneous disease classification, poorer mental health, poorer perceived physical health, greater health worry, and lower social support would be associated with more severe pain and a poorer pain prognosis. Finally, it was hypothesized that the psychosocial variables would be more important than disease type in understanding longitudinal pain.

Method

Participants

Participants were adults with early disease SSc (within approximately five years of onset) from the *G*enetics versus *EN*vironment *I*n Scleroderma *O*utcome *S*tudy (GENISOS), a prospective cohort study of SSc morbidity and mortality. All participants

lived within the geographic catchment area of one of the three study centers (University of Texas Health Science Center at Houston, University of Texas Medical Branch at Galveston, University of Texas-Health Science Center at San Antonio) and were recruited from the rheumatology faculty clinics, the county hospital, and chapters of the Scleroderma Foundation (Reveille et al., 2001).

Procedure

Institutional Review Board approval was obtained at all participating institutions. All patients gave written informed consent prior to the baseline visit. Patients attended annual study visits during regular outpatient medical appointments or inpatient services at facilities staffed by clinician investigators. At each visit, patients received a standardized clinical exam and were administered a packet of psychosocial measures. Details of the data collection procedures are detailed by Reveille et al. (2001). The current study utilizes data from the each participant's first three study visits. Because enrollment in the GENISOS is ongoing, each of the three consecutive measurement occasions took place annually between January 1998 and April 2013.

Measures

Descriptive characteristics

Demographics. Information regarding sex, age, gender, and date of disease onset were extracted from the medical record. Information regarding income, education, and marital status was collected as part of the survey packet at baseline.

Skin thickening. Skin thickening was measured using the modified Rodnan Skin Score (mRSS; Kahaleh, Sultany, Smith, Huffstutter, Loadholt, & LeRoy, 1986). The mRSS is calculated by measuring the extent and severity of skin thickening on 17 body surfaces by palpation on a 4-point scale (0 = uninvolved to 3 = severe thickening). Scores range from 0-51, with higher scores reflecting greater thickening.

SSc-related interstitial lung disease. Percent predicted forced vital lung capacity (%FVC), which indicates the ratio of the volume of air that can be forcibly exhaled after a maximum inspiration to the same volume in age, gender, weight, height, and ethnicity matched unaffected controls, was measured as an indicator of interstitial lung disease. All pulmonary measurements met criteria outlined by the American Thoracic Society/European Respiratory Society, and were reviewed by a pulmonologist. Higher scores indicate better lung functioning.

Time-varying (level-1) outcome variables

Pain. The Medical Outcomes Study Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992) pain subscale was measured at all three time-points and used to obtain a measure of pain intensity and impact over the past 4 weeks (baseline $\alpha = .88$). Scale scores are transformed into a 0-100 scale; higher scores indicate *less* pain severity and interference (i.e., better pain-related quality of life).

Time-varying (level-1) predictor variable

Disease duration. A continuous variable representing years of disease duration was created for each patient at each time-point. Disease duration was calculated by taking

the deviation between the date of each study visit and the date of a patient's first non-Raynaud's symptoms[9].

Baseline (level-2) predictor variables

Disease type. A diagnosis of diffuse or limited SSc was confirmed by the clinician investigators at the first visit. Confirmations were made using the classification system established by Leroy et al. (1988).

Mental health. The SF-36 (Ware & Sherbourne, 1992) Mental Health component score was used to evaluate overall mental health. Component scores range from 0-100; higher scores indicate better mental health, less psychological distress, and fewer limitations due to emotional problems. Baseline scores were used ($\alpha = .89$).

Perceived physical health. The SF-36 (Ware & Sherbourne, 1992) Physical Functioning subscale was used to evaluate patient beliefs about their physical health and functioning limitations in a variety of activities. Scale scores range from 0-100. Higher scores indicate a perception of better physical health and function. Baseline scores were used ($\alpha = .92$)

Health worry. The Illness Behavior Questionnaire (IBQ; Pilowsky & Spence, 1975) Health Worry scale for SSc (Merz et al., 2013) was used to evaluate health-related worries. An example item is, "Do you worry a lot about your health?" Scores range from 0-5; higher scores indicate greater worry and concern regarding one's health. Baseline scores were used ($\alpha = .72$).

[9] Because the exact time of onset cannot be absolutely determined, the first non-Raynaud's manifestation is generally recommended to denote the onset of SSc (Tashkin et al., 2006).

Social support. The Interpersonal Support Evaluation List (ISEL; Cohen, Mermelstein, Kamarck, & Hoberman, 1985) was used to derive a measure of perceived social support. The ISEL yields four subscales and an overall support score which is derived by averaging the subscales. Overall scores range from 0-10; higher scores indicate better social support. Baseline scores were used ($\alpha = .88$).

Analytic strategy

The study hypotheses were tested using multilevel modeling (MLM), a flexible data analytic technique that handles hierarchically structured data (Raudenbush & Byrk, 2002). In the current study, the hierarchical structure consisted of repeated measurements of pain (level-1) nested within each patient (level-2). Given this, an ordinary least squares framework was not appropriate to use because each patient's pain observations were related to one another, violating the assumption of independence. Rather, MLM assumes that the level-1 observations (pain) are dependent within each cluster (patient). Thus, the fixed (regression coefficients) and random (variance components) effects are estimated simultaneously, which allows for the examination of both within- and between-person variability in the same model.

There are several other advantages to using MLM in longitudinal study designs. First, missing data and attrition are common concerns in such studies, and participants often have different numbers of measurement occasions. Instead of removing cases with missing observations, the full information maximum likelihood procedure (FIML) employed by MLM allows for all available points of data to be used by estimating a likelihood function for each person based on the variables that are present. The estimates

produced are weighted by the amount of data each person contributes (e.g., participants with 2 observations contribute to the estimates more than participants who provide 1 observation). This procedure has been shown to produce unbiased parameter estimates under conditions wherein data are missing at random. Thus, even data from individuals with a single measurement occasion can be used in the analysis to stabilize mean and variance estimates.

Another advantage is that MLM allows for different starting times for the first data collection occasion and also unequal spacing between points of follow-up by modeling time as a time-varying covariate on the first level of the data structure. This is relevant to the current study given that patients enrolled in the GENISOS at different points after the onset of SSc (disease duration ranged from 0.03 and 5.95 years at the baseline visit). Incorporating these differences, rather than using each of the three assessment waves as a nominal variables (i.e., visits 1, 2, and 3), allows for a more accurate reflection of time. Additionally, the follow-up appointments were conducted annually, but ranged from 9 to 15 months between visits. As such, disease duration ranged from .98 to 8.40 years at the first follow-up and 1.97 to 8.52 years at the second follow-up.

As described below, an iterative model building process was employed to test the study hypotheses. Fixed and random effects were estimated for all models. For the three conditional models that included the level-2 predictors of pain, significant interactions were probed using the methods of Preacher, Curran, and Bauer (2006). Descriptive model fit indices were also considered as indicators of model fit. For both the Akaike information criteria (AIC) and sample size-adjusted Bayesian information criteria (sBIC),

smaller values indicated better fit. Additionally, the proportion of reduction in unexplained variance between models was calculated to provide an indication of how much additional variance was accounted for by each set of predictors.

Model building

First, the *baseline model* was estimated. This unconditional (i.e., null) model depicts each patient's pain over time as a flat line with a slope of zero located at each patient's average pain. The *baseline model* provides the intraclass correlation coefficient (ICC), which is an estimate of variance in pain between- and within- subjects. The ICC is calculated using the variance components from both levels of the data structure. In this model, the level-1 equation states that the pain at time *t* for patient *i* ($pain_{ti}$) is a function of each patient's mean pain (β_{0i}) plus a within-subjects residual term that reflects the differences between each patient's observed and predicted value (r_{ti}). The level-2 equation states that each patient's mean pain (β_{0i}) is a function of the grand mean pain for all patients (γ_{00}), plus a between-subjects residual term that reflects the deviation of each subject's mean pain from the grand mean (u_{0i}). The model was specified as follows:

$$\text{Level-1: } pain_{ti} = \beta_{0i} + r_{ti}$$

$$\text{Level-2: } \beta_{0i} = \gamma_{00} + u_{0i}$$

Second, the *disease duration model* was estimated by adding time as a level-1 predictor. This unconditional linear growth (i.e., random coefficient) model examines time effects for each patient by allowing changes in each patient's pain over time to be modeled with a straight line and a non-zero slope. Disease duration was selected as the metric of time because patients entered the study at different points in their disease

