Symptom Trajectories and Self-Management in Systemic Sclerosis

by

Robyn Katherine Wojeck

Nursing
Duke University

Date:_____
Approved:

_____
Donald "Chip" Bailey, Jr., Advisor

_____
Mitchell R. Knisely

_____
Susan G. Silva

_____
Tamara J. Somers

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in Nursing
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<u>ABSTRACT</u>

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Abstract

Systemic sclerosis is a rare, chronic, and progressive autoimmune disease associated with significant symptom burden. There is no cure for systemic sclerosis and patients are challenged with self-managing debilitating symptoms, such as anxiety, depression, fatigue, sleep disturbance, and pain. Symptom research has predominately focused on the prevalence and severity of individual symptoms and their relationship with patient outcomes. However, little is known about the synergistic effects of these symptoms and how those with systemic sclerosis self-manage their symptoms. As such, the purpose of this dissertation was to advance the science of symptom self-management by gaining a deeper understanding of the complex symptom experiences and their link to self-management outcomes in adults with systemic sclerosis.

First, we assessed the state of the science of self-management interventions in systemic sclerosis to gain a deeper understanding of the essential intervention components and their impact on key self-management outcomes. We found significant variability in the types of interventions, their components, and their impact on self-management outcomes. Second, we explored the relationship between pain and self-efficacy for managing pain, as well as changes in pain over time. Our findings underscored the presence of chronic pain and provided important insights into the longitudinal pain experiences of patients with systemic sclerosis. Building upon these

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findings, we explored the synergistic effects of anxiety, depression, fatigue, sleep

disturbance, and pain to identify five distinct subgroups of patients who shared similar

symptom experiences. We explored the individual characteristics of each subgroup and

their relationship to physical function, which provided a more comprehensive

understanding of those at greatest risk for more severe symptom burden and poorer

physical function.

     Findings from this dissertation provide a new lens for symptom self-

management research in systemic sclerosis. In our studies, we captured the unique and

complex symptom experiences of those living with systemic sclerosis and their

association with psychosocial characteristics and self-management outcomes. Our

findings underscore the importance of increased awareness and evaluation of these

symptoms as well as the need for the development and testing of symptom self-

management interventions in this population. Findings from this dissertation provide a

foundation for future studies aimed at better understanding the dynamic nature of

symptoms experienced by those with systemic sclerosis and will inform the

development of symptom self-management interventions in this population.

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1. Introduction

An estimated 2.5 million people worldwide are challenged with managing the disfiguring, debilitating, and often unremitting symptoms of systemic sclerosis (SSc; scleroderma) (World Scleroderma Foundation, 2017). SSc is a rare autoimmune connective tissue disease characterized by widespread vascular injury, autoantibody production, and fibrosis of the skin and internal organs (van den Hoogen et al., 2013). SSc has the highest mortality rate of any rheumatic condition (Poudel & Derk, 2018) and disproportionately affects women, with a disease onset often between the ages of 20 to 50 years old (Alba et al., 2014). There is no cure for SSc and the etiology remains unknown. As such, the major goals of treatment are focused on improving symptoms, physical function, and health-related quality of life (Almeida et al., 2015).

While SSc is a clinically heterogenous disease, people are often classified into two main subsets, limited and diffuse cutaneous SSc, based on the extent of skin and internal organ involvement (Ingegnoli et al., 2018). People with diffuse cutaneous SSc experience more skin thickening that extends beyond the distal extremities, earlier and more severe organ involvement, and a worse prognosis (Allanore et al., 2015). People with SSc experience significant morbidity from disease manifestations such as digital ulcers, joint contractures, skin thickening, Raynaud's phenomenon, gastrointestinal tract involvement, pulmonary hypertension, and interstitial lung disease (Thombs et al.,

2010). These disease manifestations lead to debilitating symptoms that negatively affect

patient outcomes, including physical function and health-related quality of life

(Kwakkenbos et al., 2015).

1.1 Common Symptoms of Systemic Sclerosis

Symptoms are "subjective phenomena or indicators of change from normal

functioning experienced by an individual" (Lenz et al., 1997, p. 15). While healthcare

providers emphasize objective measures of SSc, patients often perceive other aspects of

their disease as more disabling and bothersome (Bassel et al., 2011; Suarez-Almazor et

al., 2007). In particular, patients report anxiety, depression, fatigue, and pain as the most

frequent and bothersome symptoms (Bassel et al., 2011; Richards et al., 2003), yet these

symptoms are often under-recognized by healthcare providers (Thombs et al., 2010).

Due to the multisystem effects of SSc, patients experience a broad range of

symptoms. Patients have described their symptoms as draining and inescapable

(Sumpton et al., 2017). These symptoms lead to difficulty in performing daily activities

as well as physical disability and reduced health-related quality of life (Bassel et al.,

2011; Thombs et al., 2010). Additionally, these symptoms contribute to social isolation,

loss of identity, and a negative impact on relationships (Nakayama et al., 2016; Sumpton

et al., 2017). Previous symptom research in SSc has primarily focused on the

relationships between symptoms and their impact on patient outcomes. For example,

symptom research has explored the association between fatigue, sleep disturbance, depression, pain, and physical function (Sariyildiz et al., 2013). Additionally, symptom research in SSc has explored the impact of clinical characteristics on symptom severity, for which skin thickening, digital ulcers, joint contractures, and gastrointestinal symptoms have been most frequently associated with more severe symptoms and worse outcomes (Kwakkenbos et al., 2017; Peytrignet et al., 2018).

1.2 Symptom Clusters in Systemic Sclerosis

Symptoms of SSc seldom occur in isolation and have multiplicative effects on patient outcomes such as physical function. Symptom clusters, or "a group of three or more concurrent symptoms that are related to one another but are not required to share the same etiology" (Dodd et al., 2001, p. 465), have not been well characterized in patients with SSc. There are two main conceptual approaches to symptom cluster research including: (1) a de novo approach in which the number and types of symptom clusters are identified, and (2) an *a priori* approach in which subgroups of patients are identified based on their distinct symptom experiences with a prespecified symptom cluster (Miaskowski, 2016). This dissertation will use the latter approach to identity subgroups of patients with differential symptom burden based on their distinct experiences with anxiety, depression, fatigue, sleep disturbance, and pain. These symptoms were selected because they are: (1) highly prevalent and distressing

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symptoms experienced by those with SSc (Bassel et al., 2011; Del Rosso et al., 2013; Richards et al., 2003); (2) significantly correlated (Basta et al., 2018; Sandusky et al., 2009; Sariyildiz et al., 2013); and, (3) have synergistic effects on patient outcomes (Sariyildiz et al., 2013).

1.3 Trajectory Science

While progression of SSc is highly variable and persons with SSc experience heterogeneity in disease manifestations (Valentini, 2003), little is known about the changes in symptoms over time. Trajectory science is person-centered, with the goal of capturing intra-individual variation over time using longitudinal methods (Henly et al., 2011). Trajectory science promotes a deeper understanding of the influencing factors of health over time and allows for the identification of appropriate timing of interventions (Henly et al., 2011). SSc is a dynamic, progressive, and unpredictable disease; trajectory science provides a means to capture changes in symptoms over time. While previous research has explored changes in fatigue (Assassi et al., 2011), pain (Merz et al., 2017; Sekhon et al., 2010), skin thickening (Ledoult et al., 2020), and disability (Schnitzer et al., 2011) in SSc over time, additional research is needed to gain a better understanding of changes in symptoms along the disease trajectory to help guide the timing and delivery of symptom self-management interventions in this population.

1.4 Self-Management

SSc is a chronic disease in which patients are faced with self-managing their disease. Self-management is a dynamic and interactive process defined as the daily management of a chronic disease over its entirety (Grady & Gough, 2014; Grey et al., 2006). Self-management is focused on the patient's perceived problems (Lorig & Holman, 2003) and includes skills to improve a person's ability to manage his or her chronic disease on a daily basis (Grady & Gough, 2014). While research suggests improved health outcomes among 28 other chronic conditions (Barlow et al., 2002), little is known about how people with SSc self-manage.

Previous self-management research in SSc has underscored the need for additional research on symptom self-management, particularly related to the management of pain, fatigue, depression, and physical function (Buck et al., 2010). Symptom self-management involves the "implementation of behaviors that recognize, prevent, relieve, or decrease the timing, intensity, distress, concurrence, and unpleasant quality of symptoms to achieve optimal performance outcomes" (Hoffman, 2013, p. 3). Patients with SSc have reported less confidence (or lower self-efficacy) in managing pain, fatigue, and other symptoms (Thombs et al., 2017), emphasizing the need for the development and testing of symptom self-management interventions in this population. Additionally, further exploration of the impact of symptom self-management interventions on key self-management outcomes (i.e., self-efficacy, patient activation,

self-regulation, and global health) is needed. Research that focuses on extending the science of symptom self-management in SSc has the strong potential to inform treatment guidelines, as current recommendations do not include symptom self-management interventions due to lack of expert consensus on their effectiveness in patients with SSc (Kowal-Bielecka et al., 2009).

1.5 Conceptual Framework

The Systemic Sclerosis Symptom Model (SSSM) (Figure 1) was adapted from the Theory of Unpleasant Symptoms (Lenz et al., 1997) and was used as the conceptual framework for this dissertation. The Theory of Unpleasant Symptoms is a middle-range theory that was developed to provide a better understanding of the symptom experience (Blakeman, 2019; Lenz et al., 1997), and was selected to guide the development of the SSSM because it recognizes that symptoms seldom occur in isolation, are multiplicative, and interact with one another to change the symptom experience (Lenz et al., 1997). The SSSM (Figure 1) has six components: 1) *individual characteristics*, which

Figure 1: Systemic Sclerosis Symptom Model

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includes demographic and clinical characteristics that may influence the symptoms in

the prespecified symptom cluster, 2) the *prespecified symptom cluster* which includes

anxiety, depression, fatigue, sleep disturbance, and pain; these symptoms were included

in the prespecified symptom cluster because they are the most frequent and disabling

symptoms of SSc (Bassel et al., 2011; Richards et al., 2003; Suarez-Almazor et al., 2007); 3)

self-efficacy, or one's perceived confidence in performing a specific behavior or task

(Bandura et al., 1999), which has a reciprocal relationship with the prespecified

symptom cluster and an indirect relationship with physical function in this model; 4)

self-management which represents the interventions developed to help patients with SSc

self-manage the symptoms included in the prespecified symptom cluster; 5) the *outcome,*

which is physical function; and, 6) the *symptom trajectory* which captures changes in

symptoms over time. The SSSM does not include quality of life as an outcome due to its

overlap with physical function (Lenz et al., 1997).

1.6 Purpose

The purpose of this dissertation was to advance the science of symptom self-

management in patients with SSc by gaining a deeper understanding of the complex

symptom experiences and their link to self-management outcomes. This dissertation will

address a critical gap in knowledge by evaluating the state of the science of self-

management interventions in SSc, as well as by examining the relationship between self-

efficacy and pain and identifying subgroups of patients who experience similar

symptom experiences. Knowledge gained from this dissertation will uncover new areas

of symptom self-management research and will help inform future intervention

development for patients with SSc.

2. Self-Management Interventions in Systemic Sclerosis: A Systematic Review

Systemic sclerosis (scleroderma) is a rare, chronic, multisystem autoimmune disease characterized by vasculopathy, autoantibody production, and progressive fibrosis of the skin and internal organs leading to skin thickening and multiorgan dysfunction (van den Hoogen et al., 2013). Prevalence rates vary worldwide, from 7 to 489 cases per million (Chifflot et al., 2008), with women disproportionately affected and often experiencing a disease onset between the ages of 20 to 50 years old (Alba et al., 2014). Disease manifestations of systemic sclerosis such as skin thickening, finger ulcers, Raynaud's phenomenon, gastroesophageal reflux, interstitial lung disease, and pulmonary arterial hypertension lead to significant morbidity and mortality (Ingegnoli et al., 2018).

Although systemic sclerosis is a clinically heterogenous disease, patients are often divided into two main subsets-- limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis-- based on the severity of their skin involvement (van den Hoogen et al., 2013). Skin thickening is localized to the fingers, distal extremities, and face in limited cutaneous systemic sclerosis, whereas skin thickening extends to the proximal extremities and trunk in diffuse cutaneous systemic sclerosis (Allanore et al., 2015). Additionally, patients with diffuse cutaneous systemic sclerosis experience rapid disease progression leading to more severe skin thickening and earlier development of

organ complications of the gastrointestinal tract, lungs, heart, and kidneys (Allanore et al., 2015).

Patients with systemic sclerosis are challenged with managing debilitating physical and psychological symptoms such as pain, fatigue, sleep disturbance, body disfigurement, depression, anxiety, and social isolation (Almeida et al., 2015; Thombs et al., 2010). These symptoms lead to functional disability, reduced health-related quality of life, productivity losses, and high health care costs (Fischer et al., 2017), accounting for up to $1.9 billion in total costs per year in North America (Bernatsky et al., 2009). With no cure and no disease-modifying therapies, the emphasis of care is placed on reducing symptoms, minimizing functional disability, and improving one's health-related quality of life (Kwakkenbos et al., 2017).

Thus, systemic sclerosis is a chronic condition requiring patients to self-manage their disease. Self-management is defined as the daily management of a chronic condition by an individual (Grady & Gough, 2018; Lorig & Holman, 2003) and is focused on equipping patients with the skills and resources to manage their chronic condition (Lorig & Holman, 2003). More specifically, self-management interventions are focused on improving one's ability to improve their health status at any point along their disease trajectory (Grady & Gough, 2018). In a systematic review by Willems et al. (2015), variability in the content, intervention components, and outcomes of nonpharmacologic interventions for patients with systemic sclerosis was found.

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Research on nonpharmacologic, rehabilitative, and exercise interventions in systemic sclerosis has also addressed the poor methodological quality of studies, limiting the authors' ability to synthesize the data and make recommendations for the use of these interventions in patients with systemic sclerosis (Liem et al., 2019; Mugii et al., 2018; Willems et al., 2015).

Given the lack of expert consensus on the use of psychosocial, rehabilitative, and educational interventions for treatment of systemic sclerosis, the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research group (EUSTAR) have been unable to make recommendations of their use in treatment guidelines (Kowal-Bielecka et al., 2017). As such, further exploration of self-management interventions and their outcomes is needed to inform treatment guidelines and clinical practice in this population.

To establish common outcomes and to facilitate comparison of data across self-management studies in chronic conditions, the National Institute of Nursing Research (NINR) recommended four common data elements (CDEs) for self-management research, including: patient activation, self-efficacy, self-regulation, and global health (Moore et al., 2016). These CDEs represent the core concepts in existing self-management frameworks and have been used in a variety of self-management studies in persons with chronic conditions (Moore et al., 2016).

Additionally, the NINR provided a definition of each construct and the recommended measure for each self-management outcome (Moore et al., 2016). Patient activation was defined as the knowledge, skills, and confidence for self-management of one's chronic condition, as measured using the Patient Activation Measure (PAM; Hibbard et al., 2005; Hibbard et al., 2004). Self-efficacy was defined as one's confidence to manage various aspects of his or her chronic condition as measured by the Self-Efficacy for Managing Chronic Disease (SEMCD) scale (Lorig et al., 2001). Self-regulation was defined as one's effort and will to make behavioral changes as measured by the Index of Self-Regulation (ISR; Fleury, 1998; Yeom et al., 2011). Lastly, global health was defined as one's general evaluation of his or her overall health, including both physical and mental health, as measured using the Patient Reported Outcomes Measurement Information System Global Health Short Form (PROMIS SF v1.1 Global; Hays et al., 2009). Global health is an indicator of health status (Hays et al., 2009) and includes components of global physical health, such as overall physical health, physical function, pain, and fatigue, as well as components of global mental health, such as quality of life, mental health, satisfaction with social activities, and emotional problems such as anxiety and depression (Hays et al., 2009). The use of CDEs in self-management research allows for comparisons of study findings across populations, improvements in the generalizability of findings, and acceleration of research into practice (Cohen et al., 2015).

Systematic evaluation of the essential intervention components and self-management outcomes, identified as CDEs, in patients with systemic sclerosis is necessary to assess the state of the science of self-management interventions and to guide future self-management research and intervention development. As such, the purpose of this systematic review was to identify and describe self-management interventions in systemic sclerosis and their impact on specific self-management outcomes (i.e., patient activation, self-efficacy, self-regulation, and global health).

2.1 Methods

This systematic review was completed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009). In collaboration with a university librarian, a comprehensive search was conducted using PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Embase for studies published from the inception of each database to March 2020. PubMed and Embase have been identified as essential databases to be included in systematic reviews of randomized controlled trials, supporting their inclusion in this systematic review (Higgins et al., 2019). CINAHL was included as a subject-specific database to capture this systematic review's nursing lens (Higgins et al., 2019). The searches included a combination of the following index terms and free text words using Boolean operators: systemic sclerosis, scleroderma, self-

management, self-manage, and self-care (Table 1). Self-care was included as a search term given its often interchangeable use with self-management (Grady & Gough, 2018).

Table 1: Search Strategy

PubMed	(("Scleroderma, Systemic"[Mesh] OR "Scleroderma, Localized"[Mesh] OR "Scleroderma, Limited"[Mesh] OR "Scleroderma, Diffuse"[Mesh] OR "systemic sclerosis" OR scleroderma OR "CREST syndrome")) AND ("Self-Management"[Mesh] OR "self management" OR "self-management" OR "self manage" OR "self-manage" OR "self care"[MeSH Terms] OR "self care"[All Fields])
CINAHL	((MH "Scleroderma, Systemic+") OR "systemic sclerosis" OR scleroderma) AND ((MH "Self-Management") OR (MH "Self Care+") OR "self-management" OR "self management" OR "self care")
Embase	('systemic sclerosis'/exp OR 'systemic sclerosis' OR 'systemic scleroderma'/exp OR 'systemic scleroderma' OR 'scleroderma'/exp OR scleroderma) AND ('self management'/exp OR 'self management' OR 'self care'/exp OR 'self care')

Inclusion criteria for studies in this review were: (a) at least one self-management intervention; (b) patient activation, self-efficacy, self-regulation, or global health as an outcome; (c) comprised of adults ≥ 18 years with a diagnosis of systemic sclerosis as the study sample; (d) published in English; and (e) in peer-reviewed journals available in full text. Studies were excluded if they were: (a) conference abstracts, editorial letters, commentaries, unpublished manuscripts, case reports, or literature reviews; (b) not published in English; (c) not available for full-text review; (d) focused on other chronic conditions; (e) comprised of only children or adolescents; or (f) not inclusive of a self-management intervention.

For the purposes of this systematic review, a self-management intervention was defined as any program that focused on increasing one's knowledge and/or skills to improve his or her own ability to manage systemic sclerosis on a daily basis. This

definition was modified from Ryan and Sawin's (2009) definition of self-management in their Individual and Family Self-Management Theory. The four self-management outcomes were selected because they have been identified as CDEs for self-management research by the NINR and represent the core concepts of self-management frameworks (Moore et al., 2016). The searches yielded 215 studies, with an additional seven studies identified from reference lists (Figure 2).

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

2.2 Data Extraction

One author (R.W.) reviewed the titles of the 222 studies in this sample to identify

potentially relevant studies. After removing duplicates, the remaining 164 studies were

screened by the same author. A total of 138 studies were excluded, resulting in 26

studies retained for full-text review. Of these 26 studies, 16 met the eligibility criteria.

Figure 2 provides reasons for exclusion of full-text articles. Data were extracted using

the Matrix Method, which provides a structure and process for reviewing the literature

(Garrard, 2011). The steps of the Matrix Method include: (a) creating a paper trail of the

search processes and results, (b) organizing the journal articles and other materials

gathered for review, (c) abstracting data from each journal article, and (d) synthesizing

abstracted information and writing the literature review (Garrard, 2011). The following

information was abstracted and organized into tables: author, year of publication,

country, study design, inclusion criteria, sample characteristics, intervention overview,

CDE use and measures, and main findings. Two additional authors (D.B., M.K.)

reviewed the extracted data. Disagreements were resolved through discussion until

consensus was achieved.

2.2.1 Quality Assessment

The Downs and Black checklist, suitable for evaluating the quality of randomized

and nonrandomized trials, was used to assess the quality of the included studies

(Downs & Black, 1998). The Downs and Black (1998) checklist is comprised of 27

questions evaluating five subscales: study reporting, external validity, internal validity-bias, internal validity-confounding, and power. One question (question 27), evaluating the power of the study, was modified to a yes/no response (O'Connor et al., 2015; Willems et al., 2015). For each study, the scores for each question were added resulting in a total possible score of 28 (for question 5, 0=no, 1=partially, and 2=yes). The Downs and Black checklist does not provide specific score ranges to differentiate between excellent and poor study quality. As such, we defined the following study quality criteria a priori using previous publications as a guide for determining the quality scores: excellent (28-26), good (25-20), fair (19-15), and poor (≤14; Hooper et al., 2008; Silverman et al., 2012). Three authors (R.W., D.B., M.K.) assessed the methodological quality of the final 16 studies, and disagreements were resolved through discussion until consensus was achieved.

2.3 Results

An overview of the study characteristics of the 16 studies included in this review is provided in Table 2. Of the 16 studies, seven were randomized controlled trials. Studies were conducted in the United States ($n = 5$), Italy ($n = 5$), Netherlands ($n = 2$), Brazil, France, Japan, and Sweden ($n = 1$ each). Fewer than half the studies ($n = 5$) were published in the last five years. The sample sizes ranged from 6 to 267, with the majority of studies ($n = 12$) having a sample size of less than 50. Of the studies that reported

gender, race/ethnicity, and marital status, the samples were predominately comprised of

Caucasian, married females. Additionally, of the 11 studies that reported the systemic

sclerosis subset, people with the limited cutaneous subset were most represented.

Among the fourteen studies where investigators reported the disease duration, all had

samples with a mean or median disease duration of five years or greater.

Table 2: Study Characteristics

Author (year) country	Design	Inclusion criteria	N	Control (Y/N)	Sample characteristics					
					Age	Female N (%)	White N (%)	Married N (%)	SSc subset N (%)	Disease duration
Rehabilitation programs focused on improving physical function										
Antonioli et al. (2009) Italy	Case-control*	1. SSc diagnosis according to LeRoy criteria 2. Age 18-75 years 3. Stable disease 4. No change in antirheumatic treatment in the previous 3 mo.	33	Y	I: Median 66.5 (63-70.5)[a] C: Median 57 (50-67)[a]	I: 16 (100%) C: 16 (94.1%)			I: lcSSc: 12 (75%) dcSSc: 4 (25%) C: lcSSc: 11 (65%) dcSSc: 6 (35%)	I: Median 14.5 (10-21)[a] C: Median 9 (5-13)[a]
Maddali-Bongi et al. (2009) Italy	RCT*		40	Y	57.8 (11.8) I: 56.4 (10.2) C: 58.1 (13.4)	30 (75%) I: 16 (80%) C: 14 (70%)	40 (100%)			9.0 (3.8) I: 8.7 (3.5) C: 9.4 (4.2)
Maddali-Bongi et al. (2011) Italy	RCT	1. SSc diagnosis according to ACR criteria 2. Face involvement with a Rodnan skin score ≥1	40	Y	57.3 (11.3) I: 57.2 (10.2) C: 57.4 (12.6)	34 (85%) I: 18 (90%) C: 16 (80%)				9.4 (43) I: 9.7 (42) C: 9.1 (46)

Mugii et al. (2006) Japan	Pretest-posttest*	1. SSc diagnosis according to ACR criteria	45	N	48.6 (17.3)	39 (86.7%)		lcSSc: 13 (28.9%) dcSSc: 32 (71.1%)	5.0 (7.6)
Rannou et al. (2017) France	RCT	1. Diagnosis of SSc diagnosis according to ACR or LeRoy and Medsger criteria 2. Age ≥ 18 years 3. Disability rating of ≥0.5 on the HAQ-DI or symptoms of decreased mouth opening or limited range of motion of at least 1 joint	218	Y	I: 52.7 (14.8) C: 53.1 (14.4)	I: 95 (86.4%) C: 86 (79.6%)		I: lcSSc: 53 (48.2%) dcSSc: 53 (48.2%) Limited: 4 (3.6%) C: lcSSc: 50 (47.2%) dcSSc: 54 (50.9%) Limited: 2 (1.9%)	I: 6.5 (6.5) C: 6.7 (8.6)
Stefanantoni et al. (2016) Italy	RCT	1. Diagnosis of SSc according ACR criteria 2. Able to speak and read Italian 3. Have hand involvement 4. Have stable disease 5. Never underwent an OT intervention	31	Y	I: 61.4 C: 60.5	I: 15 (100%) C: 15 (93%)		I: lcSSc: 8 (53.3%) dcSSc: 7 (46.6%) C: lcSSc: 10 (62.5%) dcSSc: 5 (31.2%)	I: 10.8 (2-50)[b] C: 14.1 (2-50)[b]
Uras et al.	RCT	1. Diagnosis of	63	Y	I: 54.6 (15.8)		I: 21		I: 8.7 (6.3)

			N		Age	Female			Subtype	Disease duration
(2019) Italy		SSc according to ACR/EULAR criteria 2. Age ≥ 18 years 3. Ability to understand Italian language 4. Subjective perception of problems with opening mouth as confirmed by a dermatologist 5. Signed informed consent			C: 55.2 (13.3)	(65.6%) C: 18 (58.1%)				C: 11.8 (8.4)

Self-management programs focused on improving disease-related knowledge

			N		Age	Female			Subtype	Disease duration
Khanna et al. (2019) USA	RCT	1. Diagnosis of SSc 2. Age ≥18 years 3. US resident 4. Have basic computer literacy and access to a computer with internet and email 5. Have English communication skills 6. Be willing to	267	Y	53.7 (11.7) I: 54.3 (10.1) C: 52.9 (13.1)	243 (91%) I: 123 (91.8%) C: 120 (90.2%)	221 (82.8%) I: 112 (83.6%) C: 120 (90.2%)	170 (63.7%) I: 95 (70.9%) C: 75 (56.4%)	lcSSc/sine: 120 (44.9%) dcSSc: 115 (43.1%) Overlap: 31 (11.6%) Unknown: 1 (0.4%) I: lcSSc/sine: 57 (42.5%) dcSSc: 57 (42.5%) Overlap: 19	8.97 (8.5) I: 8.72 (7.8) C: 9.23 (9.2)

			N		Age				Subtype	
		complete the study protocol							(14.1%) Unknown: 1 (0.7%)	
									C: lcSSc/sine: 63 (47.4%) dcSSc: 58 (43.6%) Overlap: 12 (9%) Unknown: 0	
Landim et al. (2019) Brazil	Quasi-exper.	1. SSc diagnosis according to 2013 ACR/EULAR classification criteria 2. Age ≥18 years 3. Have hand involvement 4. Stable drug therapy in the last 3 mo. 5. Willingness to complete study protocol	22	N	48.1 (11.7)	18 (85.71%)	13 (61.90%)	15 (66.67%)	lcSSc: 16 (71.4%) dcSSc: 6 (28.6%)	11.19 (5.9)
Poole et al. (2013) USA	Pretest-posttest	1. Diagnosis of SSc 2. Age ≥ 21 years 3. US resident 4. Ability to communicate in	49	N	53.9 (12.5)	45 (92%)	40 (82%)	36 (73%)		6.9 (7.1)

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Author	Design	Inclusion criteria	N		Age Mean (SD)				SSc type	
Poole et al. (2014) USA	Pretest-posttest, Pilot	English 5. Willingness to complete study protocol 1. Diagnosis of SSc 2. Age ≥18 years 3. Resides in US 4. Have basic computer literacy and access to computer with internet and email 5. Ability to communicate in English 6. Have moderate to severe pain (pain score of >3 on 0-10 VAS) 7. Have poor self-efficacy pain scores (score of <7 on 0-10 VAS) 8. Willing to complete study protocol	16	N	52.2 (10.2)	87.5%	93.7%	68.8%	lcSSc: 54.4% dcSSc: 37.5% Unknown: 6.2%	7.8 (8.1)
Multidisciplinary team programs focused on improving disease-related knowledge and physical function										
Kwakkenbos	Pretest-	1. SSc diagnosis	41	N	52.8 (12.2)	Total: 83%		Total:	lcSSc: 26	9.5 (10.5)

Study	Design	Inclusion criteria	N		Age	Female		Type	Disease duration
et al. (2011) Netherlands	posttest	for more than 1 yr.				73%		(63.4%) dcSSc: 13 (31.7%) Unknown: 2 (4.9%)	
Samuelson et al. (2000) Sweden	Pilot	1. Expressed an interest in attending the education course 2. Had a multisymptomatic medical history of SSc, including pain	6	N	62 (47-74)[b]	6 (100%)			8 (4-11)[b,c]
Schouffer et al. (2011) Netherlands	RCT	1. Diagnosis of SSc according to LeRoy criteria 2. Age 18-75 years 3. Able to cycle on bicycle ergometer 4. Stable anti-inflammatory medication over the past 2 mo. 5. Fluent in Dutch	53	Y	I: 53.9 (10.8) C: 51.7 (10.8)	I: 19 (67.9%) C: 21 (84%)		I: dcSSc: 15 (53.6%) C: dcSSc: 15 (60%)	I: Median 6.5 (IQR 8.2) C: Median 8.2 (IQR 10.5)
Other									
Hunnicutt et al. (2008) USA	Cohort*	1. SSc diagnosis according ACR criteria 2. Disease	36	Y	I: 54.2 (8.9) C: 48.7 (12.2)	I: 17 (89%) C: 13 (86%)	I: 68% C: 47%	I: dcSSc: 9 (47%) C:	

		duration <5 years 3. Enrolled in GENISOS between 1997 - 2004					dcSSc: 5 (33%)
Sallam et al. (2007) USA	Explor.	1. Diagnosis of SSc according to ACR criteria 2. At least 1 upper or lower GI symptom	17	Y	57.2 (1.9)	14 (82.4%)	lcSSc: 8 (47.1%) dcSSc: 9 (52.9%)

Note. Mean (standard deviation) for age and disease duration, unless otherwise indicated; total values for the entire sample provided, unless specified by I (intervention group) and C (control group); areas left blank indicate information was not stated; *author interpretation due to unstated study design; [a] median (25th-75th percentile); [b] mean (range); [c] duration of SSc symptoms; ACR, American College of Rheumatology; C, control; dcSSc, diffuse cutaneous systemic sclerosis; EULAR, European League Against Rheumatism; Explor., Exploratory; GENISOS, Genetics versus Environment in Scleroderma Outcomes Study; GI, gastrointestinal; HAQ-DI, Health Assessment Questionnaire Disability Index; IQR, interquartile range; I, intervention; lcSSc, limited cutaneous systemic sclerosis; mo., months; OT, occupation therapy; Quasi-exper., Quasi-experimental; RCT, randomized controlled trial; SD, standard deviation; SSc, systemic sclerosis; VAS, visual analog scale; yr., year.

2.3.1 Overview of the Interventions

There was notable variability in the types of self-management interventions reported in the 16 studies (see Table 3). Self-management interventions focused on improving physical function through rehabilitation programs that included stretching, individualized exercise sessions, or physical/occupational therapy were the most common type of intervention ($n = 7$). The second most common type of self-management intervention was programs aimed at increasing participants' knowledge of systemic sclerosis and improving patient-reported outcomes ($n = 4$), followed by multidisciplinary team educational programs ($n = 3$), complementary and alternative medicine therapies ($n = 1$) and transcutaneous electrical nerve stimulation ($n = 1$). Half of the interventions ($n = 8$) included a health care professional as the interventionist, of which occupational therapists were most common. The length of the self-management interventions ranged from six days (three weekends) to one year. The investigators of ten studies included an intervention control group, however, the type of control group (e.g., waitlist control, attention control) was not described in the majority of studies. Additionally, Samuelson and Ahlmén (2000) were the only investigators to describe the theory used to guide the development of their self-management intervention (i.e., the self-efficacy theory).

Table 3: Overview of the Interventions

Author (year)	Intervention description	Length	Delivery	Interventionist
Rehabilitation programs focused on improving physical function				
Antonioli et al. (2009)	Rehabilitation program consisting of individualized exercise sessions and a home exercise program to improve disability, QOL, hand mobility, and physical activity	4 mo.	In-person & at home	
Maddali- Bongi et al. (2009)	Rehabilitation program consisting of connective tissue massage, Mc Mennell joint manipulation, and a home exercise program to improve hand function	9 wks.	In person & at home	Therapist
Maddali-Bongi et al. (2011)	Rehabilitation program consisting of Kabat's technique, connective tissue massage, kinesitherapy, and a home exercise program to improve facial function	9 wks.	In person & at home	
Mugii et al. (2006)	Self-administered finger stretching program to improve finger joint motion	1 yr.	In person & at home	OT
Rannou et al. (2017)	Physical therapy program consisting of supervised and personalized sessions and a home exercise program to improve disability	12 mo.	In-person & at home	Physio. OT
Stefanantoni et al. (2016)	Occupational therapy and self-administered stretching program for the hands to improve functional ability, health status, personal perception, and QOL	3 mo.	In-person & at home	OT
Uras et al. (2019)	Rehabilitation program including stretching exercises, educational materials (brochures & DVD), and face-to-face meetings to reduce microstomia	12 mo.	In-person & at home	Clinical & research nurse
Self-management programs focused on improving disease-related knowledge				
Khanna et al. (2019)	Self-management program including online modules and a discussion board to improve self-efficacy and patient-reported outcomes	16 wks.	Online	
Landim et al. (2019)	Self-management program including workbook and DVD for home use to improve hand function	8 wks.	At home	
Poole et al. (2013)	Self-management program including workbook and exercise DVD for home use to improve self-efficacy,	3-4 mo.	At home	

	functional ability, pain, fatigue, depression, and health-related events			
Poole et al. (2014)	Self-management program including online modules, an exercise video, worksheets, and a discussion board to improve self-efficacy, health efficacy, management of care, functional disability, pain, fatigue, and depression	10 wks.	Online	
Multidisciplinary team programs focused on improving disease-related knowledge and physical function				
Kwakkenbos et al. (2011)	Multidisciplinary team psychoeducational program with educational modules and a group Thai Chi lesson to increase patients' knowledge of SSc and its treatment, improve understanding of the multidisciplinary treatment options, and increase patient interaction	3 wknds.	In-person	SW Rheum. OT PT Psychol. Nurse
Samuelson et al. (2000)	Multidisciplinary team education program to improve patients' knowledge about SSc, reduce concerns related to SSc, facilitate daily activities, form realistic goals, and connect with other patients with SSc	5 wks.	In-person	OT (primary) Rheum. PT Dietician SW Nurse
Schouffer et al. (2011)	Multidisciplinary team care program including group exercises, group education, individual treatments, and home-based exercise program to improve measures of health status	12 wks.	In-person & at home	Rheum. OT PT SW Nurse
Other				
Hunnicut et al. (2008)	Complementary and alternative medicine therapies for symptom management			
Sallam et al. (2007)	Transcutaneous electrical nerve stimulation on GI symptoms, QOL, and heart rate variability	14 days	In-person & at home	

Note. Areas left blank indicate information was not stated; length refers to the length of the intervention; delivery refers to whether the intervention included an in-person component (e.g., group sessions) and/or was delivered at home (by self); interventionalist refers to members of the healthcare team involved in the intervention study; GI, gastrointestinal;

invn, intervention; mo., months; OT, occupational therapist; PT, physical therapist; physio., physiotherapist; psychol., psychologist; QOL, quality of life; rheum., rheumatologist; SW, social worker; SSc, systemic sclerosis; wknds., weekends; wks., weeks.