course, and annual visits were not evenly spaced. As such, the metric of time for each patient was centered based on their own disease duration. Such within-person scaling is preferable in contexts where there is significant temporal variability, as it provides the most meaningful metric of time (see Mehta & West, 2000). It is important to note that in the current study no measurement occasions took place at disease onset. Thus, the intercepts for all models that include time were estimated based on the available time-points in disease duration. As such, the intercepts are described as "initial pain" in the results section. In this model, the level-1 equation states that pain at time *t* for patient *i* ($pain_{ti}$) is a function of each patient's mean pain (β_{0i}), plus a term that reflects the estimate for each patient's pain slope over time (β_{1i}), plus the within-persons residual term (r_{ti}). The first level-2 equation states that each patient's pain at the intercept (i.e., time of disease onset, β_{0i}), is a function of the sample grand mean at the intercept (γ_{00}), plus the between-persons residual term (u_{0i}). The second level-2 equation states that each patient's pain slope (β_{1i}) is a function of the grand mean rate of pain change (γ_{10}), plus a residual term that reflects individual patient differences of change in pain about the grand mean slope (u_{1i}). The equation was specified as follows:

$$\text{Level-1: } pain_{ti} = \beta_{0i} + \beta_{1i}\,(duration_{ti}) + r_{ti}$$

$$\text{Level-2: } \beta_{0i} = \gamma_{00} + u_{0i}$$

$$\text{Level-2: } \beta_{1i} = \gamma_{10} + u_{1i}$$

Next, three conditional linear models were tested to elucidate the relationship between medical, psychological, and social variables and pain over time. Disease duration was retained as a level-1 variable in all models. The first of the three conditional models, termed the *medical model*, was estimated by adding disease classification (i.e.,

limited vs. diffuse[10]) as a level-2 predictor to explain intercept and slope variance in pain. In this model, the level-1 equation is identical to the *disease duration model*. The first level-2 equation states that a patient's pain at the intercept (β_{0i}) is a function of the average pain for diffuse patients at baseline (γ_{00}), plus the mean difference in pain between diffuse and limited patients at baseline (γ_{01}), plus the between-subjects residual term (u_{0i}). The second level-2 equation states that each patient's rate of change in pain over time (β_{1i}) is a function of the average change in diffuse patients' pain per year (γ_{10}), plus the mean slope difference in pain between diffuse and limited patients (γ_{11}), plus the variance component for the slope term (u_{1i}). The equation was specified as follows:

$$\text{Level-1: } pain_{ti} = \beta_{0i} + \beta_{1i}(duration_{ti}) + r_{ti}$$

$$\text{Level-2: } \beta_{0i} = \gamma_{00} + \gamma_{01}(type_i) + u_{0i}$$

$$\text{Level-2: } \beta_{1i} = \gamma_{10} + \gamma_{11}(type_i) + u_{1i}$$

The second of the three conditional models, the *psychosocial model*, was estimated by adding the psychosocial variables to the *disease duration model* (baseline measurements of mental health, perceived physical health, health worry, social support). All continuous predictors were grand mean centered and added as level-2 predictors to explain intercept and slope variance in pain. The level-1 equation is identical to the *disease duration model*. The first level-2 equation states that a patient's pain at the intercept (β_{0i}) is a function of the average pain for patients at baseline (γ_{00}) plus the unique relationship between each psychosocial predictor and pain (γ_{01}- γ_{04}), plus the between-subjects residual term (u_{0i}). The second level-2 equation states that each

[10] Because disease classification is a binary variable with a meaningful zero point (diffuse = 0, limited = 1) it was added to the model uncentered.

patient's rate of pain change (β_{1i}) is a function of the average rate of pain change per year (γ_{10}), plus the unique slopes attributable to each of the psychosocial predictors (γ_{11}- γ_{14}), plus the variance component for the slopes term (u_{1i}). The equation was specified as follows:

$$\text{Level-1: } pain_{ti} = \beta_{0i} + \beta_{1i}\,(duration_{ti}) + r_{ti}$$

$$\text{Level-2: } \beta_{0i} = \gamma_{00} + \gamma_{01}(mental_i) + \gamma_{02}(perceived_i) + \gamma_{03}(worry_i) + \gamma_{04}(social_i) + u_{0i}$$

$$\text{Level-2: } \beta_{1i} = \gamma_{10} + \gamma_{11}(mental_i) + \gamma_{12}(perceived_i) + \gamma_{13}(worry_i) + \gamma_{14}(social_i) + u_{1i}$$

A final conditional model incorporating both the medical and psychosocial predictors as level-2 predictors of pain was estimated and labeled the *biopsychosocial model*. Again, the level-1 equation is identical to the *disease duration model*. The first level-2 equation states that a patient's pain at the intercept (β_{0i}) is a function of the average pain for patients at baseline (γ_{00}) plus the unique relationship between all predictors and pain (γ_{01}- γ_{05}), plus the between-subjects residual term (u_{0i}). The second level-2 equation states that each patient's rate of change in pain over time (β_{1i}) is a function of the average rate of change per year (γ_{10}), plus the unique change attributable to each predictor (γ_{11}- γ_{15}), plus the variance component for the slopes term (u_{1i}). The equation was specified as follows:

$$\text{Level-1: } pain_{ti} = \beta_{0i} + \beta_{1i}(duration_{ti}) + r_{ti}$$

$$\text{Level-2: } \beta_{0i} = \gamma_{00} + \gamma_{01}(type_i) + \gamma_{02}(mental_i) + \gamma_{03}(perceived_i) + \gamma_{04}(worry_i) + \gamma_{05}(social_i) + u_{0i}$$

$$\text{Level-2: } \beta_{1i} = \gamma_{10} + \gamma_{11}(type_i) + \gamma_{12}(mental_i) + \gamma_{13}(perceived_i) + \gamma_{14}(worry_i) + \gamma_{15}(social_i) + u_{1i}$$

Missing data

Twenty-eight of the 344 patients were missing the primary variable of interest (pain) at every time-point and were not included in the analyses. Thus, the final sample size was 316. The 28 patients who were missing the pain variable did not differ from the 316 patients who had at least one data point with regard to sex, race, marital status, education, income, disease classification, disease duration, age of disease onset, death during the course of the current study, skin thickening, pulmonary functioning, or analgesic usage (*p*s > .05). The 28 individuals who were missing all three time-points were somewhat younger (M = 43.49, SD = 12.96) than the 316 individuals with at least one data point (M = 48.95, SD = 13.05), although the effect was small (t [342] = 2.12, d = .22, p = .035).

Forty-nine patients during died during the time period of the current study (after baseline: 29 diffuse, 9 limited; after first follow-up: 6 diffuse, 5 limited). These 49 patients generally did not differ from the rest of the sample on the aforementioned demographic and disease characteristics. The three exceptions were that patients who died were more likely to be African American or Latino, and have less education and annual income. However, the link between mortality status and these variables were quite small (effect sizes = |.14-.18|, *p*s < .05). Additionally, baseline pain was not different for those who died (M = 43.39, SD = 29.73) versus those who were alive throughout the current study (M = 50.29, SD = 26.52; p > .10). The pain scores for participants who died were considered "truncated by death" rather than censored or missing (Zhang & Rubin, 2003). Therefore, the distribution of missingness was not modeled in the analyses; rather,

inferences from the estimates were considered conditional on the probability of surviving (for discussions of this issue, see Kurland et al., 2009; Zhang & Rubin, 2003).

Patterns of missing data for the pain variable were evaluated in relation to the aforementioned demographic and disease characteristics. The only covariate-dependent missingness pattern that emerged was for income; individuals with a lower income were more likely to be missing more pain measurement occasions (r_s = -.12, p = .031). Because the effect was so small, income was not accounted for in the final models, heeding accepted guidelines that missing data patterns should only be accounted for when they are likely to influence the study findings in a non-ignorable fashion (Hedeker & Gibbons, 1997). However, for completeness all models were re-run including income as a covariate and the patterns of findings were unchanged.

Results

Descriptive analyses

Descriptive statistics for the full sample at the first study visit are available in Table 4.1. The sample was predominantly comprised of women from a range of ethnic backgrounds. Most participants were married and had at least a high school diploma or equivalent. Ages ranged from 16 to 86, with most participants being middle-aged. Individuals with diffuse SSc had greater skin thickening (t [311] = -15.06, p < .001; diffuse M = 22.16 [SD = 10.80]; limited M = 6.83 [SD = 5.13]) and slightly worse percent predicted forced vital lung capacity (t [273] = 1.72, p = .086; diffuse M = 79.06 [SD = 19.82]; limited M = 82.23 [SD = 20.04]) at the first measurement observation. Mean pain

scores[11] at each observation were as follows: Visit 1 (n = 302): M = 49.21, SD = 26.96; Visit 2 (n = 197), M = 55.51, SD = 26.49; Visit 3 (n = 121), M = 55.19, SD = 27.48.

Understanding pain over time

Parameter estimates, standard error, and fit indices from all models are presented in Table 4.2. There were a total of 620 observations for the 316 patients, for an average of 1.962 observations per person. The *baseline model* revealed an ICC of .612 (i.e., 61.2% of the variability in pain is between-persons, 38.8% is within-persons). There was a large amount of variability (τ_{00} = 449.20, p < .001) around the grand mean (b = 51.42, p < .001); 95% of patients had pain scores between 9.88 and 92.96. There was also significant variability between each patient's observed and predicted pain (σ^2 = 286.07, p < .001).

Next, the *disease duration model* also showed a large amount of variability (τ_{00} = 436.60, p < .001) around the grand mean at the intercept, or the point of disease onset (b = 46.03, p < .001). In the *disease duration model*, pain scores increased 1.72 points per year, on average (p = .002). Given the scoring metric of the SF-36, this suggests that, overall, pain became *lesser* over time. However, there was not significant slope variance in pain growth trajectories (τ_{11} = 0.61, p = .89), suggesting that there was no additional within-person variability to be accounted for after disease duration was included in the model. That is, the metric of time accounted for the majority of slope variance, precluding the inclusion of additional level-1 variables. This model demonstrated

[11] Note that on the SF-36, lower scores indicate greater pain severity and interference, whereas higher scores indicate less pain severity and interference.

significant variance in each patient's observed versus predicted pain after accounting for disease duration ($\sigma^2 = 281.22$, $p < .001$). Additionally, the AIC and sBIC values were lower than the *baseline model*, suggesting improved fit. The proportion of reduction in unexplained variance between these models was .017; adding the metric of time explained a small amount of total variance in pain.

The *medical model* incorporated disease classification (diffuse vs. limited) as a level-2 variable. The AIC and sBIC values for this model were approximately equal to the *disease duration model*, suggesting roughly equivalent fit. Additionally, the proportion of reduction in unexplained variance between these two models was .008; thus, disease type explained a very small amount of additional variance in pain after time was accounted for. For diffuse patients, mean pain was significant at disease onset (intercept: $b = 42.50$, $p < .001$). Limited patients had significantly higher pain scores ($b = 8.82$, $p = .049$) than diffuse patients, indicating that limited patients experienced *less* pain than diffuse patients at disease onset. The slope for diffuse patients was positive and statistically significant ($b = 2.45$, $p < .001$), and the rate of change in pain over time was not significantly different for limited patients ($b = -1.80$, $p = .12$). This means that pain changed at approximately the same rate for both diffuse and limited patients. Again, given the scoring metric of the SF-36, this suggests that patients' pain decreased over time. Variance estimates showed significant variability in observed versus predicted pain at disease onset ($\tau_{00} = 434.44$, $p < .001$) and over time ($\sigma^2 = 279.11$, $p < .001$), but there was not significant slope variability in pain growth trajectories across patients ($\tau_{11} = 0.63$, $p = .89$).

The *psychosocial model* incorporated mental health, perceived physical health, health worry, and social support as level-2 variables. The AIC and sBIC values for this model were lower than the previous models, indicated an improvement in model fit. The proportion of reduction in unexplained variance between the *psychosocial model* and both the *disease duration* (.054) and *medical* (.047) models suggested that the addition of psychological and social characteristics explained some additional variance in pain beyond time and disease type. Mean pain at disease onset (b = 46.47, p < .001) and increase in pain scores each year (b = 1.61, p = .002) were again significant. The regression coefficients relating mental health (b = 0.59, p < .001) and perceived physical health (b = 0.53, p < .001) with pain were positive and statistically significant. That is, better mental health and better perceived physical health were both predictive of *less* initial pain. The main effects for health worry (b = -1.07, p = .42) and social support (b = -0.75, p = .61) were not significant. Again, variance estimates showed significant intercept (τ_{00} = 187.70, p < .001) and residual (σ^2 = 266.04, p < .001) variability, but there was not significant slope variability in pain growth trajectories (τ_{11} = 1.95, p = .52).

Two significant cross-level interactions emerged and were further explored by computing simple regression lines at low (-1 SD from the centered mean), mean (at the centered mean) and high (+1 SD from the centered mean) values for the relevant level-2 predictors. The regression coefficient describing the interaction between disease duration and perceived physical health was statistically significant (b = -0.04, p = .04). The intercepts for low (b = 31.14), mean (b = 46.47), and high (b = 61.81) perceived physical health were all statistically significant (ps < .001). The simple slopes for low (b = 2.82, p = .0001) and mean (b = 1.61, p = .002) perceived physical health were positive and

statistically significant; however, the simple slope for high perceived physical health (b = 0.40, p = .6255) was not. This suggests that, after controlling for the other variables in the model, individuals who perceive their physical health to be good have less initial pain which remains stable over time. However, patients with average and low perceived physical health have respectively worse initial pain, but both gradually improve over time. Interestingly, the patients with the lowest perceived physical health had the steepest slope (i.e., faster recovery).

Additionally, the regression coefficient describing the interaction between disease duration and social support approached statistical significance (b = 0.72, p = .07). The intercepts for low (b = 47.68), mean (b = 46.47), and high (b = 45.26) social support were all statistically significant (ps < .001). The simple slopes for mean (b = 1.61, p = .002) and high (b = 2.77, p = .0096) social support were positive and statistically significant; however, the simple slope for low social support (b = 0.44, p = .3616) was not. Although the intercepts were statistically significant, they were quite similar, and the main effect for pain was not significant. Thus, there was little evidence that social support had a significant impact on initial pain. However, at low levels of social support, the same level of pain persisted over time, whereas at mean and high levels of social support, there was significant improvement, with the most supported individuals having the steepest slope (i.e., faster recovery).

The *biopsychosocial model* incorporated the level-2 predictors from the medical and psychosocial models in a single equation. The AIC and sBIC values for this model were smaller than the *medical model*, and there was a reduction in the proportion of unexplained variance (.047). However, the AIC and sBIC values for this model were

similar to the *psychosocial model*, and the proportion of reduction in explained variance between these two models was negligible (.000). This indicates that psychosocial characteristics, rather than disease type, are the most important predictors of pain, and that including disease type in the model does not explain additional variance in pain beyond the psychosocial characteristics. Mean pain at disease onset ($b = 48.59$, $p < .001$) and change in pain over time ($b = 1.37$, $p = .05$) were again significant. The regression coefficients for the psychosocial variables retained the same patterns as in the previous model (mental health $b = 0.59$, $p < .001$, perceived physical health $b = 0.57$, $p < .001$, health worry $b = -1.25$, $p = .36$, social support $b = -1.13$, $p = .47$). Specifically, better mental health and perceived physical health was associated with *less* initial pain, whereas health worry and social support were not significant predictors of initial pain. However, after controlling for the psychosocial variables, the main effect for disease classification was no longer significant ($b = -5.38$, $p = .21$). This suggests that when psychosocial and medical predictors are considered simultaneously, disease type is no longer significant. Variance estimates were similar to the psychosocial models ($\sigma^2 = 266.00$, $p < .001$; $\tau_{00} = 182.34$, $p < .001$; $\tau_{11} = 2.16$, $p = .49$).

The cross-level interactions for perceived physical health and social support mirrored those from *psychosocial model* and were probed using the procedure described above. Specifically, the interaction term for perceived physical health was statistically significant and the interaction term for social support approached statistical significance. When the interaction between disease duration and perceived physical health ($b = -0.05$, $p = .03$) was explored, the intercepts (low $b = 32.31$, mean $b = 48.59$, high $b = 64.87$; all ps $< .001$) and slopes (low $b = 2.70$, $p = .0008$; mean $b = 1.38$, $p = .0492$; high $b = 0.05$, p

= .959) retained the same patterns as described in the *psychosocial model*. As described in Figure 4.1, pain does not change over time for patients with high perceived physical health, but it does improve for patients with average and low perceived physical health. When the interaction between disease duration and social support (b = 0.77, p = .06) was explored, the intercepts (low b =50.42, mean b = 48.59, high b = 46.76; all ps < .001) and slopes (low b = 0.12, p = .9044; mean b = 1.38, p = .0492; high b = 2.63, p = .0032) also maintained the previous patterns. As described in Figure 4.2, pain does not change over time for patients with low social support, but it does improve for patients with average and high social support.