2.3.2 Self-Management Outcomes

Among the 16 studies, only three of the four self-management outcomes (i.e.,

patient activation, self-efficacy, and global health) were measured, and there was

significant variability in the measures used to assess these outcomes (see Table 4).

Patient activation was the only self-management outcome measured using a NINR-

recommended measure (i.e., the Patient Activation Measure). Self-regulation was not

measured as an outcome in any of the studies.

Table 4: Intervention Efficacy and Findings

Author (year)	CDE				Self-mgmt. outcomes	General outcomes
	PA	SE	SR	GH		
Antonioli et al. (2009)				SF-36 SGRQ HAQ-DI	• Improvement in the physical and mental health components of the SF-36 at 4 months in 69% and 62% of patients who received the intervention • Improvement in the perceived QOL in airway disease (SGRQ) in 67% of patients • Progressive improvement in disability (HAQ-DI) over time for patients in the intervention group, but did not reach statistical significance	• Improvement in exercise tolerance and hand mobility (HAMIS)
Hunnicut et al. (2008)				SF-36	• Higher mean physical and mental health component scores of the SF-36 at year 2 in CAM users (compared to non-CAM users) • CAM users had significantly higher SF-36 scores for the physical component, role physical, bodily pain, and vitality at year 2	• CAM therapies were used for symptoms such as arthritis, pain, GI dysfunction, and fatigue • Approximately 70% used a CAM therapy for more than 1 year
Khanna et al. (2019)	PAM	PROMIS Self-Efficacy		PROMIS-29v2 EQ-5D QALYs PHQ-8	• No significant difference in PAM, PROMIS Self-Efficacy, PROMIS-29v2, and PHQ-8 scores between the intervention and control groups • Significant change in EQ-5D index scores from baseline to follow up	• No significant difference in Brief-SWAP scores between the intervention and control group
Kwakkenbos et al. (2011)				HAQ-DI SHAQ	• No significant change in depressive mood and physical functioning (HAQ-	• Patients had lower levels of helplessness and higher

	IRGL Pain VAS Fatigue VAS	DI, pain, fatigue) after the intervention	acceptance of limitations post-intervention and after 6 months • No significant change in coping
Landim et al. (2019)	SF-36 HAQ-DI SHAQ Pain VAS	• Significant improvement in physical and mental health components of SF-36 (role physical, physical functioning, social functioning, bodily pain, vitality, and mental health) after the intervention • Significant improvement in HAQ and SHAQ scores after the intervention	• Significant improvement in finger motion, hand strength, moisturizing and cold avoidance habits, hand pain, CHFS, and impact of Raynaud's phenomenon after the intervention
Maddali- Bongi et al. (2009)	SF-36 HAQ	• In intervention group, significant improvement in the physical and mental health components of the SF-36 and HAQ scores	• In intervention group, significant improvement in fist closure, HAMIS test, and CHFS after the intervention • Control group which included only at home daily exercises showed improvement in fist closure only
Maddali-Bongi et al. (2011)	SF-36 HAQ-DI	• No significant change in SF-36 and HAQ scores in intervention group at the end of treatment (T1) and after 9 weeks of follow up (T2)	• Mouth opening improved for the intervention and control group at the end of treatment, but only stayed significant after 9 weeks of follow up for the intervention group • Significant decrease in facial skin score after the end of treatment and at 9 weeks;

Study	PAM		Measures	Results	
					• no change in the control group
					• MHISS scores improved significantly in the intervention group at the end of treatment; no change in the control group
Mugii et al. (2006)			HAQ-DI	• After 1 year of the intervention, there was no significant change in the mean HAQ-DI score • When the individual components of the HAQ-DI were explored, only eating and gripping significantly improved after one year; components requiring lower extremity function did not change (i.e., dressing, arising, walking, hygiene, reaching, activities)	• Total passive range of motion improved in each finger after 1 month of the intervention and was maintained 1 year after
Poole et al. (2013)		ASES	HAQ SFAQ CES-D Pain VAS MAF	• Self-efficacy for controlling pain and self-efficacy "other" improved after the intervention, but only self-efficacy for pain had a statistically significant change • Depression, pain, and fatigue decreased after the intervention, but were not statistically significant • Participants felt they could better manage their pain after the intervention	• No significant change in the number of doctor or emergency department visits, and number of hospital night stays in the past 6 months
Poole et al. (2014)	PAM	CDSES	HAQ-DI CES-D Pain VAS Fatigue VAS	• Significant improvements in patient activation scores after the intervention • Self-efficacy improved after the	• Significant improvements in health efficacy and ability to manage care • No significant changes in

			• intervention, but not significantly • No significant change in functional ability or pain • Significant changes in depression and fatigue scores	self-reported health
Rannou et al. (2017)		SF-36 HAQ-DI SHAQ MACTAR Pain VAS	• No significant between-group difference in the primary outcome, disability (HAQ-DI), after the intervention was delivered (at 12 months) • HAQ-DI, SHAQ, and MACTAR scores improved at 1 month in the intervention group	• Microstomia improved at 1,6, and 12 months in the intervention group • Reduction in microstomia, improvement in global hand mobility, and reduction in hand disability at 1 month in the intervention group
Sallam et al. (2007)		SF-36	• Prolonged TENS to GI acupoints resulted in improvement in physical functioning scores of the SF-36; no significant change in other domains of SF-36	• TENS application significantly improved sympathetic and vagal activities versus baseline in the acute study phase • Prolonged TENS resulted in significant decreases in GI symptom scores and normalized sympathetic balance
Samuelson et al. (2000)	ASES	HAQ GH VAS PDWB Pain VAS	• Improvement in the self-efficacy pain subscale in 3 out of 5 patients after the intervention • The self-efficacy function subscale remained stable • Improvement in self-efficacy to cope with physical and psychological symptoms	• The professional medical information met the participants' needs • Participants were satisfied with the program and felt they had adequate opportunities to connect with and share their SSc experiences

			• Goal setting was an unfamiliar task for participants
Schouffer et al. (2011)	SF-36 SHAQ	• Significant improvement in SHAQ scores in the intervention group at 12 weeks • No significant improvement in SF-36 scores between those in intervention group and control group	• Significant improvement in grip strength, MMO, 6MWD in the intervention group at 12 weeks • Significant improvement in grip strength persisted at 24 months
Stefanantoni et al. (2016)	SF-36 HAQ COPM	• At 3 months, HAQ and mental health component of the SF-36 improved in the intervention group • In the control group, significant improvement in the HAQ scores and mental health component of SF-36 at 1 month and 3 months • Significant improvement in COPM Satisfaction and COPM Performance scores in the intervention group after 1 and 3 months	• No significant improvement in hand function (DHI) scores over time in the intervention or control group
Uras et al. (2019)	Skindex-17 GHQ-12 SySQ	• No significant difference in QOL between the intervention and control group	• Significant increase in mouth opening in the intervention group at 12-month follow up • The difference in mouth opening between the intervention and control group was not significant, but reached significance in per-protocol analysis

Note. Global Health included both physical and mental health, such as physical function, quality of life, and psychological measures; location-specific disability scales (i.e., hand function, mouth function) were not included in global health; self-management outcomes refer to study findings related to the four common data elements; general outcomes refer to other study findings; areas left blank indicate information was not stated; 6MWD, 6-minute walk distance; ASES, Arthritis Self-Efficacy Scale; Brief-SWAP, Brief Satisfaction with Appearance Scale; CAM, complementary and alternative medicine; CDE, common data element; CDSES, Chronic Disease Self-Efficacy Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CHFS, Cochin Hand Function Scale; COPM, Canadian Occupational Performance Measure; DHI, Duruoz Hand Index; EQ-5D, EuroQol 5D; GH, global health; GH, global health; GHQ-12, General Health Questionnaire-12; GI, gastrointestinal; HAMIS, Hand Mobility in Scleroderma; HAQ-DI, Health Assessment Questionnaire Disability Index; IRGL, Impact of Rheumatic Diseases on General Health and Lifestyle; MACTAR, McMaster Toronto Arthritis Patient Preference Disability Questionnaire; MAF, Multidimensional Assessment of Fatigue; MHISS, Mouth Handicap in Systemic Sclerosis; MMO, maximal mouth opening; PA, patient activation; PAM, Patient Activation Measure; PDWB, Psychological General Well-Being index; PHQ-8, Patient Health Questionnaire 8; PROMIS-29v2; Patient-Reported Outcomes Measurement Information System-29 Profile version 2.0; PROMIS Self-Efficacy, Patient-Reported Outcomes Measurement Information System Self-Efficacy for Managing Chronic Conditions; QOL, quality of life; QALYs, quality-adjusted life years; SE, self-efficacy; self-mgmt., self-management; SF-36, 36-Item Short Form Survey; SFAQ, Scleroderma Functional Assessment Questionnaire; SGRQ, Saint George's Respiratory Questionnaire; SHAQ, Scleroderma Health Assessment Questionnaire; SR, self-regulation; SySQ, Systemic Sclerosis Questionnaire; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

2.3.2.1 Patient Activation

As shown in Table 4, Khanna et al. (2019) and Poole et al. (2014) evaluated patient activation before and after an online self-management program. Both studies used the NINR-recommended measure for patient activation in self-management research (i.e., the Patient Activation Measure) to assess this outcome. In the study by Poole et al. (2014), the investigators found significant improvements in patient activation scores and moderate effect sizes post-intervention among 16 participants. In a randomized controlled trial consisting of 267 participants with relatively high levels of patient activation, Khanna et al. (2019) found no statistically significant difference in patient activation scores between participants randomized to an internet-based self-management program and those that received a patient-focused educational book.

2.3.2.2 Self Efficacy

Self-efficacy was included as an outcome in four studies. Khanna et al. (2019) and Poole et al. (2013; 2014) evaluated the effectiveness of a self-management program on patient-reported measures including self-efficacy. Samuelson and Ahlmén (2000) evaluated the effectiveness of a multidisciplinary team education program on self-efficacy. Different measures were used to assess self-efficacy, including the Arthritis Self-Efficacy Scale (ASES; Poole et al., 2013; Samuelson & Ahlmén, 2000), the Chronic Disease Self-Efficacy Scale (CDSES; Poole et al., 2014), and the Patient Reported

Outcomes Measurement Information System Self-Efficacy for Managing Chronic

Conditions measure (PROMIS Self-Efficacy; Khanna et al., 2019).

The interventions used in these studies demonstrated differing effects on self-efficacy. For example, Poole et al. (2013) found that self-efficacy for controlling pain improved after participation in a mail-delivered self-management program. Similarly, Samuelson and Ahlmén (2000) found that self-efficacy for controlling pain and other disease-related symptoms improved after a multidisciplinary team education program, however, the sample only had six participants. For the two studies in which investigators evaluated participation in an online self-management program, no statistically significant improvements in self-efficacy were found (Poole et al., 2014, Khanna et al., 2019).

2.3.2.3 Global Health

Global health, another self-management CDE which reflects one's overall health, was described through measures of physical and/or mental health. Physical health was most frequently assessed using a functional disability measure ($n = 12$) and mental health was most frequently measured through quality of life ($n = 9$). The investigators of nearly half the studies ($n = 7$) evaluated both functional disability and quality of life, of which the Health Assessment Questionnaire and the 36-Item Short Form Survey were

most commonly used. No studies, however, used the NINR-recommended outcome measure for global health (i.e., PROMIS SF v1.1 Global).

The investigators reported improvements in global health (i.e., physical and/or mental health) after the intervention in half the studies ($n = 8$). Among the different types of interventions, rehabilitation programs consisting of stretching and/or at home exercises were most commonly associated with improved global health (Antonioli et al., 2009; Maddali Bongi et al., 2009; Stefanantoni et al., 2016). Next most common were self-management programs that focused on increasing participants' disease-related knowledge (Landim et al., 2019; Poole et al., 2014) and multidisciplinary team education programs that included educational sessions and exercise information (Schouffoer et al., 2011). Other self-management interventions such as complementary and alternative medicine therapies (Hunnicutt et al., 2008) and transcutaneous nerve stimulation (Sallam et al., 2007) also led to improvements in global health.

2.3.3 Self-Management Intervention Efficacy

Effect sizes (Cohen's d) were reported in three studies (Kwakkenbos et al., 2011; Landim et al., 2019; Poole et al., 2014). Effect sizes below 0.50 were considered small, above 0.50 but below 0.80 were considered medium, and above 0.80 were considered large. Kwakkenbos and colleagues (2011) evaluated a multidisciplinary team psychoeducational program and found no improvement in self-management outcomes

as demonstrated by effect sizes (physical functioning: d = -0.06 and -0.09; pain: d = 0.10 and 0.13; fatigue: d = 0.02 and 0.05). Poole et al. (2014) found small effect sizes for self-efficacy (d = 0.46) and pain (d = -0.31), and medium effect sizes for patient activation (d = 0.62), depression (d = -0.71), and fatigue (d = -0.55). In a self-management program focused on improving hand function, Landim et al. (2019) reported medium and large effect sizes for components of global health including role physical (d = 0.61), social function (d = 0.64), bodily pain (d = 0.58), and mental health (d = 0.84) of the 36-Item Short Form Survey. Medium effect sizes were reported for functional disability (d = 0.53) using the Health Assessment Questionnaire Disability Index, whereas large effect sizes were found using a more disease-specific measure (i.e., the Scleroderma Health Assessment Questionnaire) for functional disability (d = 1.01; Landim et al., 2019).

2.3.4 Study Quality

The methodological quality of the sixteen studies ranged from poor to good (see Table 5). Almost half the studies were classified as having poor methodological quality (*n* = 7; quality score ≤ 14). No studies had excellent methodological quality. The most common limitations were related to power and external validity—the majority of studies did not include a power analysis (*n* = 12) and nearly half (*n* = 7) did not meet any of the

criteria for external validity (e.g., representativeness of the participants to their source

population, representativeness of where treatment was received by the majority of

patients).

Table 5: Quality Assessment

Author (year)	Study quality (11)*	External validity (3)*	Internal validity-bias (7)*	Internal validity-confounding (6)*	Power (1)*	Total score✦ (28)
Antonioli et al. (2009)	8	1	4	2	0	15
Hunnicut et al. (2008)	6	0	3	2	0	11
Khanna et al. (2019)	9	1	5	5	1	21
Kwakkenbos et al. (2011)	8	0	2	1	0	11
Landim et al. (2019)	9	1	3	3	0	16
Maddali- Bongi et al. (2009)	8	1	4	3	0	16
Maddali-Bongi et al. (2011)	8	1	4	3	0	16
Mugii et al. (2006)	5	0	4	0	0	9
Poole et al. (2013)	7	0	4	1	0	12
Poole et al. (2014)	6	0	4	1	0	11
Rannou et al. (2017)	11	1	6	6	1	25
Sallam et al. (2007)	6	0	4	0	0	10
Samuelson et al. (2000)	3	1	3	0	0	7
Schouffer et al. (2011)	10	0	6	6	1	23
Stefanantoni et al. (2016)	8	2	6	4	0	20
Uras et al. (2019)	9	1	5	5	1	21

Note. *maximum score in each subscale; ✦interpretation of total score: excellent (26–28), good (20–25), fair (15–19), and poor (≤14).

2.4 Discussion

In this systematic review, we evaluated the state of the science of self-management interventions and their impact on self-management outcomes in adults with systemic sclerosis. The significant variability in the types of self-management interventions, their content, and measured outcomes posed limitations in interpreting and recommending the use of self-management interventions in adults with systemic sclerosis. Additionally, fewer than half the studies included in this systematic review (n = 5) were conducted in the last five years, over which time treatment for systemic sclerosis has changed (Barsotti et al., 2019).

Findings from this systematic review highlight the poor methodological quality of studies on self-management interventions in systemic sclerosis and underscore the need for larger and more rigorously designed self-management studies, such as randomized controlled trials, in this population. The studies included in this systematic review had predominately small samples, contributing to their poor methodological quality due to inadequate power and external validity. For example, only four studies were adequately powered (Khanna et al., 2019; Rannou et al., 2017; Schouffoer et al., 2011; Uras et al., 2019), and only three studies calculated effect sizes for the outcomes after intervention delivery (Kwakkenbos et al., 2011; Landim et al., 2019; Poole et al., 2014).

Our findings are similar to those found in a systematic review exploring nonpharmacologic interventions in systemic sclerosis in which only three high-quality randomized controlled trials reported medium to large effect sizes out of 23 total studies (Willems et al., 2015). An obstacle to conducting well-powered randomized controlled trials in this population is the small number of patients at a single study center (Willems et al., 2015). As such, international collaborations have been established to conduct large, adequately powered, multi-site randomized controlled trials to improve patient-centered care (Kwakkenbos et al., 2013).

Patient-activation, self-efficacy, self-regulation, and global health were included as self-management outcomes in this systemic review. Many studies, however, did not assess all four outcomes. Self-regulation was not evaluated as an outcome in any of the studies. Instead, many interventions included self-regulation activities such as goal setting, planning and action, and self-evaluation. Global health was most commonly evaluated through a variety of patient-reported outcomes including physical function, pain, fatigue, depression, and quality of life. Only two studies used a NINR-recommended measure (i.e., both used the Patient Activation Measure). No studies, however, used the NINR-recommended outcome measures for self-efficacy, self-regulation, or global health (i.e., Self-Efficacy for Managing Chronic Disease scale, Index of Self-Regulation, and PROMIS Global Health scale). Only one of the recommended

measures, the Self-Efficacy for Managing Chronic Disease scale, has been validated in systemic sclerosis (Riehm et al., 2016).

Large systemic sclerosis databases such as the Scleroderma Patient-centered Intervention Network (SPIN), the Canadian Scleroderma Research Group (CSRG), and the European Scleroderma Trials and Research group (EUSTAR) should consider the inclusion of key self-management outcomes and their recommended measures. Such an approach would support evaluating the unique constructs of self-management and comparing findings across studies and populations to advance the science of self-management.

2.4.1 Limitations

This systematic review had several limitations. Only studies published in English were included, potentially leading to missed studies and a limited ability to assess all self-management interventions. Only studies that evaluated the effect of a self-management intervention on one or more of the self-management outcomes were included. The studies included in this systematic review did not report treatment fidelity, thereby limiting the ability to determine if the intervention had a true effect or if bias was potentially introduced. Additionally, the majority of studies included in this systematic review were inadequately powered. The studies included in this systematic

review were also limited by homogenous samples, thereby reducing generalizability of their findings.

2.5 Conclusion

In this systematic review we assessed the components of self-management interventions and their efficacy on key self-management outcomes in adults with systemic sclerosis. A variety of self-management interventions were included but lacked consistency in their effects on self-management outcomes. The low methodological quality of the studies included in this systematic review, however, limited synthesis of and recommendations for self-management interventions in adults with systemic sclerosis. Larger and more rigorously designed self-management studies are needed to support their use in future treatment recommendations. Future research should consider the use of key self-management outcomes, identified as CDEs, in systemic sclerosis to allow for comparisons across studies, improve generalizability of study findings, and advance the science of self-management in systemic sclerosis.

3. Pain and Self-Efficacy Among Patients with Systemic Sclerosis: A Scleroderma Patient-centered Intervention Network (SPIN) Cohort Study

Systemic sclerosis (SSc; scleroderma) is a rare, progressive, multisystem autoimmune disease characterized by immune dysfunction, vasculopathy, and fibrosis of the skin and internal organs (Van Den Hoogen et al., 2013). While prevalence rates vary worldwide (7 to 489 cases per million; Chifflot et al., 2008), SSc is more common in women and can present at any age, with a peak disease onset often between 20 to 50 years old (Alba et al., 2014). SSc is associated with significant morbidity and mortality, as well as high health care costs and reduced productivity resulting in a total cost of $1.9 billion per year in North America (Fischer et al., 2017). Patients with SSc exhibit a variety of clinical manifestations, but are often divided into two subsets, limited or diffuse cutaneous SSc, based on the extent of skin involvement (Denton & Khanna, 2017). There is no cure for SSc and major goals of treatment are aimed at ameliorating symptoms, reducing functional disability, and improving health-related quality of life (Almeida et al., 2015).

Pain is one of the most common and debilitating symptoms experienced by patients with SSc, leading to functional disability and reduced health-related quality of life (Haythornthwaite et al., 2003). Pain is experienced by up to 83% of patients with SSc with more than a third of patients rating their pain as moderate to severe (Schieir et al.,

2010). The most common source of pain is joint pain (Ostojic et al., 2019); other sources of pain include finger ulcers, joint contractures, gastrointestinal symptoms, synovitis, joint tenderness, and Raynaud's phenomenon (Malcarne et al., 2007; Merz et al., 2017; Schieir et al., 2010). Patients with SSc have described their pain as excruciating, debilitating, and draining (Suarez-Almazor et al., 2007; Sumpton et al., 2017). In addition, nearly half of patients with SSc experience pain on a daily basis (Ostojic et al., 2019), underscoring the importance of effective pain management in this population.

SSc is a chronic and progressive disease in which patients are challenged with managing their symptoms on a daily basis, however, patients with SSc report less confidence in their ability to perform self-care tasks related to managing their pain (Thombs et al., 2017). More severe symptoms, such as higher levels of pain, have also been associated with lower levels of self-efficacy, or one's perceived confidence in performing a specific behavior or task (Bandura, 1999), in patients with SSc (Buck et al., 2010; Thombs et al., 2017). Self-efficacy is an essential component of chronic disease self-management (Moore et al., 2016), and gaining a better understanding of the relationship between pain and self-efficacy is essential for future development of self-management interventions in this population.

Additionally, little is known about changes in self-efficacy and pain over time. To our knowledge, only two studies have explored changes in pain over time (Merz et al., 2017; Sekhon et al., 2010). Sekhon et al. (2010) found little change in pain among 109

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patients with SSc who were evaluated at two consecutive visits (ranging from 4.2 to 10.9 months between visits), and Merz et al. (2017) found a slight improvement in pain among patients with early disease who were followed for three annual visits. These studies were limited by small sample sizes, limited data collection points (i.e., two consecutive visits or three annual visits), and limited exploration of factors that influence pain across time. Additionally, these studies did not explore self-efficacy and its potential mediating effect on pain which has been supported in other rheumatic diseases (Somers et al., 2010). As such, the aims of this study were to (a) describe the relationship between self-efficacy for managing pain and pain outcomes (i.e., pain interference and pain intensity), (b) examine self-efficacy for managing pain and pain trajectories across three years, and (c) determine whether changes in self-efficacy for managing pain mediate changes in pain outcomes across three years in patients with SSc.

3.1 Methods

3.1.1 Design

This study utilized prospective longitudinal cohort data collected at enrollment and each subsequent three-month follow-up assessment across three years (baseline to 36 months) from patients with SSc enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort. Self-efficacy for managing pain, pain interference, and pain intensity scores were evaluated at each assessment time point. The baseline assessment included patient data collected upon enrollment in the SPIN Cohort. This

study was approved by the Institutional Review Board of Duke University Health System; the SPIN Cohort study was approved by the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada and by the Institutional Review Boards of each participating SPIN Center.

Cross-sectional analyses were conducted to determine whether self-efficacy was associated with pain outcomes at baseline. Trajectory analyses were performed to examine change in self-efficacy, pain interference, and pain intensity across 36-months. Finally, we explored whether change in self-efficacy was a mechanism that influenced pain trajectories across 36-months. Patient characteristics associated with pain scores based on published findings were included as covariates in the analyses. A 36-month period was selected based on two considerations: (1) examining a time period that was long enough to capture change or flares in pain outcomes, and (2) 78% of those enrolled had not completed a 36-month assessment at the time of the analysis.

3.1.2 Data Source

The SPIN Cohort was established in 2011 to collect patient-reported data to better understand the problems faced by patients with SSc, and to develop and test interventions to improve quality of life for patients with SSc (Kwakkenbos et al., 2019). The SPIN Cohort includes adult patients with SSc from 45 SPIN Centers in the United States, Canada, the United Kingdom, France, Spain, Mexico, and Australia. The SPIN

sample is a convenience sample in which eligible participants are invited to participate

by a local SPIN physician or supervised nurse coordinator. Written informed consent is

obtained and the SPIN physician or supervised nurse coordinator complete and submit

an online medical data form, which initiates patient registration into the SPIN Cohort.

After completion of online registration, participants receive an automated welcoming

email with instructions on how to activate their online SPIN account and how to

complete the SPIN Cohort online patient-reported measures. Participants complete the

online patient-reported measures at enrollment and every three months.

Eligibility criteria for inclusion in the Cohort were: (1) diagnosis of SSc according

to the 2013 American College of Rheumatology/European League Against Rheumatism

classification criteria (Van Den Hoogen et al., 2013) confirmed by a SPIN-affiliated

physician, (2) 18 years of age or older, (3) ability to give informed consent, and (4) fluent

in English, French, or Spanish. Exclusion criteria included not having access to the

internet or otherwise not being able to respond to the patient-reported measures via the

internet.

3.1.3 Selected Sample

This study included a baseline sample of 1,903 patients with SSc who completed

an enrollment assessment from January 2013 through December 2018, and a trajectory

subsample comprised of 427 who completed the enrollment and month-36 assessments.

Participants with missing self-efficacy and pain (interference and intensity) scores at enrollment were excluded from the baseline sample. Of those, participants without self-efficacy and pain scores at month-36 were omitted from the trajectory subsample. Trajectory subsample participants, however, were not required to have self-efficacy and pain scores at each interim assessment. A sensitivity analysis was conducted to compare baseline participants included and excluded from the trajectory subsample (see data analysis plan and results). Figure 3 provides a flow diagram of the final analysis samples for this study.
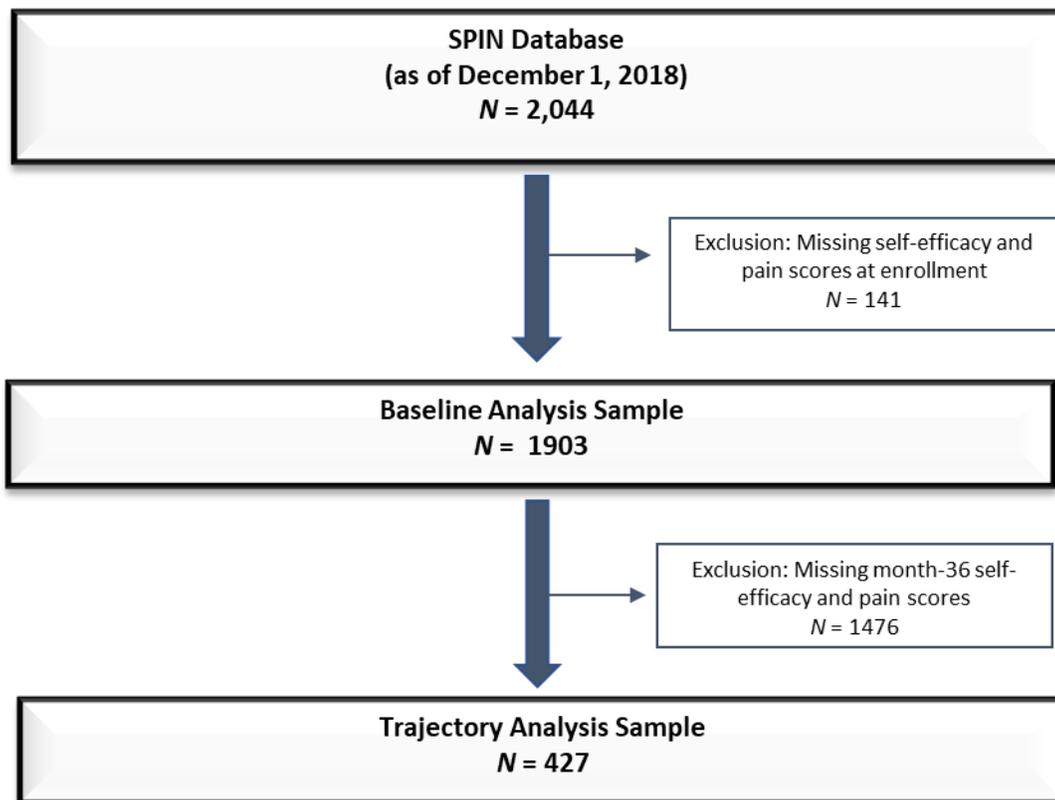

Figure 3: Determination of the Final Analysis Samples

3.1.4 Data Collection

Participants completed patient-reported measures at enrollment (baseline) and every three months thereafter via the internet. Each online assessment included items to measure self-reported outcomes.

3.1.4.1 Baseline Patient Characteristics

Participants provided demographic data upon enrollment. The SPIN-affiliated physician reported age and gender as well as clinical data, such as the SSc subtype (limited or diffuse cutaneous SSc), time since SSc diagnosis, and the presence or absence of disease manifestations.

3.1.4.2 Self-Efficacy for Managing Pain

One item from the Self-Efficacy for Managing Chronic Disease (SEMCD) scale (Ritter & Lorig, 2014) was used to measure self-efficacy for managing pain. The SEMCD scale consisted of six items measuring one's confidence in managing various aspects of his or her disease regularly at the present time. The single item related to self-efficacy for managing physical discomfort or pain was used to measure self-efficacy for managing pain. The item was rated on a scale from 1 (not confident at all) to 10 (totally confident), with higher scores indicating greater self-efficacy. The SEMCD scale is a valid and reliable measure in patients with SSc with established convergent validity and high internal consistency (Cronbach's α=0.93; Riehm et al., 2016), however, the reliability and

validity of the single item related to pain has not been tested. For the participants in the trajectory subsample, self-efficacy was assessed at baseline and every three-months, except for months 3, 9, and 15.

3.1.4.3 Pain Interference and Intensity

The pain interference domain and pain intensity item of the Patient-Reported Outcomes Measurement Information System-29 version 2.0 (PROMIS-29v2; HealthMeasures, 2011) were used to evaluate pain in the past seven days. The pain interference domain score was comprised of four items rated on a scale of 1 (not at all) to 5 (very much), with higher scores indicating greater pain interference. Raw domain scores, calculated by adding the ratings for the four pain interference items, had a possible range of 4 to 20. These scores were converted to T-scores standardized for the general U.S. population (Mean=50, Standard Deviation=10). The single pain intensity item was measured on an 11-point scale, ranging from 0 (no pain) to 10 (worst imaginable pain). Psychometric studies have demonstrated that these measures are valid and reliable in SSc, with convergent validity and Cronbach's α values ranging from 0.86 to 0.96 for domain scores (Kwakkenbos et al., 2017). Pain interference and pain intensity were assessed at enrollment and every three months.

3.1.5 Data Analysis

Non-directional tests were performed with significance set at 0.05 for all tests. The significance level was not adjusted for multiple testing due to the exploratory nature of this study. Effect sizes were calculated to address clinical significance. Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

3.1.5.1 Baseline Patient Characteristics

Descriptive statistics were used to summarize participant characteristics of the baseline sample and trajectory subsample. A sensitivity analysis using General Linear Models for scalar measures and chi-square tests for categorical data were performed to compare the baseline characteristics of those included in the trajectory subsample to those excluded from the subsample.

3.1.5.2 Baseline Covariates

Eight patient characteristics were selected *a priori* as covariates in the baseline and trajectory analysis. The three demographic covariates were age (at completion of baseline assessment), female gender, and married/living with a partner. The five clinical covariates were the presence of: (1) finger ulcers (i.e., digital pulp ulcers distal to the distal interphalangeal joints (DIPs) or anywhere else on the finger); (2) moderate or severe small joint contractures (i.e., to the DIP, proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs), and/or wrists); (3) esophageal gastrointestinal

symptoms (i.e., dysphagia, heartburn, and/or reflux, due to SSc at any time, now or in

the past); (4) time since diagnosis (i.e., time since diagnosis to completion of baseline

assessment); and (5) diffuse SSc subset (i.e., defined as skin sclerosis involving the limbs

proximal to the elbows and knees and/or the chest and/or trunk, at any time). These

covariates were examined in previous studies exploring pain and have been associated

with pain outcomes (Malcarne et al., 2007; Merz et al., 2017; Ostojic et al., 2019; Schieir et

al., 2010). Although considered, the Modified Rodnan Skin Score (MRSS) was not

included due to the 18% missing rate and its high overlap with disease subset.

3.1.5.3 Baseline Sample: Self-Efficacy and Pain Relationships

Bivariate regression was used to examine the relationship of (a) self-efficacy for

managing pain with pain interference and intensity scores and (b) eight participant

characteristics with these pain scores at enrollment in the baseline sample. Next,

hierarchical (sequential) forward multivariable regression models were conducted to

determine the influence of self-efficacy on pain scores, covarying for the eight

participant characteristics. Variance inflation factors (VIF) scores were used to check for

multicollinearity (VIF $\geq$ 5.0 indicating concern) among the predictors in each model. For

this hierarchical approach, Model 1 included self-efficacy, Model 2 included self-efficacy

and demographic covariates, and Model 3 (final model) included self-efficacy,

demographic covariates, and clinical covariates. Adjusted R^2 (aR^2, adjusting for the

number of predictors in the model) was used as an indicator of effect size and clinical significance. Small, medium, and large effects were indicated by an aR^2 of 0.02, 0.13, and 0.26, respectively. These aR^2 values are equivalent to Cohen's f^2 values of 0.02 (small), 0.15 (medium), and 0.35 (large) effects (Lenhard & Lenhard, 2016).

3.1.5.4 Trajectory Analyses

Random coefficients regression models for longitudinal data, a type of multi-level, mixed-effects model for repeated measures, were employed to determine the trajectories of change in self-efficacy and pain outcomes across 36 months in the trajectory subsample, covarying for patient characteristics. A hierarchical forward (sequential) modeling approach was used to build towards a final trajectory model for each outcome that included time and the eight patient characteristics. Model 1 included time, Model 2 included time and demographic covariates, and Model 3 (final model) included time, demographic covariates, and clinical covariates. Fixed effects were time (months) and covariates (baseline patient characteristics), while random effects were participant and participant-by-time. Baseline was defined as month-0. As needed, trajectories were fitted for a non-linear pattern of change. The assumption of data missing at random was evaluated.

Trajectory analyses, covarying for patient characteristics, were applied to test for the mediating effect of change in self-efficacy on pain trajectories across 36 months, in

accordance with recommended guidelines and path criteria for establishing mediation

(Baron & Kenny, 1986; Bennett, 2000).