As a final step, and to ensure that the coefficients were not affected by pain medication usage, all conditional models (i.e., the *medical*, *psychosocial*, and *biopsychosocial* models) were re-run, controlling for analgesic use at each time-point. During each measurement occasion, participants were asked whether they had taken acetominophen, non-steroidal anti-inflammatory drugs, tramadol, or narcotics at any point during the past month. When analgesic use was entered as a time-varying covariate (i.e., level-1 predictor of pain), the patterns of findings were not changed. As such, the coefficients from the primary analyses were considered to be the best representation of the longitudinal course of pain in the current sample.

Discussion

Pain is a considerable quality of life issue in patients with SSc, although surprisingly there have been few reports on this topic to date. This study used data from an ongoing prospective cohort of SSc patients within approximately 5 years of disease

onset to describe the course and correlates of pain over three years. Because there is progressive skin thickening and disease activity during this early stage, and because there is a general pattern of deterioration, it was hypothesized that pain would also become poorer over time. Contrary to this prediction, pain changed very little over the three years of the study, and the change that did occur suggested a slight overall *improvement* in pain. From a biomedical perspective, it was unexpected that pain would actually remit during the disease phase wherein the greatest amount of inflammatory damage takes place. However, this finding was less surprising from the standpoint of psychological adjustment. The onset and diagnosis of a chronic disease such as SSc is generally a distressing, life-disrupting event. However, over time, many people with a chronic disease eventually accept their new reality and adapt well (Stanton, Revenson, & Tennen, 2007). Acceptance, which is a paramount task of the adjustment process (Stanton et al., 2007) has also been shown to affect perceptions of chronic pain (McCracken, 1998; McCracken, Carson, Eccleston, & Keefe, 2004), offering a potential explanation for this paradoxical result.

Next, a series of predictors were added to the longitudinal model. Because disease severity and clinical manifestations have been previously implicated in SSc pain (Malcarne et al., 2007; Schieir et al., 2010; Toffolo et al., 2008), disease type, which is a proxy for disease severity, was added first. In this model, diffuse disease was associated with worse initial pain, although both types had approximately the same rate of improvement in pain over time. This provided initial support for the second hypothesis: diffuse (vs. limited) classification was predictive of worse pain. However, because the

addition of disease type explained very little additional variance in pain, the effect was quite small.

In the second conditional model, time-invariant psychosocial predictors (but not disease classification) were considered. The results from this model provided partial support for the second hypothesis. There was a main effect for mental health, although the interaction term was not significant. That is, good emotional health was linked with less initial pain, but the rate of pain change was not dependent on emotional health. This extends cross-sectional findings (Kwakkenbos et al., 2012; Schieir et al., 2010) by suggesting that patients with better emotional health will continue to have less pain than patients with poorer emotional health, even though pain does improve for all patients over time. From a clinical perspective, this suggests that addressing mental health concerns may be an important goal for pain management in this population.

Two cognitive variables, perceived physical health and health worry, were also included in this model. For perceived physical health, both main and moderating effects emerged. When the interaction was examined, the results suggested that high levels of perceived physical health predicted less initial pain that remained consistent over time. Additionally, average and low levels of perceived physical health were correlated with respectively worse pain. However, both groups exhibited some pain remission over time. Interestingly the slope for poor perceived physical health also demonstrated the fastest recovery, suggesting that patients who initially believed their physical health was poor were most likely to see improvements in pain over time. Health worry, the second cognitive variable in the study, was not related to pain over time, which was contradictory to the second study hypothesis. However, this does not suggest that

cognitive style is unimportant. In other samples of patients with rheumatic disease, rumination, catastrophizing, and feelings of helplessness have all been implicated in pain (Edwards et al., 2011). Because these were not measured as part of the larger GENISOS project, they could not be evaluated in the current analysis. It is therefore recommended that future studies evaluate the predictive utility of these constructs in SSc-related pain.

When social support was added to the model, the main effect was not significant. However, there was a statistical trend for the interaction term. High and average levels of social support predicted improvement in pain over time, whereas pain levels remained the same for the lowest level of support. Although both average and high levels of social support demonstrated benefit, the highest level was associated with the most rapid improvement in pain across the study (an increase of 2.77 points annually, in the psychosocial model). This suggests that social support may play an important role in pain recovery, a finding that has been observed in other rheumatic diseases (Savelkoul et al., 2000). As such, improving social resources may be an important point of intervention in comprehensive SSc pain management. It is worth mentioning that the social support scores in the current sample were quite high (M = 8.22 on a scale from 0-10). While this does not imply that the parameter estimates are problematic (MLM does not assume that predictor variables are normally distributed), it does suggest that individuals represented by the average and high social support slopes had fairly similar levels of support, whereas the low social support group had relatively much less support. The generally high levels of social support in the current study are somewhat unsurprising, given that psychometric evaluations of the Interpersonal Support Evaluation List frequently demonstrate negative skew in non-clinical samples (e.g., Brookings & Bolton, 1998). However, given that

inadequate social support is frequently reported as a problem in rheumatic disease (Kool & Geenen, 2012), it is possible that the current sample is not representative of the social support experienced by the SSc population as a whole. Additional research is needed to clarify normative levels of social support in this population and to confirm the potential impact of social support on pain.

Results from the final conditional model, which included the medical, psychological, and social predictors together, provided support for the third study hypothesis. Specifically, the relationship between disease severity and pain was reduced to nonsignificance after the patterns of psychosocial influence were accounted for. This corroborates a number of other reports that diffuse or limited classification does not explain clinically meaningful differences in pain (e.g., Benrud-Larson et al., 2002; Georges et al., 2006; Malcarne et al., 2007; Schieir et al., 2010). That is, even in the context of a disease characterized by significant damage of bodily tissue, the overall experience of pain is best explained by psychological and social phenomena.

From a clinical standpoint, these findings are quite encouraging. Disease type is a permanent classification and cannot be changed. Although medical treatments that target inflammation are routinely used in this population, they are not sufficient to manage SSc pain (Borenstein, 2010). Rather, a pain management program should be multifaceted, incorporating both pharmacologic and nonpharmacologic pain treatments. Because the findings suggest that emotional health and social support are important predictors of SSc pain, a cognitive-behavioral therapy protocol aimed at these risk factors should be included in comprehensive pain management plans. Such interventions have been widely disseminated in other pain populations (for recent reviews see Ehde, Dilworth, & Turner,

2014; McCracken & Vowles, 2014). These treatments may be useful in SSc patients as well, but controlled trials of targeted interventions are warranted to clarify this. Rheumatology health professionals are encouraged to adopt a biopsychosocial conceptualization when assessing a patient's pain. At the very minimum, information regarding a patient's mental health and social support should be collected along with medical data. Understanding a patient's psychosocial functioning will offer valuable information on the best way to approach a patient's individualized pain care.

There were several limitations to the current study. First, although the sample size was quite large for this relatively rare disease, statistical power was compromised due to the extensive heterogeneity of the pain scores. That is, there was a great deal of "noise" relative to the "signal" of the relationships between the putative predictors and pain. For example, after including disease duration into the models, there was no longer systematic variance in pain at the first level of the data structure (i.e., within-patients); therefore, testing the time-varying effects of other disease severity indicators (e.g., fluctuations in skin thickening) and psychosocial predictors was not feasible. Consequently, all of the predictors were tested at the second level of the data structure and evaluated as between-person variables. While this decision is defensible given that the test-retest correlations[12] of these variables indicated that they were fairly stable, trait-like constructs, it would have been more ideal to also evaluate changes in biopsychosocial functioning relative to pain over time. The second limitation concerns substantial amounts of missing data at both points of follow-up. Although the FIML procedure in MLM is generally able to

[12] Test-retest correlations between time-points were fairly high (*r*s = .40-.72 for mental health, .65-.74 for perceived physical health, .69-.75 for health worry, .64-.75 for social support).

accommodate this, it would be preferable to have less attrition over time to enhance precision of the estimates. Relevantly, there were several additional measurement occasions in the GENISOS cohort beyond the third time-point that could not be used to answer the study questions, given the significant attrition and related power concerns. A third limitation is that the cohort design restricted the ability to determine true causality. Although the observed relationships are likely bidirectional, ongoing, and mutually influential, not causal per se, other non-experimental methodologies (e.g., ecological momentary assessment) might better elucidate the patterns and strength of influence. A final limitation of the study pertains to the use of retrospective pain questions. It is well-known that relying on memory-based self-report assessments is subject to bias. This extends to the recall of pain, which is influenced both by the greatest severity of pain one has experienced over a given time period, but also the most recent level of pain (Redelmeier et al., 2003). However, given that one's memory of pain is more influential on behavior than their true momentary experiences (Redelmeier et al., 2003), such a retrospective assessment may be more clinically useful, even if the patients' responses were not a perfect reflection of the actual pain they experienced over the previous 4 weeks.

In sum, despite being a hallmark of SSc, pain has been understudied in this population. This is the first longitudinal examination of the nature of pain in early disease, when the greatest amount of physical change takes place. Although pain was heterogeneous across patients there was evidence that all patients had a similar recovery pattern and that perceived physical health, emotional health, and social support are important predictive characteristics. Future research endeavors are necessary to replicate

these findings and to clarify several of the issues described above and to translate these findings into comprehensive pain management plans. This report suggests a clear need to address the psychological and social concomitants of pain, in addition to medically managing SSc disease manifestations.

Chapter 4, in part is currently being prepared for submission for publication of the material. Merz, Erin L. ; Malcarne, Vanessa L.; Roesch, Scott C.; Nair, Deepthi K.; Salazar, Gloria; Assassi, Shervin; Mayes, Maureen D. The dissertation author was the primary investigator and author of this paper.

Table 4.1: Descriptive characteristics of sample at first study visit

Variable		*n*	percent
Sex	Women	266	84.2%
	Men	50	15.8%
Race/Ethnicity	White	155	49.1%
	Latino	90	28.5%
	Black	61	19.3%
	Asian	9	2.8%
	American Indian	1	0.3%
Marital status	Married/Partnered	179	56.6%
	Not Married/Partnered	127	40.2%
Education	Less than High School	46	14.6%
	High School/GED	149	47.2%
	Associate's Degree	25	7.9%
	Bachelor's Degree	44	13.9%
	Post-graduate	28	8.9%
Family income	≤ $29,999	139	44.0%
	$30,000-$49,999	61	19.3%
	$50,000-$99,999	59	18.7%
	≥ $100,000	43	13.6%
Disease type	Limited cutaneous	131	41.5%
	Diffuse cutaneous	185	58.5%

	M	*SD*
Age (years)	48.95	13.05
Age at disease onset (years)	46.47	13.09
Disease duration (years)	2.48	1.56
Skin thickening	15.74	11.66
Percent predicted forced vital lung capacity	80.90	19.99
Mental health	46.40	11.42
Perceived physical health	43.70	28.85
Health worry	2.21	1.62
Social support	8.22	1.63

Table 4.2: Parameter estimates (SE) of models predicting SSc patient pain over time

Parameters	Intercept Model	Linear Growth Model	Conditional Models		
	Baseline	Disease Duration	Medical	Psychosocial	Biopsychosocial
Fixed Effects					
Intercept	51.42 (1.40)***	46.03 (2.26)***	42.50 (3.03)***	46.47 (1.88)***	48.59 (2.60)***
Slope		1.72 (0.57)**	2.45 (0.77)***	1.61 (0.52)**	1.37 (0.71)*
Disease type			8.82 (4.49)*		-5.38 (4.28)
Mental health				.59 (0.17)***	.59 (0.17)***
Perceived health				.53 (0.07)***	.57 (0.08)***
Health worry				-1.07 (1.33)	-1.25 (1.36)
Social support				-.75 (1.47)	-1.13 (1.56)
Type x Duration			-1.80 (1.17)		.64 (1.13)
Mental x Duration				-.05 (0.05)	-.05 (0.05)
Perceived x Duration				-.04 (0.02)*	-.05 (0.02)*
Worry x Duration				.05 (0.35)	.06 (0.35)
Social x Duration				.72 (0.40)†	.77 (0.41)†
Variance components					
Residual	286.07 (30.19)***	281.22 (29.67)***	279.11 (29.20)***	266.04 (28.40)***	266.00 (28.51)***
Intercept	449.20 (45.25)***	436.60 (65.25)***	434.44 (65.54)***	187.71 (44.37)***	182.34 (43.70)***
Slope		.61 (4.45)	.63 (4.41)	1.95 (3.06)	2.16 (3.10)
Model summary					
AIC	5698.87	5684.75	5684.96	5125.65	5127.53
sBIC	5702.64	5691.01	5693.74	5140.96	5145.20

Note. Regression coefficient symbols in the parameters column (i.e., γ_{01}- γ_{15}) reflect the terms for the biopsychosocial model; †p ≤ .07, **p* < .05, ***p* < .01, ****p* < .001

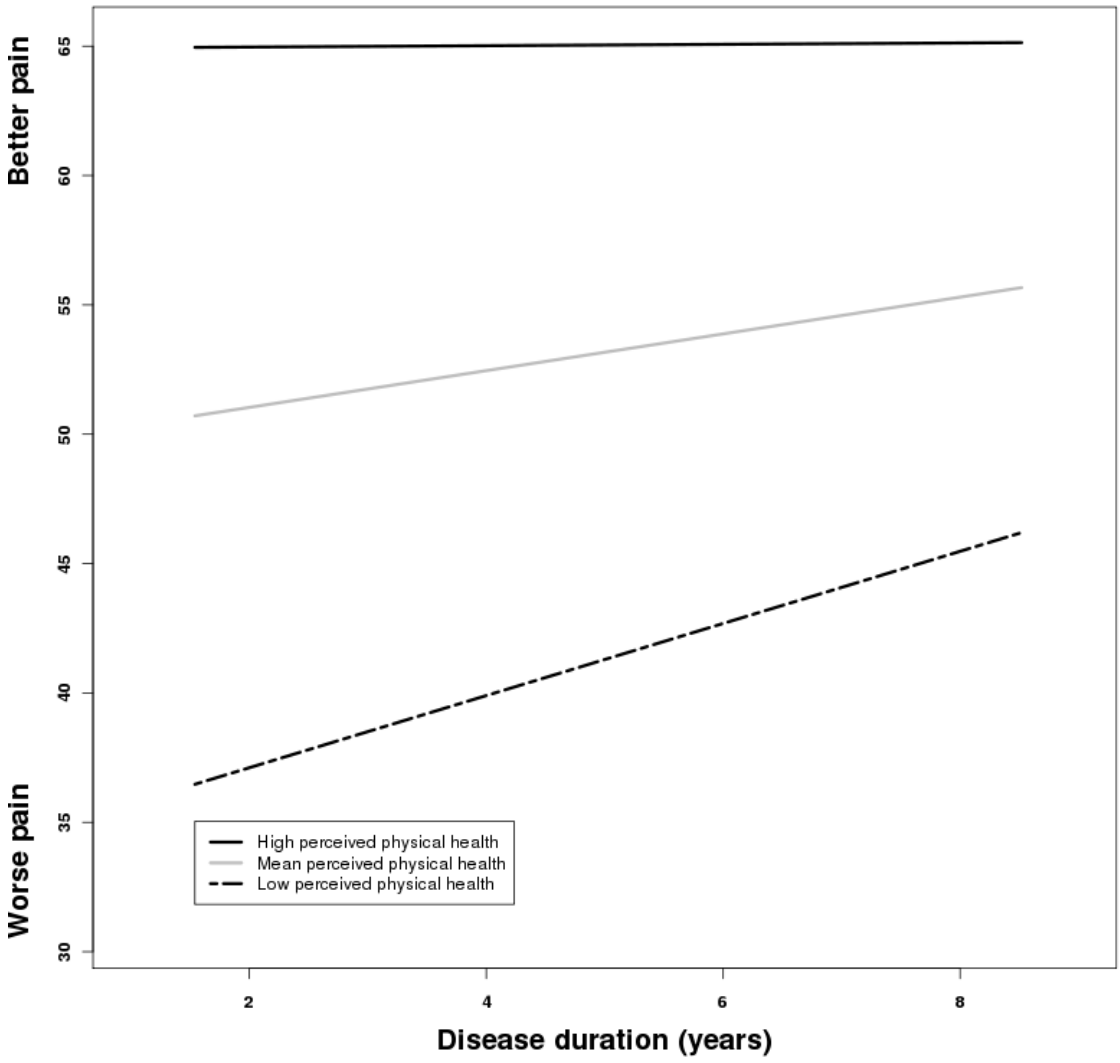

Figure 4.1: Simple slopes describing the relationship between baseline perceived physical health on the course of pain-related quality of life for patients with SSc