3.1.5.5 Statistical Power

The baseline sample of 1,903 provided greater than 80% statistical power to

examine the relationship between self-efficacy and patient characteristics with the pain

outcomes using a hierarchical forward regression, assuming nine explanatory variables

(self-efficacy and eight covariates), small effect sizes (aR^2=0.02), and two-tailed tests with

significance set at 0.05 per test for the final and most complex model (Model 3). Based on

these assumptions, it was estimated that a sample size of 788 would be required to

achieve 80% power (G*Power3 software; Faul et al., 2007). The trajectory subsample of

427 with time and eight covariates in the model did not provide 80% power, assuming

two-tailed tests, significance set at 0.05 per test, and the smallest clinical meaningful

effect size for the time would be small effect sizes (aR^2=0.01), as determined using

SuperMix software for longitudinal analyses (Hedeker et al., 2008).

3.2 Results

3.2.1 Baseline Patient Characteristics

The baseline sample was comprised of 1,903 adults with SSc. Of those, the 427

who completed a month-36 outcome assessment were included in the trajectory

subsample. Table 6 presents the characteristics of the baseline sample and trajectory

subsample at enrollment. For the baseline sample, the mean age was 54.8 years (range:

18.3 to 88.6), the majority were female (87.5%), the mean time since diagnosis was 9.5

years (range: 0.0 to 55.8), and 39.2% had the diffuse SSc subset. The patients who

performed serial measures over three years were comparable to the overall sample.

Table 6: Patient Characteristics

Characteristics	Baseline Sample (*N*=1903)	Trajectory Subsample (*N*=427)
Age, in years	54.8 (12.6)	56.7 (11.7)
Female	1666 (87.5%)	377 (88.3%)
Race		
White	1589 (83.6%)	379 (89.0%)
Black	115 (6.1%)	20 (4.7%)
Other	197 (10.4%)	27 (6.3%)
Married/Living with partner	1358 (71.4%)	326 (76.4%)
Time since diagnosis, in years	9.5 (8.0)	10.0 (8.3)
Diffuse subtype	739 (39.2%)	159 (37.8%)
Raynaud's phenomenon	1853 (98.0%)	416 (98.4%)
Modified Rodnan Skin Score	7.2 (8.2)	7.3 (7.7)
Distal digital tip ulcers	655 (35.0%)	144 (33.7%)
Digital tip ulcers anywhere	306 (16.7%)	62 (15.0%)
Tendon friction rubs	395 (23.7%)	83 (21.8%)
Moderate - severe small joint contractures	472 (26.2%)	97 (24.1%)
Moderate - severe large joint contractures	227 (12.9%)	48 (11.9%)
Esophageal GI symptoms	1602 (85.0%)	366 (85.9%)
Stomach GI symptoms	572 (31.1%)	119 (28.8%)
Intestinal GI symptoms	727 (39.0%)	157 (37.6%)

Note. n (%) reported for categorical measures; mean (standard deviation) provided for scalar measures; GI, gastrointestinal.

Table 7 details self-efficacy for managing pain and pain scores at enrollment for the baseline sample and trajectory subsample. Pain interference scores for the baseline sample were converted to T-scores and revealed that the mean pain interference T-score of 55.5 (SD=9.7) was significantly higher than the mean of 50 (*SD*=10, *z*=24.0, *p*<.001) estimated for the general U.S. population. A sensitivity analysis did not reveal significant differences in the baseline patient characteristics, self-efficacy scores, and pain scores for those included in the trajectory subsample (*N*=427) compared to those excluded from the subsample (*N*=1476).

Table 7: Baseline Self-Efficacy for Managing Pain and Pain Scores

Baseline Measure	Baseline Sample Mean (SD) (*N*=1903)	Trajectory Subsample Mean (SD) (*N*=427)
Self-efficacy scores	6.1 (2.7)	6.3 (2.7)
Pain interference scores	9.4 (4.7)	9.2 (4.8)
Pain interference T-scores	55.5 (9.7)	55.1 (9.8)
Pain intensity scores	3.6 (2.6)	3.5 (2.7)

Note. SD = Standard Deviation; Self-efficacy range was 1 to 10, with higher scores indicating greater self-efficacy; Pain interference range was 4 to 20, with higher scores indicating greater pain interference; Pain intensity range was 0 to 10, with higher scores representing greater pain intensity.

3.2.2 Baseline Analysis: Bivariate Relationships

Bivariate regression indicated that self-efficacy for managing pain was significantly related to pain interference (*β*= -0.60, *p*<0.001, *aR²*=0.36) and intensity (*β*= -

0.55, $p<0.001$, $aR^2=0.30$), with an $aR^2 \geq 0.26$ indicating large effects (Table 8, Model 1). As self-efficacy increased (greater confidence), pain interference and pain intensity scores significantly decreased (less pain). As expected, pain interference and pain intensity scores were positively correlated ($\beta= +0.85$, $p<0.001$, $aR^2=0.72$).

Patient characteristics were significantly associated with both pain interference and intensity ($p\leq0.05$). Exceptions were age and time since diagnosis. Younger age was significantly related to greater pain interference ($\beta= -0.05$, $p=0.034$, $aR^2=0.01$); however, age was not associated with intensity ($\beta= -0.04$, $p=0.093$, $aR^2=0.00$). Time since diagnosis was not significantly related to pain interference ($\beta= +0.03$, $p=0.188$, $aR^2=0.00$) or intensity ($\beta= +0.04$, $p=0.124$, $aR^2=0.00$). Finger ulcers explained 3% of variability of pain interference and intensity (both $\beta= +0.17$, $p<0.001$, $aR^2=0.03$, small effects). Moderate or severe small joint contractures also explained 3% of variability of both pain interference and intensity (both $\beta= +0.18$, $p<0.001$, $aR^2=0.03$, small effects). Although statistically significant, the remaining characteristics individually explained 1% or less of the variability of the pain scores ($aR^2\leq0.01$, weak effects).

3.2.3 Baseline Analysis: Multivariable Relationships

Table 8 provides the hierarchical forward multivariable regression results. The final full covariate-adjusted model (Model 3) indicated that self-efficacy was significantly related to both pain interference ($\beta= -0.58$, $p<0.001$) and intensity ($\beta= -0.53$,

p<0.001), after adjusting for all eight patient characteristics. Specifically, increasing self-efficacy was associated with less pain interference and intensity. This final model explained 38% of the variability of pain interference (aR^2=0.38) and 32% of the variability of intensity (aR^2=0.32), which was a 2% improvement in aR^2 for both pain outcomes compared to the initial model that included only self-efficacy (Model 1). VIF scores were <1.2 for the final model, indicating that multicollinearity was not a concern.

Table 8: Baseline Analysis: Hierarchical Forward Multivariable Regression Models

Pain Outcome	Block	Explanatory Variable	Model 1 (*N*=1903) aR² = 0.36			Model 2 (*N*=1899) aR² = 0.36			Model 3 (*N*=1689) aR² = 0.38		
			b	*SE*	*β*	*b*	*SE*	*β*	*b*	*SE*	*β*
Interference	1	Self-efficacy	-1.05 ***	0.03	-0.60	-1.05***	0.03	-0.60	-1.01***	0.03	-0.58
	2	Age, in years				+0.01	0.01	+0.03	+0.02*	0.01	+0.04
		Female				+0.88 ***	0.26	+0.06	+0.89***	0.28	+0.06
		Married/living with partner				-0.50**	0.19	-0.05	-0.36	0.20	-0.03
	3	Finger ulcers							+0.85***	0.27	+0.07
		Small joint contractures							+0.50*	0.23	+0.05
		Esophageal GI symptoms							+0.82***	0.25	+0.06
		Time since diagnosis							+0.01	0.01	+0.12
		Diffuse subset							+0.37	0.20	+0.04

Pain Outcome	Block	Explanatory Variable	aR² = 0.30			aR² = 0.31			aR² = 0.32		
			b	*SE*	*β*	*b*	*SE*	*β*	*b*	*SE*	*β*
Intensity	1	Self-efficacy	-0.53 ***	0.02	-0.55	-0.54***	0.02	-0.55	-0.51 ***	0.02	-0.53
	2	Age				+0.01*	0.00	+0.04	+0.01*	0.00	+0.04
		Female				+0.58***	0.15	+0.07	+0.58***	0.16	+0.07
		Married/living with partner				-0.33**	0.11	-0.06	-0.23*	0.12	-0.04
	3	Finger ulcers							+0.42**	0.15	+0.06
		Small joint contractures							+0.39**	0.13	+0.07
		Esophageal GI symptoms							+0.28	0.15	+0.04

			+0.01	0.01	+0.02
Time since diagnosis					
Diffuse subset			+0.10	0.12	+0.02

Note. aR²=adjusted R²; *b*=unstandardized regression coefficient; *SE*=standard error; *β* =standard regression coefficient; *p≤0.05; **p≤0.01; ***p≤0.001; Block 1=self-efficacy; Block 2=baseline demographic characteristics; Block 3=baseline clinical characteristics; Self-efficacy: higher scores=greater self-efficacy for managing pain; Pain interference: higher scores=greater pain interference; Pain intensity: higher scores=greater pain intensity. Self-efficacy and age were continuous variables; Remaining characteristics coded 0=absent and 1=present; aR²:0.02=small, 0.13=medium, 0.26=large effect sizes.

The final model indicated the following statistically significant relationships between each covariate and the pain outcomes, after adjusting for self-efficacy and other patient characteristics: (1) increasing age was associated with greater pain interference and intensity; (2) females reported greater pain interference and intensity; (3) adults married/living with a partner reported less pain intensity, but this covariate was not related to pain interference; (4) finger ulcers were associated with greater pain interference and intensity; (5) moderate or severe small joint contractures were related to greater pain interference and intensity; and (6) esophageal gastrointestinal symptoms were associated with greater pain interference, but not intensity. Neither time since diagnosis nor diffuse SSc subset were significantly related to pain outcomes. In contrast to the bivariate results, the results from the full regression model indicated: (a) older age was significantly associated with both pain outcomes; (b) married/living with a partner was only related to pain intensity; (c) esophageal gastrointestinal symptoms were associated with pain interference only; and (d) the diffuse SSc subset was not related to pain interference or intensity.

3.2.4 Trajectories Analysis: Change in Self-Efficacy and Pain Outcomes

Table 9 presents descriptive statistics and the completion rates for self-efficacy, pain interference, and pain intensity at each assessment across the 36 months. All 427 patients in the trajectory subsample completed the baseline (Month-0) and final (Month-

36) assessment. The completion rate was 85% or higher for most of the other assessments included in each analysis. For each outcome, a linear trajectory model best fitted the longitudinal data.

Table 9: Trajectories Analysis: Unadjusted Means for Self-Efficacy and Pain Outcomes

Outcome	M0	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36
Self-Efficacy													
Unadjusted N	427	---	364	---	387	---	389	---	375	---	378	333	427
Completion rate	100%	---	85%	---	91%	---	91%	---	88%	---	89%	78%	100%
Unadjusted Mean	6.3	---	6.3	---	6.4	---	6.5	---	6.4	---	6.5	6.5	6.5
Unadjusted SD	2.7	---	2.8	---	2.6	---	2.7	---	2.8	---	2.7	2.8	2.7
Pain Interference													
Unadjusted N	427	316	366	386	388	381	388	379	374	388	378	381	427
Completion rate	100%	74%	88%	90%	91%	89%	91%	89%	88%	91%	89%	89%	100%
Unadjusted Mean	9.2	8.6	8.9	9.0	8.9	8.9	8.8	9.2	8.8	8.8	8.8	9.1	8.9
Unadjusted SD	4.8	4.5	4.8	4.7	4.5	4.5	4.6	4.8	4.7	4.6	4.5	4.7	4.7
Unadjusted Mean T-score	55.1	53.8	54.2	54.7	54.3	54.4	54.2	54.9	54.1	54.4	54.3	54.8	54.5
Unadjusted T-score SD	9.8	9.6	9.9	9.6	9.5	9.5	9.6	9.8	9.8	9.6	9.4	9.7	9.7
Pain Intensity													

Unadjusted N	427	316	366	386	388	381	388	379	374	388	378	381	427
Completion rate	100%	74%	88%	90%	91%	89%	91%	89%	88%	91%	89%	89%	100%
Unadjusted Mean	3.5	3.3	3.4	3.4	3.3	3.3	3.3	3.5	3.4	3.4	3.4	3.6	3.5
Unadjusted SD	2.7	2.6	2.6	2.6	2.6	2.7	2.6	2.7	2.7	2.7	2.7	2.7	2.8

Note. M = Month; M0 = Month 0 (baseline); SD = Standard Deviation; Self-efficacy was not assessed at months 3, 9, and 15. Additionally, the following self-efficacy assessments were omitted from the trajectory analysis due to a completion rate less than 50%: (a) month 21 had only 60 assessments completed and 14% completion rate and (b) month 27 had 206 assessments completed and 48% completion rate

Table 10 presents the trajectory model results for self-efficacy and pain outcomes, applying a forward model building approach. The time effect in the initial model (Model 1) and two covariate-adjusted models (Models 2 and 3) for each outcome were not statistically significant, indicating no significant change across the 36 months in self-efficacy, pain interference, or pain intensity. With regard to magnitude of change across the 36 months, minimal to very small effect sizes were observed for each outcome (intraclass correlation coefficients < 0.15).

Table 10: Trajectory Analysis Hierarchical Forward Mixed-Effects Models

Outcome	Block	Explanatory Variable	Model 1 (N=427)	Model 2 (N=424)	Model 3 (N=377)
			p	p	p
Interference	1	Time, in months	0.382	0.548	0.719
	2	Age, in years		0.215	0.591
		Female		0.832	0.956
		Married/living with partner		**0.044**	0.215
	3	Finger ulcers			**0.005**
		Small joint contractures			**0.007**
		Esophageal GI symptoms			**0.001**
		Time since diagnosis			0.195
		Diffuse subset			0.844
Intensity	1	Time, in months	0.298	0.323	0.158
	2	Age, in years		0.400	0.824
		Female		0.942	0.761
		Married/living with partner		**0.033**	0.181
	3	Finger ulcers			**0.001**
		Small joint contractures			**0.001**
		Esophageal GI symptoms			**0.006**
		Time since diagnosis			0.147
		Diffuse subset			0.126
Self-efficacy	1	Time, in months	0.101	0.217	0.984
	2	Age, in years		**0.033**	0.135
		Female		0.110	0.158
		Married/living with partner		**0.039**	0.107
	3	Finger ulcers			**0.042**
		Small joint contractures			**0.012**
		Esophageal GI symptoms			**0.001**
		Time since diagnosis			0.125
		Diffuse subset			0.444

Note. Mixed-effects trajectory models with time and baseline patient characteristics (covariate) as fixed effects; patient and patient-by-time interaction as random effects; Block 1=time, in months; Block 2=baseline demographic characteristics; Block 3=baseline clinical characteristics; Significant results are bolded.

Figure 4 presents the adjusted mean trajectory for each outcome, covarying for

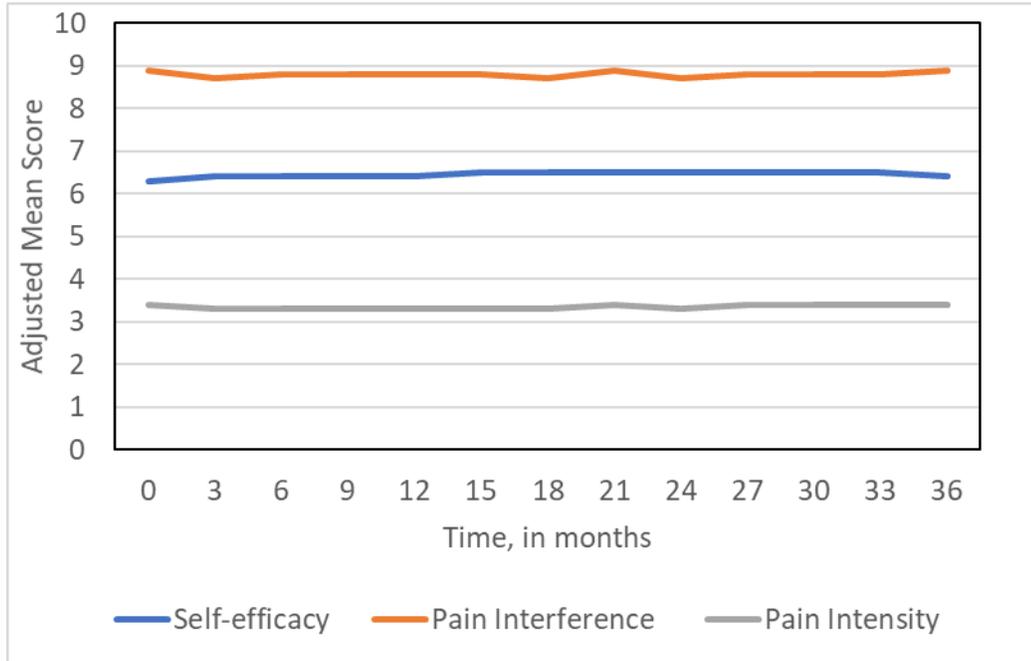the patient characteristics (Model 3).

Figure 4: Trajectories for Self-Efficacy for Managing Pain and Pain Scores, Adjusting for Baseline Patient Characteristics

Three baseline covariates were significantly related to all three outcomes in the

final model (Model 3). Finger ulcers were associated with greater pain interference

(unstandardized regression coefficient (b)= +1.81, SE=0.63, p=0.005), greater pain

intensity (b= +1.21, SE=0.37, p=0.001), and less self-efficacy (b= -0.75, SE=0.37, p=0.042).

Moderate-to-severe small joint contractures were associated with greater pain

interference (b= +1.43, SE=0.52, p=0.007), greater pain intensity (b= +1.00, SE=0.31,

p=0.001), and less self-efficacy (b= -0.75, SE=0.30, p=0.012). Finally, esophageal

gastrointestinal symptoms were associated with greater pain interference (b= +1.91,

SE=0.57, p=0.001), greater pain intensity (b= +0.93, SE=0.33, p=0.006), and less self-efficacy

(b= -1.13, SE=0.33, p=0.001). Thus, finger ulcers, small joint contractures, and esophageal

gastrointestinal symptoms were related to higher levels of pain and less self-efficacy for

managing pain.

3.2.5 Change in Self-Efficacy as a Mediator of Pain

Change in self-efficacy over 36 months did not mediate the trajectories of pain

interference or intensity, covarying for patient characteristics. Not all four criteria

(paths) for establishing mediation were met. Path A (impact of time on self-efficacy) was

not met due to the minimal, non-significant change in self-efficacy over time (noted

above). Path B (association between self-efficacy and pain outcomes) was met for

improvements in self-efficacy and were significantly associated with reductions in pain

interference (b= -0.43, SE=0.07, p<0.001, aR^2=0.09, small effect) and intensity (b= -0.24,

SE=0.04, p<0.001, aR^2=0.08, small effect). Path C (impact of time on pain outcomes) was

not met due to the minimal, non-significant change in pain interference and intensity

over time (noted above). Path C' (impact of time on pain outcomes, covarying for self-

efficacy over time) was not tested due to the non-significant change in pain interference

and intensity and low statistical power for this analysis.

3.3 Discussion

SSc is a chronic and progressive disease in which patients frequently experience pain and are challenged with self-managing their symptoms throughout the disease course. In this study, self-efficacy for managing pain and pain interference and intensity did not significantly change over the three-year period. One potential explanation for the stable pain trajectories found in our study is that our sample consisted of patients who had lived with their disease for approximately nine years. Previous research found that patients experience higher levels of disease activity, more rapid progression, and worsening skin thickening within the first five years of symptom onset, after which the overall disease course remains relatively stable (Medsger, 2003). Given patients had stable disease, the occurrence of chronic pain is unsurprising. Chronic pain, or pain that occurs for more than three months (Treede et al., 2015), has been reported in up to 75% of patients with SSc and is often refractory to treatment (Thombs et al., 2008). While our trajectories supported the chronicity of pain, patients have also described their disease as progressive in nature with superimposed flares lasting for three days to three months (Suarez-Almazor et al., 2007). While qualitative studies have captured descriptions of symptom flares in patients with SSc, quantitative studies have yet to quantify or characterize such flares. One potential explanation for this is that the longitudinal data used to establish trajectories in SSc does not include time points frequent enough to capture periods of intense symptoms, subsequently resulting in relatively stable

trajectories as seen in this study. Future studies that capture these distinct periods of symptom flares are needed to guide the timing and delivery of pain management interventions in this population.

In our study, the presence of finger ulcers, small joint contractures, and esophageal gastrointestinal symptoms were associated with baseline pain outcomes. While our study underscored the association between finger ulcers and pain, we did not explore the frequency or chronicity of finger ulcers. This is an important consideration given that previous research has identified that patients who experience more frequent digital ulcers, such as those with recurrent or chronic ulcers, often have a higher disease burden and a greater need for interventions (Matucci-Cerinic et al., 2016).

Additionally, we found that small joint contractures and esophageal gastrointestinal symptoms (i.e., dysphagia, heartburn, and/or reflux) were significantly associated with pain interference and intensity. Previous studies have also described an association between joint contractures and esophageal gastrointestinal symptoms (Ashida et al., 2007; Johnson et al., 2006), however, these studies did not explore differences in pain outcomes separately among small and large joint contractures, or explore the extent and severity of the gastrointestinal symptoms. This is an important consideration given that small joint contractures of the hand often do not improve with pharmacological therapy (Young et al., 2016) and many patients do not respond to existing treatments for esophageal gastrointestinal symptoms (Denaxas et al., 2018).

Future studies might explore differences in pain outcomes in patients who experience more frequent and/or chronic finger ulcers, and differences in the extent and severity of gastrointestinal symptoms extending beyond esophageal symptoms to inform future pain management interventions in patients with SSc.

Greater self-efficacy for managing pain was associated with less pain interference and lower pain intensity. Patients with SSc report worse self-efficacy than patients with other chronic diseases (i.e., multiple sclerosis, cardiovascular disease, and breast cancer), particularly related to performing self-care tasks for pain (Thombs et al., 2017). Despite the correlation between self-efficacy and pain in this population (Buck et al., 2010), self-management interventions aimed at improving self-efficacy have mixed results. For example, there was no significant difference in self-efficacy in a randomized controlled trial comparing an internet-based self-management program with a patient-focused educational book (Khanna et al., 2019). However, online self-management programs for patients with chronic diseases (i.e., arthritis, diabetes, hypertension, lung and heart disease) such as the Chronic Disease Self-Management Program (CDSMP) have been associated with improvements in self-efficacy and health outcomes (Lorig et al., 2006), with sustained improvements in outcomes over time (Barlow et al., 2005). While self-efficacy for managing pain did not change over time and was not a mediator of the pain trajectories in our study, future studies might explore the timing and impact of self-management interventions on pain outcomes, such as the delivery of a self-management

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intervention during a period of high disease activity (i.e., within the first five years of

disease onset).

3.3.1 Limitations

Our study had many strengths, including a large sample, validated SSc diagnosis

by a health care provider, inclusion of patient-reported measures, and use of

longitudinal, multicenter data. The SPIN Cohort is a convenience sample of patients

receiving care at a SPIN Center with access to the internet and the ability to complete

online measures, which may limit the generalizability of findings. Additionally,

participants in this study had a mean disease duration of 9.5 years, and results may

differ for patients with a shorter or longer disease duration. While patient-reported

measures were used, our study only used a single item of the Self-Efficacy for Managing

Chronic Disease scale; future studies should consider use of the full Self-Efficacy for

Managing Chronic Disease scale. Finally, while the baseline sample size provided power

to detect statistically significant relationships with small, non-clinically meaningful

effects, such findings should be interpreted in terms of their clinical relevance. The

sample size for the trajectory analysis did not provide adequate power for the very small

time-effects observed. Thus, this analysis was exploratory in nature.

3.4 Conclusion

This study examined the relationship between self-efficacy for managing pain and pain outcomes upon enrollment and over three years in adults with SSc. Our findings indicate that self-efficacy for managing pain was strongly and inversely related to pain outcomes and that self-efficacy for managing pain and pain outcomes remained stable over a three-year period. We identified important correlates (i.e., self-efficacy for managing pain, age, gender, finger ulcers, small joint contractures, and esophageal gastrointestinal symptoms) associated with pain outcomes in adults with SSc which may serve as important factors to consider in the development of pain management interventions. Additionally, our findings provide important insights into the longitudinal pain experiences of patients with SSc and can inform the assessment and management of pain in this population.

4. Symptom Clusters in Systemic Sclerosis

4.1 Background

Systemic sclerosis (SSc; scleroderma) is a rare, chronic, and progressive autoimmune disease associated with a complex symptom profile. SSc is characterized by vasculopathy, production of autoantibodies, and fibrosis that affects the skin and internal organs (van den Hoogen et al., 2013). Women are predominately affected, with a disease onset often between the ages of 20 to 50 years old (Alba et al., 2014). There is no cure for SSc and patients experience significant morbidity as a result of debilitating symptoms. As such, a primary goal of treatment is to improve symptom burden, physical function, and health-related quality of life (Almeida et al., 2015).

Previous symptom research in SSc has focused on the experience of living with SSc. For example, patients with SSc have described distressing appearance changes, bodily malfunction, social impairment, loss of identity, uncertainty, and social isolation (Nakayama et al., 2016; Suarez-Almazor et al., 2007; Sumpton et al., 2017). Symptom research in SSc has also focused on the prevalence and severity of individual symptoms such as anxiety, depression, fatigue, sleep disturbance, and pain (Del Rosso et al., 2013; Frech et al., 2011; Sandusky et al., 2009; Schieir et al., 2010), as well as their impact on patient outcomes (Nguyen et al., 2014; Sariyildiz et al., 2013). While prior research has recognized the complex symptom experience of living with SSc, little is known about the

prevalence or impact of multiple concurrent symptoms, or symptom clusters, and their

relationship with physical function in this population.

A symptom cluster is defined as "a group of three or more concurrent symptoms

that are related to one another but are not required to share the same etiology" (Dodd et

al., 2001, p. 2). One method of symptom cluster research is an *a priori* approach which is

used "to identify patient subgroups based on their distinct experiences with a

prespecified symptom cluster" (Miaskowski, 2016, p. 406). A prespecified symptom

cluster is defined based on a number of considerations, including patient self-report that

specific symptoms represent a cluster, highly correlated symptoms, symptoms that

share a common etiology, or symptoms that have a synergistic effect on patient

outcomes (Miaskowski, 2016). In patients with SSc, anxiety, depression, fatigue, sleep

disturbance, and pain have been reported as some of the most frequent and bothersome

symptoms (Bassel et al., 2011; Del Rosso et al., 2013; Richards et al., 2003; Suarez-

Almazor et al., 2007). Additionally, these five symptoms have a synergistic effect on

functional disability (Sariyildiz et al., 2013) and share a common etiology (i.e., altered

inflammatory processes) (Dantzer, 2001; Doong et al., 2015; Gilbertson-White et al.,

2011). Identification of subgroups of patients with SSc at increased risk of greater

symptom burden is a critical step to guide the development of targeted symptom

management interventions for those who share distinct symptom experiences.

The purpose of this study was to address critical gaps in knowledge by identifying subgroups of patients with SSc who share distinct symptom experiences with anxiety, depression, fatigue, sleep disturbance, and pain, and to determine the relationship of these subgroups with physical function to inform future intervention development. The specific aims were to: (1) identify subgroups of patients with SSc who share common symptom experiences using a prespecified symptom cluster (i.e., anxiety, depression, fatigue, sleep disturbance, and pain); (2) determine individual characteristics (i.e., demographic and clinical characteristics) associated with each subgroup; and (3) determine the relationship between subgroup membership and physical function.

4.2 Methods

4.2.1 Design

This study used a descriptive cross-sectional design that utilized enrollment data from the Scleroderma Patient-centered Intervention Network (SPIN) Cohort (Kwakkenbos et al., 2013). The prespecified symptom cluster included measures of anxiety, depression, fatigue, sleep disturbance, and pain intensity derived from the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) which was completed at the enrollment visit. Domain subscales from the PROMIS-29 measure were used to assess the severity of each symptom in the prespecified symptom cluster as well as physical function. This study was approved by the Institutional Review Board at Duke University Health System, and the SPIN Cohort study was approved by the

Research Ethics Committee of the Jewish General Hospital, Montreal, Canada and by the

Institutional Review Board of each participating SPIN Center.

4.2.2 Data Source

The SPIN Cohort was created in 2011 to collect patient-reported data to better

understand the problems faced by patients with SSc and to provide a framework for the

development and testing of online interventions to help patients manage their

symptoms (Kwakkenbos et al., 2013). Patients were recruited from among 45 SPIN

Centers in the United States, Canada, the United Kingdom, France, Spain, Mexico, and

Australia. The SPIN Cohort is a convenience sample in which eligible participants were

invited to participate by a SPIN physician or supervised nurse coordinator. Written

informed consent was obtained and an online medical data form was completed by the

SPIN physician or supervised nurse coordinator. Participants completed online patient-

reported measures at enrollment and every three months.

Participants were included in the SPIN Cohort if they: (1) had a confirmed

diagnosis of SSc by a SPIN physician according to the 2013 American College of

Rheumatology/European League Against Rheumatism classification criteria (van den

Hoogen et al., 2013), (2) were 18 years of age or older, (3) had the ability to give

informed consent, and (4) were fluent in English, French, or Spanish (Kwakkenbos et al.,

2013). Exclusion criteria for participation in the SPIN Cohort included not having access

to the internet or not being able to complete the patient-reported measures via the internet.

4.2.3 Analysis Sample

This study utilized enrollment (baseline) data from the SPIN database available as of July 13, 2020, which was the date in which the current study analysis was initiated. Participants who met the inclusion criteria for the SPIN Cohort were included. Among 2,347 adults with SSc who had enrollment data, 135 were excluded from the analysis sample due to the following: (1) the PROMIS-29 measure was not completed or (2) there were incomplete PROMIS-29 items for any domain of interest in this study, with incomplete defined as less than 80% of the items comprising a domain subscale completed. These exclusions were applied to avoid the application of imputation methods for domain items or subscale scores when 20% or more of the items comprising the domain were missing. The final analysis sample included 2,212 adults with SSc who completed the symptom domains included in the prespecified symptom cluster as well as the physical function domain of the PROMIS-29 measure at enrollment. Figure 5 displays how the final analysis sample for this study was determined.
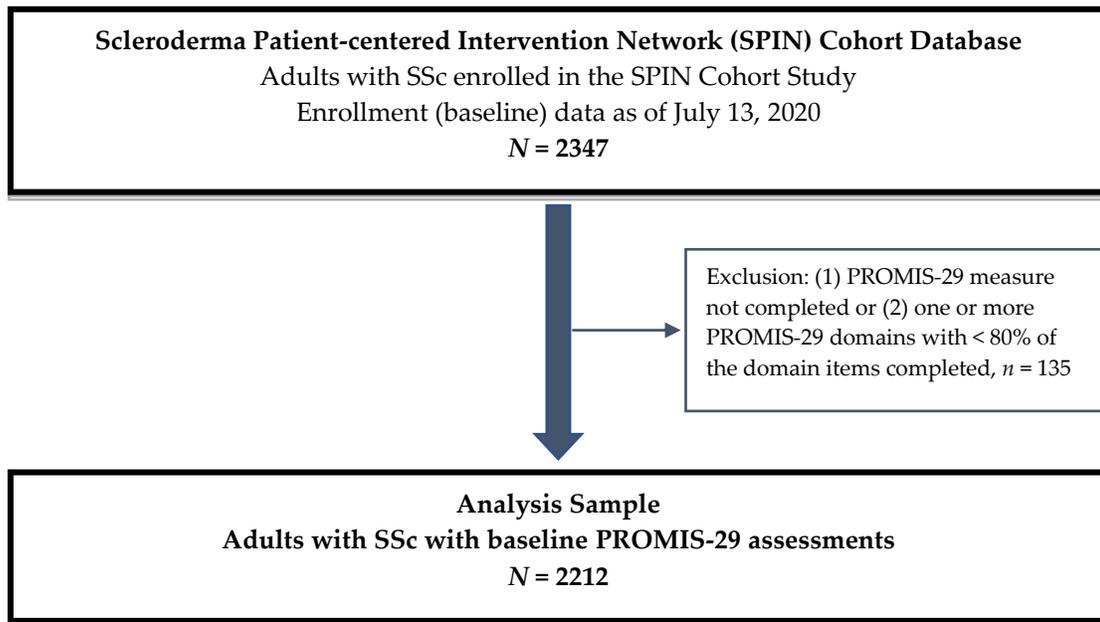
Figure 5: Determination of the Final Analysis Sample

Note. SSc=systemic sclerosis; PROMIS-29=Patient-Reported Outcomes Measurement Information System-29

4.2.4 Measures

4.2.4.1 Individual Characteristics

Individual characteristics were obtained using a demographic questionnaire and medical data form. The demographic questionnaire was completed by the SPIN participant (except for age and gender, which was completed by the SPIN physician), and the medical data form which included clinical information was completed by the SPIN physician. Categorical variables were coded as no (0) and yes (1).

Demographic characteristics were age in years, years of education, gender, race/ethnicity, and married/living with a partner. Clinical characteristics were time since

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SSc diagnosis in years, diffuse SSc subset (i.e., skin sclerosis involving the limbs proximal to the elbows and knees and/or the chest and/or trunk at any time), Raynaud's phenomenon, Modified Rodnan Skin Score (MRSS), distal digital tip ulcers (i.e., digital ulcers distal to the distal interphalangeal joints (DIPs)), digital tip ulcers anywhere else on the finger, tendon friction rubs (i.e., palpable crepitus over flexor or extensor tendons, particularly over the wrists, fingers, knees, and ankles), telangiectasia, abnormal pigment of the face or body, moderate to severe small joint contractures (i.e., to the DIPs, proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs), and/or wrists), large joint contractures (i.e., to the elbows, knees, hips, or ankles), esophageal gastrointestinal (GI) symptoms (i.e., dysphagia, heartburn and/or reflux due to SSc at any time, now or in the past as reported by the patient or documented by a physician), stomach GI symptoms (i.e., early satiety and/or vomiting due to SSc at any time, now or in the past as reported by the patient or documented by a physician), and intestinal GI symptoms (i.e., diarrhea, bloating and/or constipation due to SSc at any time, now or in the past as reported by the patient or documented by a physician).

4.2.4.2 Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)

The PROMIS-29 Version 2 (Hays et al., 2009) measure was used to assess the five symptoms in the prespecified symptom cluster and the outcome, physical function. The PROMIS-29 measure evaluated overall health status by assessing seven domains (i.e.,

fatigue, sleep disturbance, anxiety, depression, physical function, ability to participate in

social roles and activities, and pain interference) along with a single pain intensity score.

The reliability and validity of the PROMIS-29 measure have been demonstrated in SSc

(Hinchcliff et al., 2011; Hinchcliff et al., 2015; Khanna et al., 2012) with high internal

consistency for each domain (Cronbach's α of 0.86 to 0.96) (Kwakkenbos et al., 2017).