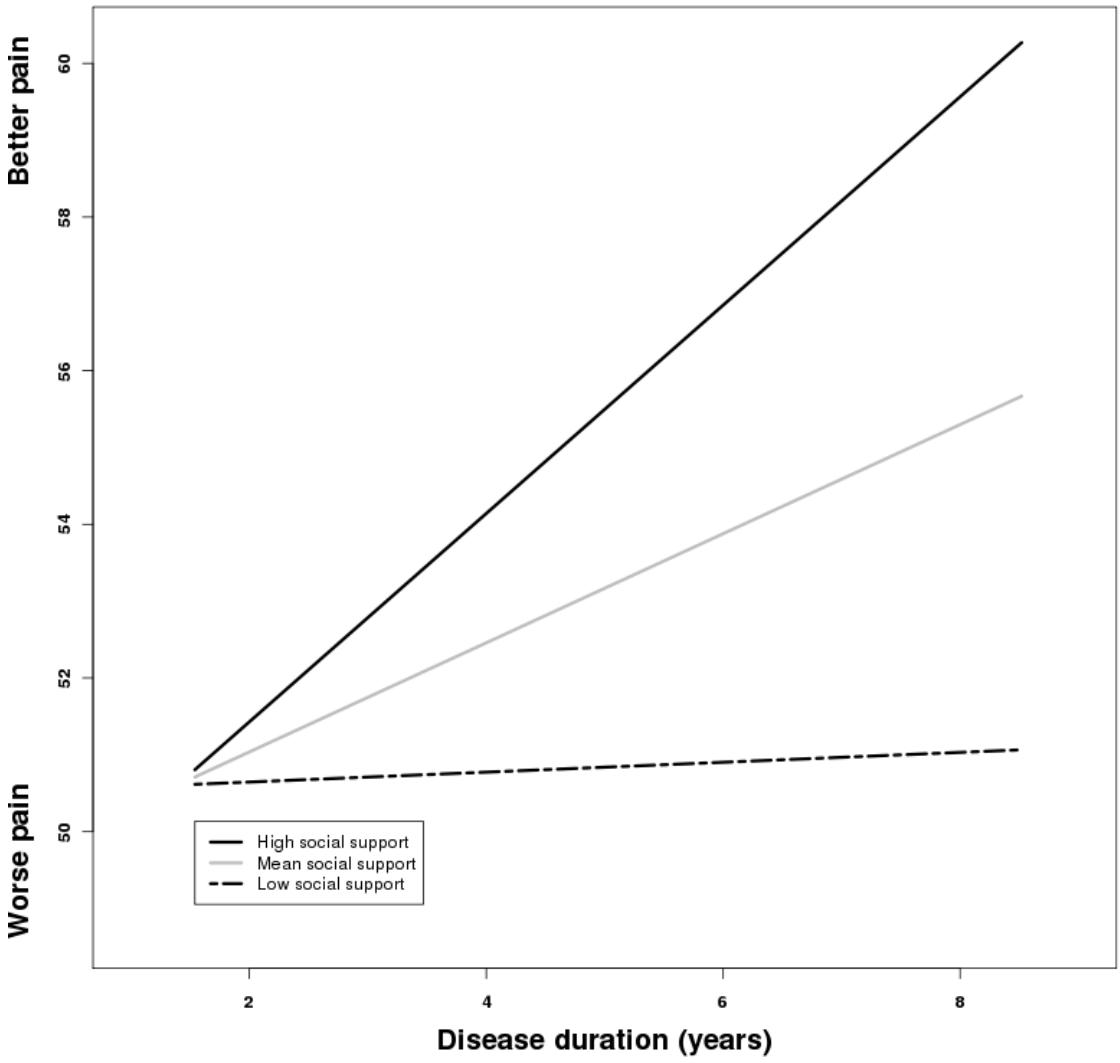

Figure 4.2: Simple slopes describing the relationship between baseline social support on the course of pain-related quality of life for patients with SSc

CHAPTER 5: DISCUSSION

Overview

This series of studies sought to evaluate pain-related quality of life in SSc. Traditionally, SSc pain has been defined and treated within the biomedical model; however, a growing literature has suggested that such a conceptualization is insufficient. A number of studies have demonstrated that disease severity does not adequately explain SSc pain (e.g., Benrud-Larson et al., 2002; Edwards et al., 2011). This is unsurprising, given decades of research suggesting that pain is modulated by psychological and social factors (Fava & Sonino, 2008). Together, the current studies provide preliminary evidence that pain is more complex than might be ascribed by an individual's disease physiology. Rather, SSc pain is best understood within a biopsychosocial framework and should not be defined through a single pathway.

Chapter 2: Illness behavior in systemic sclerosis

The purpose of the first study (Merz et al., 2013) was to utilize items of the IBQ (Pilowsky & Spence, 1983) to gain a better understanding of illness behaviors in SSc and to evaluate the psychometric properties of its factors for use in the subsequent studies. Historically, the factor structure of this measure has been unstable across samples, in part due to the possibility that different aspects of illness behavior may be more or less relevant for different disease groups (Prior & Bond, 2008; 2010). As such, this study sought to evaluate the factor structure of the measure in order to determine the most relevant aspects of illness behavior for use with SSc patients.

Four factor structures, which were previously derived from primarily psychiatric populations, were tested first. Because these did not replicate well in the GENISOS sample, an exploratory analysis was conducted. A five-factor solution provided the best overall fit to the data. These five subscales comprised illness-related (*Symptom Bother*, *Health Worry*), social (*Interpersonal Functioning*), and affective (*Other Life Worries*, *Affective Inhibition*) domains. The bivariate relationships between each factor and skin thickness, pulmonary functioning, fatigue, pain, disability, social support, and mental health were also evaluated. In general, indicators of disease severity (i.e., skin thickening, pulmonary functioning) were not related with each illness behavior factor. However, the psychosocial variables (i.e., fatigue, pain, disability, social support, mental health) correlated with the factors in the expected directions, providing some evidence of convergent validity.

Of particular interest with regard to pain were the variables representing cognitive reactions to disease (Pilowsky & Spence, 1975). Indeed, the two factors that represented illness-related cognitions (*Symptom Bother*, which indicates the perceived intensity and life-interference of disease symptoms, and *Health Worry*, which indicates the level of one's preoccupation with their physical health) were both significantly correlated with pain. Both were considered for inclusion in the subsequent cross-sectional and longitudinal pain analyses. However, because two items on the *Symptom Bothe*r factor directly referred to pain (i.e., *Are you bothered by many pains and aches?* and *Do you experience a lot of pain with your illness?*), whereas the *Health Worry* factor represented

health-related worries more generally (e.g., *Do you worry a lot about your health?*), the *Health Worry* construct was utilized in the subsequent studies.

Chapter 3: Understanding biopsychosocial contributions to systemic sclerosis pain

The purpose of the second study (Merz et al., 2014) was to evaluate the interrelationships of disease (skin thickening, pulmonary functioning), psychological (mental health, health worry), and social (social support) variables by deriving homogeneous biopsychosocial trait profiles of SSc patients, and evaluating the cross-sectional relationship of these profiles to pain and analgesic use. Although a number of studies have suggested that each of these constructs may contribute to SSc-related pain (e.g., Benrud-Larson et al., 2002; Edwards, Goble et al., 2006), none have considered all of them together in a single model. Accordingly, this study sought to model these variables as combined effects at the level of the person in order to describe heuristic biopsychosocial "types" or profiles of SSc patients. Next, comparisons between the different profiles were made with regard to two indicators of pain-related quality of life (i.e., pain and analgesic use).

A three-class solution provided the best fit to the data. Patterns of differences among the five indicator variables were examined and the classes were termed *Managing*, *Resilient*, and *Distressed*, based on the interpretation of the conditional responses. The *Managing* and *Resilient* groups were functioning similarly well with regard to mental health, health worry, and social support, whereas the *Distressed* group was doing more poorly in these domains. The starkest differences between groups

emerged for mental health and social support; the *Distressed* group yielded scores that were 1 and 2 standard deviations below the sample mean, respectively. With regard to objective indicators of disease severity, the *Managing* and *Distressed* groups had similarly good skin thickening scores and pulmonary functioning, whereas the *Resilient* group had a much more severe disease manifestation. Accordingly, the *Managing* group perceived their physical health to be relatively good, and the *Resilient* group perceived their physical health to be quite poor. However, this pattern did not match patient perceptions of physical health for the *Distressed* class. Instead, *Distressed* patients perceived their physical health to be just as poor as the *Resilient* class.

When the classes were compared with regard to pain, group differences emerged. The *Managing* group reported the lowest levels of pain, the *Distressed* group reported the highest levels of pain, and the *Resilient* group fell approximately in the middle. Group differences for analgesic use also emerged. Approximately one-third of the *Managing* group, half of the *Resilient* group, and two-thirds of the *Distressed* group reported taking pain medication over the past month. With respect to the specific medications, a greater proportion of the *Distressed* group had taken acetaminophen/NSAIDS, tramadol, and narcotics. The largest observed differences in pain medication usage occurred between the *Managing* and *Distressed* groups, which, notably, were very similar with regard to their disease severity.