Raw subscale scores for the domains of anxiety, depression, fatigue, and sleep

disturbance were derived. Raw subscale scores were calculated by summing the four

subscale item scores (range 4-20). For anxiety, depression, fatigue, and sleep disturbance,

higher scores indicated greater symptom severity (e.g., more severe anxiety). The raw

subscale scores were converted to subscale T-scores standardized for the general U.S.

population (Mean=50, Standard Deviation=10). T-scores allowed for comparison of the

severity of the symptoms in the prespecified cluster (Davis et al., 2016). For anxiety,

depression, fatigue, and sleep disturbance, T-scores at or near the following scores were

used to differentiate the levels of symptom severity: 50 = normal to mildly symptomatic,

60 = mildly to moderately symptomatic, 70 = moderately to severely symptomatic (Cella

et al., 2010).

Pain intensity was measured using a single item from the PROMIS-29 measure,

rated using a Likert scale ranging from 0 (no pain) to 10 (worst imaginable pain) (Hays

et al., 2009; Kwakkenbos et al., 2017). However, a T-score was not available for pain

intensity. The single item raw score was converted to a 0 to 100 scale to improve

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interpretation and symptom severity comparison during the latent profile analysis. For

example, a converted score of 40 represented a rating of 4 on the original scale. The

following pain scores on a 0-100 scale were used in this study: $\leq$ 40 (mild pain), 40.1-70

(moderate pain), and >70 (severe pain). These pain scores were derived from previous

research exploring pain severity in SSc using a 0-10 scale, in which $\leq$ 4 represented mild

pain, 5-7 represented moderate pain, and >7 represented severe pain (Schieir et al., 2010).

For physical function, a raw subscale score was derived. The raw subscale score

was calculated by summing the four subscale item scores (range 4-20). For physical

function, higher scores indicated better physical function. The raw subscale score was

converted to subscale T-score standardized for the general U.S. population (Mean=50,

Standard Deviation=10).

4.2.5 Data Analysis

Descriptive statistics were used to detail the individual characteristics and

PROMIS-29 measure. Non-directional statistical tests were performed with the level of

significance set at 0.05 for each statistical significance test. Effect sizes and their 95%

confidence intervals (CI) were reported to address clinical significance. Analyses were

performed using SAS version 9.4 (SAS Institute, Cary, NC); Mplus version 8.3 was used

to conduct the latent profile analysis (Muthen & Muthen, Los Angeles, CA).

4.2.5.1 Aim 1 - Latent Profile Analysis

A latent profile analysis (LPA) was used to identify latent classes, or subgroups of patients who shared common symptom experiences, using a prespecified symptom cluster. In LPA, the construct of interest is a <u>latent variable</u>, which is comprised of <u>subgroups of patients that are referred to as latent classes</u>. The domains (symptoms) of the construct are continuous in nature and represent the severity of the symptoms in the prespecified symptom cluster. The identified latent classes are assumed to be mutually exclusive. A set of LPA models based on the number of specified latent classes (subgroups) to be derived were evaluated to determine the best model. Each model included the T-scores for the symptoms of anxiety, depression, fatigue, and sleep disturbance and the converted pain intensity score.

The following model fit indicators were used to determine the optimal number of latent classes (subgroups): the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), Bootstrapped Likelihood Ratio Test (BLRT), sample size adjusted Bayesian Information Criteria (ssBIC), and the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR). A LPA model that fits the data best is the one with the lowest AIC, BIC, BLRT, ssBIC, and VLMR (Nylund et al., 2007). Additionally, entropy was considered when determining the best fitting model as well-fitting models produce entropy levels $\geq$ 0.8 (Celeux & Soromenho, 1996). In order to determine the LPA model that fit the data best, we considered the goodness of model fit indices, the level of

entropy, and whether the identified latent classes "made sense conceptually" (Miaskowski et al., 2015, p. 30). We also applied the criterion that a model with any latent class that included 5% or less of the sample would not be considered.

4.2.5.2 Aim 2 – Latent Class Comparisons of Individual Characteristics

One-way analysis of variance models (ANOVA) and 5 x 2 chi-square tests were used to compare latent class differences in each individual characteristic. These bivariate analyses examined 16 individual characteristics (6 demographic and 10 clinical). ANOVAs were performed using a General Linear Model approach due to unequal latent class sizes. When a statistically significant latent class effect was detected, *a posteriori* pairwise contrasts were conducted with independent t-tests for continuous measures and 2 x 2 chi-square for categorical measures.

Individual characteristics were selected based on previous literature in which they have been independently associated with the symptoms included in the prespecified symptom cluster as well as physical function (Kwakkenbos et al., 2017). The six demographic characteristics were: (1) age, (2) years of education, (3) female gender, (4) white race/ethnicity, (5) black race/ethnicity, and (6) married/living with a partner. The ten clinical characteristics included: (1) time since diagnosis, (2) diffuse SSc subset, (3) distal digital tip ulcers, (4) digital tip ulcers anywhere else on the finger, (5) tendon friction rubs, (6) moderate to severe small joint contractures, (7) moderate to severe large

joint contractures, (8) esophageal GI symptoms (i.e., dysphagia, heartburn and/or reflux), (9) stomach GI symptoms (i.e., early satiety and/or vomiting), and (10) intestinal GI symptoms (i.e., diarrhea, bloating and/or constipation). Although considered, the Modified Rodnan Skin Score, telangiectasia, and abnormal pigment of the face or body were excluded due to a high missing data rate; Raynaud's phenomenon was excluded due to lack of variability (i.e., approximately 98% of the sample had Raynaud's phenomenon). Due to severe skewness, time since diagnosis was log transformed to normalize the data distribution.

4.2.5.3 Aim 3 – Latent Class Relationship to Functional Outcome

Using a General Linear Model approach, a one-way ANOVA without covariates and ANCOVA with the covariates were conducted to determine the relationship between the latent classes with physical function T-scores. Covariates were only the set of individual characteristics for which the latent classes significantly differed at the 0.05 level in the Aim 2 analysis. *A posteriori* pairwise contrasts were conducted using an independent t-test if a significant latent class effect was detected. Eta-squared and partial eta-squared were derived to address effect size for the latent class variable and each covariate.

4.3 Results

4.3.1 Sample Characteristics

Table 11 presents the sample characteristics for the 2,212 adults with SSc. The mean age was 54.8 years (range: 18.3 to 88.6) and median time since diagnosis was 7.3 years (range: 0.0 to 55.8). The majority of the sample was female (87.7%), white (83.0%), and married/living with a partner (71.0%). Only 39.1% had the diffuse SSc subset, while almost all had Raynaud's phenomenon (98.1%) and over 85% had esophageal GI symptoms (i.e., dysphagia, heartburn and/or reflux).

Table 11: Patient Characteristics (N=2212)

Characteristics	Statistics
Age, in years	54.8 (12.7)
Female	1939 (87.7%)
Race	
White	1834 (83.0%)
Black	144 (6.5%)
Other	232 (10.5%)
Years of education	14.8 (3.2)
Married/Living with partner	1570 (71.0%)
Time since diagnosis, in years	7.3 (3.0, 13.8)
Diffuse subtype	856 (39.1%)
Raynaud's Phenomenon	2152 (98.1%)
Modified Rodnan Skin Score (MRSS)	6.0 (3.0, 12.0)
Distal digital tip ulcers	784 (36.2%)
Digital tip ulcers anywhere	359 (16.9%)
Telangiectasia anywhere	1473 (69.0%)
Telangiectasia on face	1004 (83.3%)
Pigment changes anywhere	664 (32.1%)
Pigment changes on face	315 (53.6%)
Tendon friction rubs	451 (23.2%)
Moderate - severe small joint contractures	541 (25.9%)
Moderate - severe large joint contractures	257 (12.5%)
Esophageal GI symptoms	1855 (85.1%)
Stomach GI symptoms	643 (30.2%)
Intestinal GI symptoms	836 (38.8%)
Interstitial lung disease	768 (35.5%)
Pulmonary arterial hypertension	186 (8.9%)

Note. n (%) reported for categorical measures; median (25th, 75th percentile) provided for time since diagnosis and MRSS scores due to skewness; mean (SD) provided for age and years of education; GI= Gastrointestinal.

Table 12 details the symptom cluster and physical function scores. The mean T-scores for anxiety, depression, fatigue, and sleep disturbance were above the mean of 50 estimated for the general U.S. population. The observed range of T-scores was 42.2 to 62.2 for anxiety, 42.0 to 60.8 for depression, 43.8 to 66.0 for fatigue, and 43.9 to 61.1 for sleep disturbance. The mean raw pain intensity score of 3.6 (range: 1 to 6.2) indicated that, on average, the patients rated their pain intensity as mild when asked "in the past 7 days, how would you rate your pain on average?" In terms of physical function, lower scores represented poorer physical function. The mean physical function T-score was 43.5 (range: 34.6 to 52.4), which was well below the mean of 50 for the general U.S. population and, therefore, indicated that, on average, adults with SSc had poorer physical function relative to the general U.S. population.

Table 12: Symptom Cluster Domains and Physical Function (N=2212)

Measure	Raw Score Mean (SD)	T-Score Mean (SD)
Symptom Cluster		
Anxiety	7.6 (3.7)	52.2 (10.0)
Depression	7.3 (3.8)	51.4 (9.4)
Fatigue	11.4 (4.7)	54.9 (11.1)
Sleep Disturbance	11.3 (3.9)	52.5 (8.6)
Pain Intensity	3.6 (2.6)	---
Functional Outcome		
Physical Function	15.3 (4.4)	43.5 (8.9)

Note. SD=Standard Deviation; No T-scores available for pain intensity; Anxiety, depression, fatigue, sleep disturbance, and physical function raw scores had a possible range of 4 to 20, with higher raw scores and T-scores indicating (a) greater anxiety, depression, fatigue, and sleep disturbance and (b) better physical function; Pain intensity possible range was 0 to 10, with higher scores representing greater pain intensity. The mean pain intensity when converted to 0 to 100 scale was 36.0 (SD=26.0).

4.3.2 Identification of the Latent Classes

Five distinct latent classes were identified. Each latent class represented a subgroup of adults with SSc who shared common symptom experiences with anxiety, depression, fatigue, sleep disturbance, and pain intensity. Table 13 presents the model fit indices, entropy level, and the smallest sample size for the eight LPA models tested. Model fit differed based on the number of classes specified for the LPA model. The five-class model was selected because it had lower fit indices than the 2-, 3-, and 4-class models, higher entropy than the 6-class model, contained at least 5% of the total sample in the smallest class sample, and yielded clinically meaningful classes.

Table 13: Latent Profile Analysis (LPA): Model Fit Information for the Number of Specified Latent Classes

Classes	Number of Parameters	Log-likelihood	AIC	BIC	ssBIC	Entropy	VLMR	BLRT	Size of smallest class (n, %)
2	16	-41329.445	82690.890	82782.117	82731.282	0.831	p=0.0000	p=0.0000	992 (44.9%)
3	22	-40907.162	81858.325	81983.761	81913.864	0.819	p=0.0008	p=0.0000	446 (20.2%)
4	28	-40630.925	81317.849	81477.496	81388.535	0.802	p=0.0003	p=0.0000	330 (14.9%)
5	34	-40370.683	80809.366	81003.222	80895.199	0.885	p=0.0000	p=0.0000	195 (8.8%)
6	40	-40235.250	80550.500	80778.566	80651.480	0.863	p=0.0002	p=0.0000	188 (8.5%)
7	46	-39869.354	79830.707	80092.983	79946.834	0.923	p=0.0000	p=0.0000	19 (0.9%)
8	52	-39741.213	79586.426	79882.912	79717.700	0.906	p=0.0061	p=0.0000	19 (0.9%)

Note. AIC=Akaike Information Criteria; BIC=Bayesian Information Criteria; BLRT=parametric Bootstrapped Likelihood Ratio Test; ssBIC=sample size adjusted Bayesian Information Criteria; VLMR=Vuong-Lo-Mendell-Rubin Likelihood Ratio test.

Table 14 provides an overview of the five classes and their symptom scores. Latent classes were labeled based on their T-score means and standard deviations (SD) using the following scores as a guide for anxiety, depression, fatigue, and sleep disturbance: 50 = normal to mildly symptomatic, 60 = mildly to moderately symptomatic, 70 = moderately to severely symptomatic (Cella et al., 2010). Pain intensity was interpreted using the following scores: ≤ 40 (mild pain), 40.1-70 (moderate pain), and >70 (severe pain).

Table 14: Latent Classes and Their Symptom Scores (N=2212)

Symptoms	5 Latent Classes Mean (SD)				
	Class 1 (*N* = 565, 25.5%)	Class 2 (*N* = 234, 10.6%)	Class 3 (*N* = 651, 29.4%)	Class 4 (*N* = 569, 25.7%)	Class 5 (*N* = 193, 8.7%)
Anxiety	42.7 (4.9)	47.0 (7.3)	50.8 (6.9)	60.1 (5.4)	67.7 (5.7)
Depression	41.1 (0.8)	41.0 (0.0)	52.0 (2.7)	59.4 (2.8)	69.0 (3.9)
Fatigue	43.3 (7.5)	59.1 (7.3)	53.9 (8.6)	61.7 (7.8)	66.9 (6.6)
Sleep Disturbance	46.3 (7.2)	54.7 (7.6)	51.3 (7.8)	56.1 (7.0)	60.7 (7.2)
Pain Intensity	14.5 (15.2)	49.7 (20.2)	31.2 (22.0)	49.9 (23.1)	63.1 (21.1)
Descriptor	No/Minimal	Fatigue/Sleep/Pain	Mild	Moderate	Severe
Clinical Interpretation	-No/minimal anxiety -No/minimal depression -No/minimal fatigue -No/minimal sleep -Mild pain	-No/minimal anxiety -No/minimal depression -Moderate fatigue -Mild sleep -Moderate pain	-Mild anxiety -Mild depression -Mild fatigue -Mild sleep -Mild pain	-Moderate anxiety -Moderate depression -Moderate fatigue -Moderate sleep -Moderate pain	-Severe anxiety -Severe depression -Severe fatigue -Severe sleep -Moderate pain

Note: SD= Standard Deviation; Sleep=sleep disturbance; Each class (subgroup) is summarized based on the mean score for each symptom. For anxiety, depression, fatigue, and sleep disturbance, T-scores at or near the following scores were used to differentiate the levels of symptom severity: 50 = normal to mildly symptomatic, 60 = mildly to moderately symptomatic, 70 = moderately to severely symptomatic (Cella et al., 2010). Using the numeric cutoff scores ≤ 4 (mild), 5-7 (moderate), and >7 (severe) that have been used to measure pain severity in SSc (Schieir et al., 2010), the following pain scores on a 0-100 scale were interpreted as such: ≤ 40 (mild pain), 40.1-70 (moderate pain), and >70 (severe pain).

Figure 6 displays the mean symptom scores for each class in relationship to the

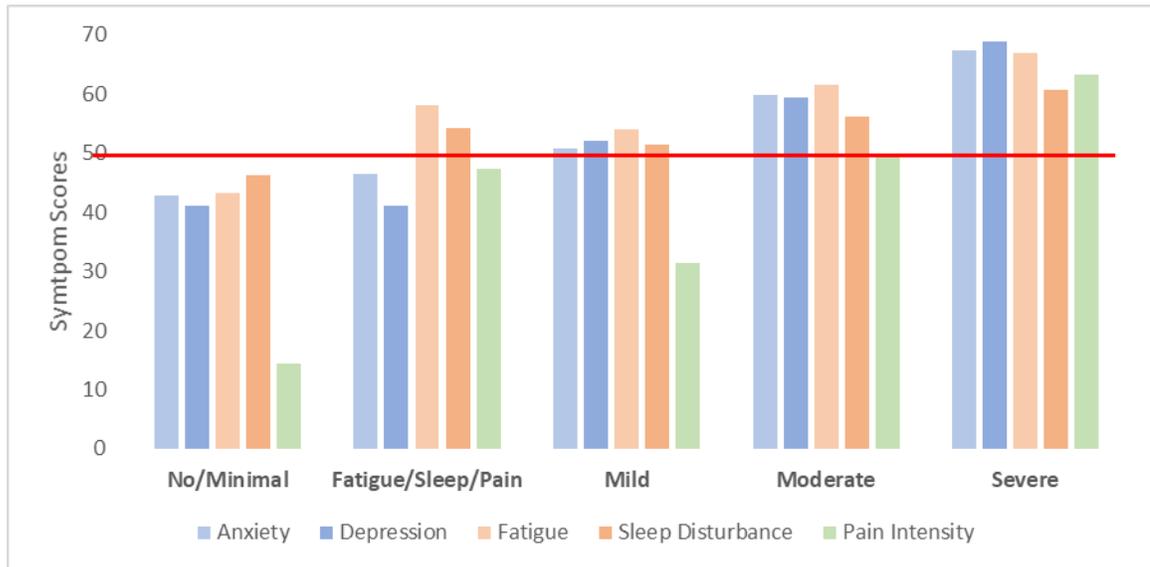mean T-score for the U.S. general population.

Figure 6: Symptom Scores in Comparison to the General U.S. Population

Note. The red line indicates a T-score of 50, which is the mean score of the general U.S. population for anxiety, depression, fatigue, and sleep disturbance.

Class 1 (25.5%, *N*=565), labeled the "no/minimal" symptom class, was

characterized by T-scores that were notably lower than the mean of the general U.S.

population (T-score ≤ 50) for anxiety, depression, fatigue, and sleep disturbance, as well

as a pain intensity score that was mild (≤ 40). Class 2 (10.6%, *N*=234), labeled the

"fatigue/sleep/pain" symptom class, was characterized by moderate fatigue, mild sleep

disturbance, moderate pain, and no/minimal anxiety and depression. Class 3 (29.4%,

N=651), labeled the "mild" symptom class, was the largest class and was characterized

by mild anxiety, depression, fatigue, sleep disturbance, and pain, with T-scores similar

in severity to that of the general U.S. population (at or near 50). Class 4 (25.7%, *N*=569), labeled the "moderate" symptom class was characterized by moderate levels of all symptoms and Class 5 (8.7%, *N*=193), the "severe" symptom class, included those who reported the most severe levels of all five symptoms.