This study presented new evidence that there is a distinct biopsychosocial pattern of SSc patients and that these patterns are predictive of pain-related quality of life. Disease severity was certainly relevant to pain in the current sample, but it was not the essential element in understanding which patients had more severe pain. Extrapolating

from the specific profile patterns, both mental health and social support appear to be critical features of pain in SSc, substantiating other reports (Benrud-Larson et al., 2002; Franck-Larsson et al., 2009; Georges et al., 2006; Schieir et al., 2010). However, like most investigations of SSc pain, the current study captured a single moment in time. Thus, the final study was designed to provide further insight into SSc pain by evaluating its prospective course and biopsychosocial contributions thereof.

Chapter 4: The longitudinal course and correlates of pain in systemic sclerosis

Despite the chronic and progressive nature of SSc, most disease-related quality of life studies have been cross-sectional. Therefore, the purpose of the third study was to describe the (in)stability of SSc pain over three years during the early phase of the disease when the majority of physical changes take place. Additionally, the roles of medical, psychological, and social constructs in longitudinal pain were examined.

In general, pain changed very little over the three years of the study. The change that did occur suggested a slight overall *improvement* in pain scores. That is, on average, SSc pain diminished over time. Sets of predictors (i.e., biomedical, psychosocial, biopsychosocial) were tested in subsequent models to allow for an appraisal of the relative importance of each. In the biomedical model, which included disease classification, diffuse disease was predictive of more initial pain and limited disease was predictive of less initial pain. However, the rate of change was equivalent for both disease classifications. This suggests that both groups improve over time, and the discrepancy in pain scores between diffuse and limited patients persists throughout the disease course.

However, adding the biomedical predictor into the model explained very little additional variance in pain.

However, in the psychosocial model, which did *not* include an indicator of disease severity, more variance in pain was explained. Significant relationships emerged for emotional health, perceived physical health, and social support in this model. Specifically, the significant intercepts suggested that both better emotional health and better perceived physical health were predictive of less initial pain. The interaction term for perceived physical health was also significant, and the interaction term for social support approached significance. Both suggested that poorer initial functioning (i.e., perceptions of poor physical health, low levels of social support) predicted worse pain over time.

In the final biopsychosocial model, which included all predictors, the relationship between disease severity and pain (i.e., the biomedical conceptualization) was reduced to nonsignificance. The observed patterns matched those of the psychosocial model and demonstrated that emotional health, perceived physical health, and social support were predictive of pain, even after accounting for disease severity. Better emotional health scores were linked with less initial pain, but not the rate of pain change. Thus, the pain discrepancy for emotional health persists over time. Additionally, better perceived physical health was predictive of less initial pain and also different longitudinal trajectories. Patients with poor perceived physical health had more initial pain but also the fastest recovery. This suggests that, over time, patients who initially believe that their physical health is very poor may "catch up" to those who have a better initial outlook. For social support, there were no initial differences in pain, although this variable was

predictive of different pain trajectories over time. Individuals with poor social support reported similar pain over the three years, whereas pain improved for individuals with average and high social support.

The results from this study suggest that there is enormous heterogeneity in pain and that, on average, pain improves minimally over time. From a biomedical perspective the slight improvement in pain scores was unexpected, given that the greatest amount of inflammatory damage takes place during the early disease phase (Medsger, 2003). However, from the standpoint of psychosocial adjustment, this was less surprising. The onset of a chronic disease is a significant, life-disrupting event that causes significant distress (Stanton et al., 2007). However, over time, the majority of people adjust well, with general improvements in their quality of life (Stanton et al., 2007). That is, pain may be exacerbated by initial distress, but time-dependent adjustment to the disease could promote some level of depreciation. Although the average rate of pain change was quite small in the current study, emotional health and social support were key predictors of the severity of longitudinal pain. It is important to note that the observed relationships were not causal per se, but more likely bidirectional, ongoing, and mutually influential. Nevertheless, these potentially modifiable constructs may represent points of intervention in this cycle.

Limitations

Limitations to each of the specific studies are discussed in their respective chapters. However, there are also a number of limitations that apply to all three studies. First, generalizability of the findings is limited by the characteristics of the sample. The

cohort was comprised of a non-probability convenience sample from one geographic region. Also, the analyzed data only represent patients in the early- to mid-disease phase, limiting implications for individuals who are in a later stage of disease. However, it should be noted that the sample was representative of the disease population (i.e., predominantly middle-aged females) and was comprised of patients with diverse disease characteristics (i.e., roughly equivalent proportions of patients with diffuse and limited disease). Additionally, the sample was ethnically and socio-economically diverse. Therefore, the current sample is likely a close representation of the general SSc population.

The second limitation concerns sample size. Although power was adequate, and the sample was sizeable for the disease population, a larger sample would have been preferred, particularly for the longitudinal analyses. It is therefore possible that the considerable attrition could have introduced bias. There are a number of potential reasons for missing data: (1) a patient may have attended a study visit but not provided all data for that visit; (2) a patient may have missed an annual visit but is still in the study; (3) a patient may have permanently dropped out from the study (e.g., relocation, quitting); (4) a patient may not have reached that study visit yet (i.e., a patient who recently enrolled and completed the baseline visit would not have annual follow-up data for another year); or (5) a patient may have become deceased. The reasons for missing data were not recorded, other than information regarding whether a patient passed away during the course of the study. Therefore, patterns related to specific reasons for missingness could not be considered. However, patterns of overall missingness were evaluated in each study, with no clear relationships to disease characteristics and only minimal patterns for

sociodemographic variables. It is therefore likely that any effects resulting from missing data were small, although the possibility that missing data influenced the results cannot be completely ruled out.

Third, there were some limitations due to the types of psychosocial data that were collected. Key variables representing cognitions that are theoretically related to pain (e.g., catastrophizing, acceptance) were not collected as part of the GENISOS and therefore could not be evaluated in the studies. Although two cognitive variables were included in the studies (i.e., perceived physical health, health worry) these do not adequately capture other cognitions that may be relevant to SSc pain. Future studies should collect data on these other potential predictors. Additionally, the retrospective nature of the pain questions may have introduced an element of response bias. The recall of pain is influenced both by the greatest severity of pain one has experienced over a given time period and also the most recent level of pain (Redelmeier et al., 2003). However, given that one's memory of pain is more influential on behavior than their true momentary experiences (Redelmeier et al., 2003), such a retrospective assessment may still be clinically useful, even if the patients' responses were not a perfect reflection of their actual pain over four weeks. It is also worth noting that all of the assessment tools used in the three studies had good psychometric properties, suggesting that there were no major problems with measurement of the study variables. Finally, the information regarding analgesics was limited to whether a patient had ever taken a particular medication during the past month. It was therefore unknown whether a patient was receiving pain relief from a medication during each point of data collection, which could have biased pain assessments.

Implications

SSc is a disease characterized by physical deterioration due to fibrosis of body tissue and a host of clinical symptoms that are implicated in pain (Medsger, 2003). The etiology of pain in this population is clearly linked to a pathological process, and contains nociceptive, neuropathic, and central characteristics (Borenstein, 2010). However, these studies also provide evidence that psychosocial phenomena are also important in understanding the experience of SSc pain, perhaps even more so than the severity of disease.

Emotional health was linked with SSc pain in this set of studies, a relationship that has been acknowledged in other reports (Benrud-Larson et al., 2002; Georges et al., 2006; Hansdottir et al., 2004; Hyphantis et al., 2007; Kwakkenbos et al., 2012; Milette et al., 2010; Richards et al., 2004; Schieir et al., 2010; Wafki et al., 2012). The psychological mechanisms underlying this relationship likely involve components of both the person and their context. For example, some individuals may have an underlying vulnerability for both negative affect and greater pain sensitivity (Wiech & Tracey, 2009). Thus, individuals who develop SSc and are also prone to emotional problems may be at a higher risk for significant pain. There is also evidence for a cyclic relationship wherein the experience and consequences of pain produce depressed mood, which leads to maladaptive pain responses and an increased perception of pain (Wiech & Tracey, 2009). Moreover, both chronic pain and chronic depression can be self-perpetuating problems that can actually alter the nervous system (Wiech & Tracey, 2009). Pain and emotion share common neurological pathways (e.g., limbic system, hypothalamic-

pituitary-adrenal axis) and neurotransmitters (e.g., serotonin, norepinephrine), underscoring the intimate connection between these constructs at even the most fundamental levels (Robinson et al., 2009; Wiech & Tracey, 2009). Indeed, the link between emotion and pain has been confirmed in a number of laboratory experiments. For example, depressed people may have a lower pain threshold than non-depressed controls (for a meta-analysis see Dickens, McGowan, & Dale, 2003). Even among healthy pain-free subjects, inducing depressed mood has been shown to decrease pain tolerance, but interestingly, not the subjective report of pain (Zelman, Howland, Nichols, & Cleeland, 1991).

Social support also emerged as an important concomitant of pain in these studies, corroborating observations from other rheumatic diseases (Savelkoul et al., 2000). This is a particularly important finding given evidence that deteriorating health leads to poorer social support (Victor, Scambler, Bowling, & Bond, 2005) and that the enhanced social support patients receive after diagnosis diminishes over time as their supportive others become acclimated to their condition (Ussher, Kirsten, Butow, & Sandoval, 2006). While social support and emotional health are inherently linked constructs (Cohen et al., 1985), they each relate to pain in unique ways. A number of mechanisms have been proposed to explain the connection between social support and pain (Uchino, 2006; Thoits, 2011). Social support may be related to pain either directly (i.e., a patient who has adequate support will generally have less pain) or as a buffering process (i.e., the relationship between stress or poor mood and pain will be mitigated by adequate support), although it is likely that it serves both purposes in the current context. Additionally, pain and social support may also share a common neural basis. There is some evidence that the dorsal

anterior cingulate cortex, which is part of the limbic system, is activated by both physical pain and social support (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). This suggests that the body may experience social and pain processes in a similar manner. Several experimental studies have also suggested that individuals who feel socially supported also perceive pain at lower levels. Using pain-free samples, Brown, Sheffield, Leary, and Robinson (2003) showed that cold-pressor pain was buffered in the context of real-time social support, and Jackson, Iezzi, Chen, Ebnet, and Eglitis (2005) demonstrated that this phenomenon was true for women but not men. In a rheumatologic sample, the presence of a supportive other led to decreased pain sensitivity to tactile stimulation at painful tender points among fibromyalgia patients (Montoya, Larbig, Braun, Preissl, & Birnhaumer, 2004).

SSc pain management

Although emotional health and social support emerged as particularly important in the current investigation, it is important to note that there was great heterogeneity in both pain and the related biopsychosocial constructs in these studies. This highlights the inherently "individual" nature of SSc pain. It follows that a single type of treatment will not provide adequate relief for all patients. Turk (2005) has proposed that chronic pain treatment should be matched to the predictive characteristics of each patient. Indeed, a number of promising interdisciplinary treatments have been proposed for chronic pain populations (see Ehde, Dilworth, & Turner, 2014; McCracken & Vowles, 2014 for reviews). It follows that similar strategies aimed at disrupting the cycle of pain for patients with SSc are worth considering.

Effective pain management should be a primary goal of total patient care in rheumatology. However, it is not well investigated among patients with SSc (Giuggioli et al., 2010), perhaps in part because an aggregate understanding of SSc pain is lacking. Following the historically biomedical conceptualization of rheumatologic pain, most therapies have focused on tissue injury, inflammation, and the biomechanics of pain signaling only (Borenstein et al., 2010). Medical treatments such as oxycodone (Giuggioli, Manfredi, Colaci, & Ferri, 2010) and surgery (Tomaino, Goitz, & Medsger, 2001) have been identified as effective in treating SSc pain; however, both are associated with significant morbidity. Oxycodone has a number of negative side effects such as itchiness, nausea, dizziness, and constipation, all of which have been reported in SSc patients taking the drug on a short-term basis (Giuggioli et al., 2010). There are a host of other problems with prolonged, including dependence (Trescot et al., 2008); although notably, there have been no studies on the long-term side effects of the drug in SSc. The adventitial stripping surgical procedure for SSc pain is very invasive, and involves removing the sympathetic nerves involved in pain signaling (Tomaino et al., 2001). It is also notable that not all SSc patients respond well to these methods, and there has been little published evidence on their long-term effectiveness (Borenstein, 2010; Giuggioli et al., 2010; Lundborg, Nitescu, Appelgren, & Curelaru, 1999; Tomaino et al., 2001). To break the cycle of pain it may be important to first take a more conservative and holistic approach, addressing various aspects of the patient and their pain.

The current findings suggest that there are modifiable non-medical risk factors for SSc pain. Therapies that target these constructs may be promising for use in SSc. Indeed, Borenstein (2010) has stated that pharmacologic treatment is not sufficient to adequately

manage rheumatic pain. Moreover, given the chronic nature of SSc, and the likelihood that patients will already have a complicated regimen of medications, less invasive methods for managing pain would be ideal. A number of psychotherapeutic approaches, including cognitive-behavioral therapy (which involves skill building in areas such as mindfulness, exercise, weight control, relaxation training, development of active coping strategies, increasing social support, changing maladaptive beliefs about pain, and activity pacing) have already been identified and used in chronic pain populations (Fava & Sonino, 2008; Gatchel et al., 2007; Hassett & Williams, 2011; Kerns, Sellinger, & Goodin, 2011), including the rheumatic diseases (Borenstein, 2010; Edwards et al., 2011).

While there is high promise for such treatments, rigorous testing of psychosocial interventions specifically targeting pain and its psychosocial correlates in SSc needs to be undertaken (see Thombs et al., 2010). It is also important to note that the outcomes associated with these treatments are multifaceted. Adequate pain management will likely not indicate that SSc pain has been eliminated. Rather, a successful outcome could mean that pain is partially alleviated, a patient is experiencing their pain differently, a patient is less disabled by their pain, or a patient's healthcare costs have decreased.

Future Directions

The results of these studies suggest that pain-related quality of life is a multifactorial problem in SSc and that psychosocial functioning is fundamental to understanding pain in this population. However, further investigation is warranted, given

that many questions regarding the mechanisms and treatment of SSc pain remain unanswered.

Cognitive variables that were not included in this cohort should be included in the protocols of future observational studies. There is particular merit in including variables such as catastrophizing and acceptance, given the well-established relationships in other rheumatic populations (Borenstein et al., 2010; Edwards Goble et al., 2006; Gatchel et al., 2007; McCracken et al., 2004). Inclusion of these constructs may proffer additional explanation to the cognitive component of SSc pain over and above one's perception of physical health and disease-related worries.

Additional clarity on the prospective nature of pain over a more extensive course of the disease is also needed. It will be particularly important to clarify whether pain recovery eventually plateaus, or if pain generally continues to improve over the long course of the disease. Studies should also evaluate the course of pain at individual sites (e.g., hand pain), not just overall pain, given that some pain may be localized to particular clinical features and physical locations (Schier et al., 2010). Given the rarity of SSc and the difficulties related to attrition in prospective cohort studies, retaining a sample that is large enough to achieve this will be a challenge. Researchers who are conducting cohort studies with similar designs may want to consider combining their longitudinal samples to accomplish this. A recent intiative using this approach, the Scleroderma Patient-Centered Intervention Network (SPIN), has been designed to develop and evaluate internet-based nonpharmacological interventions for a number of common SSc problems including hand functioning, distress, body image concerns, and disease self-management

(Thombs et al., 2012). Such an approach could also be useful for testing behavioral pain interventions.

There are several potential foci for interventional research. As noted above, there have been no randomized trials of interdisciplinary pain management for patients with SSc. Following examples in other disease groups (e.g., Ehde et al., 2014; McCracken & Vowles, 2014), there are opportunities to design studies that implement educational, psychological, and pharmacological pain management protocols. Relevant research questions involve the efficacy of different treatments, effectiveness of implementing long-term interdisciplinary pain care on an outpatient basis, and the advantages and disadvantages of general (i.e., patients receive an identical treatment) vs. individualized protocols (i.e., matching a patient to a treatment). Additionally, the preventive utility of such treatments should be explored by implementing empirically-supported treatments earlier in the disease course.

SSc pain is a complex phenomenon that is not well understood. The current studies add to a growing literature on the topic and indicate that SSc pain is best conceptualized within a biopsychosocial framework, rather than a reductionistic biomedical model. In these studies, psychosocial constructs were particularly powerful markers of SSc pain. These should be included in pain assessments and also targeted in pain management treatment plans. Indeed, there seems to be a growing interest among researchers and clinicians on SSc pain, reflecting a shift from a narrow focus on disease manifestations to aspects of survivorship and restoring and maintaining patient quality of life. Over the next several years there will likely be exciting and innovative efforts to

enhance quality of life and better manage SSc pain, with psychologists and other rheumatology health professionals aligning to make key contributions to this end.

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