4.3.3 Latent Class Comparisons of Individual Characteristics

Tables 15 and 16 present the results of bivariate analysis testing for latent class differences in each individual characteristic. The latent classes significantly differed in 12 characteristics (four demographic and eight clinical): age, years of education, white race/ethnicity, married/living with a partner, diffuse SSc subset, digital tip ulcers, tendon friction rubs, moderate to severe small joint contractures, moderate to severe large joint contractures, esophageal GI symptoms, stomach GI symptoms, and intestinal GI symptoms.

Table 15: Latent Class Differences in Patient Demographic Characteristics: Bivariate Relationships (N=2212)

Characteristics	Total N	Class 1 (No/Minimal)	Class 2 (Fatigue/Sleep/Pain)	Class 3 (Mild)	Class 4 (Moderate)	Class 5 (Severe)	p-value	*A posteriori* Pairwise Contrasts
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Age, in years	2212	56.6 $\pm$ 0.5	55.1 $\pm$ 0.8	55.5 $\pm$ 0.5	53.2 $\pm$ 0.5	51.0 $\pm$ 0.9	**<.0001**	(1=2=3) > 4 > 5
Years of education	2208	15.1 $\pm$ 0.1	14.8 $\pm$ 0.2	15.0 $\pm$ 0.1	14.6 $\pm$ 0.1	14.2 $\pm$ 0.2	**0.0017**	(1=3) > (4=5)
		n (%)	n (%)	n (%)	n (%)	n (%)		
Female gender	2212	482 (85.3)	208 (88.9)	569 (87.4)	507 (89.1)	173 (89.6)	0.2828	
White race/ethnicity	2210	490 (86.7)	198 (84.2)	535 (82.4)	459 (80.7)	153 (79.3)	**0.0400**	1 > (3=4=5)
Black race/ethnicity	2210	28 (5.0)	17 (7.3)	41 (6.3)	43 (7.6)	15 (7.8)	0.4022	
Married/living with partner	2212	422 (74.7)	162 (69.2)	472 (72.5)	388 (68.2)	126 (65.3)	**0.0397**	1 > (4=5); 3 > 5

Note: One-way ANOVAs using General Linear Models to test for latent class differences in means for continuous characteristics; 5 x 2 chi-square tests employed to compare latent class differences in proportions for categorical characteristics. For significant effects of latent class, <u>statistically significant</u> pairwise contrasts at the 0.05 level are indicated by the > or < signs. The sign = indicates the classes in the parentheses ( ) did not significantly differ.

Table 16: Latent Class Differences in Patient Clinical Characteristics: Bivariate Relationships (N=2212)

Characteristics	Total N	Class 1 (No/Minimal)	Class 2 (Fatigue/Sleep/Pain)	Class 3 (Mild)	Class 4 (Moderate)	Class 5 (Severe)	p-value	*A posteriori* Pairwise Contrasts
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Time since diagnosis, in years	2129	9.8 $\pm$ 0.3	10.4 $\pm$ 0.5	9.3 $\pm$ 0.3	8.9 $\pm$ 0.4	8.8 $\pm$ 0.6	---	
Time since diagnosis, in year (log)	2129	2.1 $\pm$ 0.8	2.1 $\pm$ 0.9	2.0 $\pm$ 0.8	2.0 $\pm$ 0.9	2.0 $\pm$ 0.8	0.1153	
		n (%)	n (%)	n (%)	n (%)	n (%)		
Diffuse	2190	197 (35.1)	83 (35.6)	260 (40.2)	228 (40.6)	88 (46.8)	**0.0329**	5 > (1=2)
Distal digital tip ulcers	2168	198 (35.6)	80 (34.9)	217 (34.2)	215 (38.5)	74 (39.2)	0.5118	
Digital tip ulcers anywhere	2123	73 (13.5)	44 (19.5)	95 (15.2)	101 (18.5)	46 (24.7)	**0.0033**	(2=4=5) > 1; 5 > 3
Tendon friction rubs	1946	87 (16.7)	61 (30.1)	139 (24.2)	118 (23.9)	46 (29.9)	**0.0002**	(2=3=4=5) > 1
Moderate-severe small joint contractures	2092	104 (19.3)	61 (28.2)	145 (23.5)	164 (30.4)	67 (37.2)	**<.0001**	(2=4=5) > 1; (4=5) > (1=3)
Moderate-severe large joint contractures	2049	50 (9.5)	30 (14.0)	72 (11.8)	69 (13.1)	36 (20.7)	**0.0033**	5 > (1=3=4)
Esophageal GI symptoms	2181	439 (78.1)	208 (90.0)	543 (84.6)	489 (87.8)	176 (93.1)	**<.0001**	(2=4) > 1; 5 > 3 > 1; (2=5) > 4; 2 > (3=4)
Stomach GI symptoms	2130	116 (21.4)	76 (33.3)	79 (28.5)	200 (36.8)	72 (38.5)	**<.0001**	(2, 3, 4, 5) > 1; (4=5) > 3
Intestinal symptoms	2156	152 (27.8)	109 (47.2)	236 (37.0)	249 (45.0)	90 (47.9)	**<.0001**	(2,3,4,5) > 1; (2=4=5) > 3

Note: One-way ANOVAs using General Linear Models to test for latent class differences in means for continuous characteristics; 5 x 2 chi-square tests employed to compare latent class differences in proportions for categorical characteristics. For significant effects of latent class, statistically significant pairwise contrasts at the 0.05 level are indicated by the > or < signs. The sign = indicates the classes in the parentheses ( ) did not significantly differ. GI=Gastrointestinal.

Table 17 provides an overview of the key significant differences in individual characteristics between the latent classes.

Table 17: Summary of Significant Latent Class Differences in Individual Characteristics

Characteristics	Class 1 (No/Minimal)	Class 2 (Fatigue/Sleep/Pain)	Class 3 (Mild)	Class 4 (Moderate)	Class 5 (Severe)
Demographic					
Younger in age				√	√√
More years of education	√		√		
White race/ethnicity	√				
Married/living with partner	√		√		
Clinical					
Diffuse subset					√
Digital tip ulcers anywhere		√		√	√
Tendon friction rubs		√	√	√	√
Moderate-severe small joint contractures		√		√	√
Moderate-severe large joint contractures					√
Esophageal GI symptoms		√			√
Stomach GI symptoms		√	√	√	√
Intestinal GI symptoms		√√	√	√√	√√

Note. √ indicates a significant latent class difference in the patient characteristic ($p \leq 0.05$) from those without a check mark (√); √√ represents a significant difference from those without a check mark *and* those with a single check mark; GI= Gastrointestinal.

The "no/minimal" symptom class was comprised of relatively older adults with more years of education who were primarily white and married/living with a partner, and had a lower proportion of SSc clinical characteristics. The "fatigue/sleep/pain" symptom class included relatively older adults and was similar to other classes in terms of other demographic characteristics. Notably, the "fatigue/sleep/pain" symptom class

had a greater proportion of patients with many (six) clinical characteristics compared to the "no/minimal" symptom class, including a particularly high percent of patients with GI symptoms of the esophagus, stomach, and intestine. The "mild" symptom class was similar to the "no/minimal" symptom class in that patients were relatively older with more years of education and married/living with a partner. This class had fewer (three) clinical characteristics than the "fatigue/sleep/pain" symptom class. The "moderate" symptom class was comprised of relatively younger adults and had a higher proportion of adults with many (five) clinical characteristics, particularly GI symptoms of the stomach and intestine. The "severe" symptom class included the youngest patients and had a high proportion of patients with all (eight) clinical characteristics.

4.3.4 Latent Class Relationship to Functional Outcome

Tables 18 and 19 present the one-way ANOVA and ANCOVA results of the latent classes to physical function. For the ANCOVA, the 12 individual characteristics for which significant latent class differences were demonstrated at the 0.05 level in the above analysis were included as covariates (see Table 17). The ANOVA and ANCOVA results both indicated a significant effect of latent class on physical function T-scores (both $p < 0.0001$), with pairwise contrasts showing that all five classes significantly differed from each other in terms of least squares adjusted means for the physical function T-scores (Table 19, all $p \leq 0.05$). The adjusted means for the physical function T-scores revealed that the "no/minimal" symptom class had the highest adjusted mean

(better physical function) and the "severe" symptom class had the lowest adjusted mean (poorer physical function). Adjusted means arranged from highest to lowest were as follows: "no/minimal", "mild", "fatigue/sleep/pain", "moderate", and "severe." Of note, the adjusted mean physical function T-score for the "no/minimal" symptom class was close to 50 which is similar to the mean T-score for the general U.S. population. The eta-squared of 0.27 for the ANOVA and partial eta-squared of 0.23 for the ANCOVA indicated a very large effect size (large effect=0.14 or greater) with regard to the amount of variability in physical function explained by the latent class variable.

Table 18: Physical Function Outcome: ANOVA and ANCOVA Results

Explanatory Variables	N	F	df, df	p-value	Partial η²	Partial η² 95% CI
Analysis of Variance (ANOVA)	2212					
Latent class (subgroup)		198.96	4, 2207	**<0.0001**	0.27	0.23, 0.29
Analysis of Covariance (ANCOVA)	1815					
Latent class (subgroup)		135.83	4, 1798	**<.0001**	0.23	0.20, 0.26
Age, in years		50.67	1, 1798	**<.0001**	0.03	0.01, 0.04
Years of education		1.65	1, 1798	0.1997	0.00	0.00, 0.01
White race/ethnicity		2.73	1, 1798	0.0984	0.00	0.00, 0.01
Married/living with partner		1.28	1, 1798	0.2573	0.00	0.00, 0.01
Diffuse		16.76	1, 1798	**<.0001**	0.01	0.00, 0.02
Distal digital ulcers anywhere		1.26	1, 1798	0.2615	0.00	0.00, 0.01
Tendon friction rubs		0.68	1, 1798	0.4114	0.00	0.00, 0.00
Moderate-severe small joint contractures		11.65	1, 1798	**0.0007**	0.01	0.00, 0.02
Moderate-severe large joint contractures		8.28	1, 1798	**0.0040**	0.00	0.00, 0.01
Esophageal GI symptoms		9.04	1, 1798	**0.0027**	0.01	0.00, 0.13
Stomach GI symptoms		12.81	1, 1798	**0.0004**	0.01	0.00, 0.02
Intestinal GI symptoms		4.44	1, 1798	**0.0353**	0.00	0.00, 0.01

Note: η²=eta-squared effect size; Partial η²=partial eta-squared effect size; cutoff for η² and Partial η²: 0.01= small, 0.06=medium, and 0.14=large effects; CI = Confidence Interval; ANOVA and ANCOVA using General Linear Model; Type III Sum of Squares reported for ANCOVA; The η² for the ANOVA was 0.27 (95% CI=0.23, 0.29); The η² for the ANCOVA was 0.33 (95% CI=0.29, 0.36); GI= Gastrointestinal.

Table 19: ANOVA and ANCOVA Results: Latent Class Subgroup and Physical Function T-score Outcome

Analytic Model	Class 1 (No/Minimal)	Class 2 (Fatigue/Sleep/Pain)	Class 3 (Mild)	Class 4 (Moderate)	Class 5 (Severe)	*A posteriori* Pairwise Contrasts
Analysis of Variance (ANOVA)						
N	2212	2212	2212	2212	2212	
Adjusted Mean	50.35	41.34	43.95	39.72	35.92	1 > 3 > 2 > 4 > 5
95% CI for Adjusted Mean	(49.71, 50.98)	(40.36, 42.33)	(43.36, 44.54)	(39.09, 40.35)	(34.83, 37.00)	
Analysis of Covariance (ANCOVA)						
N	1815	1815	1815	1815	1815	
Covariate-Adjusted Mean	48.16	40.06	42.23	38.30	35.38	1 > 3 > 2 > 4 > 5
95% CI for Covariate-Adjusted Mean	(47.22, 49.10)	(38.95, 41.28)	(41.33, 43.13)	(37.38, 39.22)	(34.01, 36.76)	

Note: Adjusted=Least squares mean from the ANOVA; Covariate-adjusted=least squares mean from ANCOVA after adjusting for covariates; CI=Confidence Interval; Physical function=PROMIS-29 physical function T-scores, with higher scores indicating better physical function; Significant pairwise contrasts at the 0.05 level are indicated by the > or < signs.

Among the 12 individual characteristics included as covariates, seven were significantly related to physical function (see Table 18). Specifically, patients with (1) diffuse SSc subset, (2) moderate to severe small joint contractures, (3) moderate to severe large joint contractures, (4) esophageal GI symptoms, (5) stomach GI symptoms, and (6) intestinal GI symptoms had significantly lower adjusted mean physical function T-scores when compared to those without these clinical characteristics (all $p \leq 0.05$). Table 20 provides the physical function T-scores for these significant covariates. In addition, increasing age was associated with lower mean physical function T-scores, indicating poorer physical function (unstandardized regression coefficient (b) = -0.10, standard error 0.01, p<0.0001). Interestingly, the overall eta-squared effect size for the ANCOVA model was 0.33 (95% CI=0.29, 0.36), indicating a very large effect for the latent class and the seven covariates when combined into a single model.

Table 20: ANCOVA Results: Significant Covariate Effects on Physical Function T-score Outcome

ANCOVA: Significant Covariates	Physical Function T-Scores Covariate-adjusted Mean	Physical Function T-scores 95% CI for Covariate-adjusted Mean
Diffuse subset	40.03	(39.22, 40.85)
Not diffuse subset	41.62	(40.75, 42.49)
Mod-severe small joint contractures	40.02	(39.14, 40.91)
No mod-severe small joint contractures	41.63	(40.75, 42.51)
Mod-severe large joint contractures	39.96	(38.83, 41.09)
No mod-severe small joint contractures	41.69	(40.95, 42.44)
Esophageal GI symptoms	40.09	(39.42, 40.76)
No esophageal GI symptoms	41.56	(40.49, 42.63)
Stomach GI symptoms	40.06	(39.13, 40.99)
No stomach GI symptoms	41.60	(40.81, 42.39)
Intestinal GI symptoms	40.40	(39.53, 41.27)
No intestinal GI symptoms	41.26	(40.42, 42.09)

Note: Physical function=PROMIS-29 physical function T-scores, with higher scores indicating better physical function; Covariate-adjusted=least squares mean from ANCOVA after adjusting for other variables in the model; CI=Confidence Interval; Mod=Moderate; GI=Gastrointestinal. Age relationship to physical function, after adjusting for other covariates in model: unstandardized regression coefficient=-0.10, standard error=0.01, $p<0.0001$, that is as age increases, physical function scores decrease (physical function worsens).

4.2.4.6 Statistical Power

A sample size of 2,212 adults with SSc was sufficiently large and heterogenous to accurately extract up to eight classes based on five symptoms in the prespecified symptom cluster. The recommended sample size for a LPA depends on a number of considerations, such as the number of classes expected to be extracted and the targeted margin of error (accuracy). Further, the sample size provided greater than 80% statistical power to test for latent class differences using ANOVAs with five classes and corresponding ANCOVA with 12 covariates assuming: (1) two-tailed statistical tests with a significance level set at 0.05 per test, and (2) small effects sizes for the latent class variable (partial eta-squared equivalent of 0.01).

4.4 Discussion

To our knowledge, this was the first study to identify distinct classes of patients with SSc who shared similar symptom experiences with anxiety, depression, fatigue, sleep disturbance, and pain. Interestingly, our "no/minimal" symptom class included a subgroup of patients who had notably lower levels of symptoms (i.e., T-scores $\leq$ 50) than the general U.S. population, suggesting less symptom severity than the population norm. Our findings were similar to those in rheumatoid arthritis in which the median T-scores for depression, sleep impairment, and pain intensity indicated less severe symptoms than the general U.S. population (Bartlett et al., 2015). These findings

underscore the need for further evaluation of symptom "norms" in patients with

rheumatic diseases, including SSc. One potential explanation for our finding is that

patients experience a response shift, or a change in their evaluation of their symptoms,

due to changes in their internal measurement of their symptoms (recalibration), changes

in their values (reprioritization), or reconceptualization of their symptoms (Schwartz et

al., 2007). Another potential explanation is the role that psychosocial factors such as

coping, self-efficacy, and social support have in determining how patients perceive their

symptoms and subsequently rate their symptom severity. Additional research is needed

to evaluate the influence of these psychosocial mechanisms, as well as the stability of

class membership over time to capture potential response shifts in symptoms

experienced by patients with SSc along the disease trajectory.

Interestingly, the five classes we identified in our study are similar to those

found in other chronic conditions including cancer, inflammatory bowel disease,

mothers with chronic pain, and rheumatoid arthritis. For example, Miaskowski et al.

(2006) and Pud et al. (2008) identified a "low" symptom class, "high" symptom class,

and a "high fatigue/low pain" symptom class characterized by higher levels of fatigue,

sleep disturbance, and depression with minimal pain in oncology patients. Researchers

also identified the "fatigue/sleep/pain" symptom class in patients with inflammatory

bowel disease (Conley et al., 2017), rheumatoid arthritis (Oh et al., 2019), and in breast

cancer survivors (Lee et al., 2020). Our findings highlight the similarities in symptom

experiences across chronic conditions, suggesting that individuals living with a chronic condition share similar symptom experiences with anxiety, depression, fatigue, sleep disturbance, and pain. Our study further underscores important questions regarding the underlying biological mechanisms of the symptoms included in our prespecified symptom cluster across chronic conditions. A better understanding of the underlying biological mechanisms will allow for more comprehensive assessment of symptoms using a biopsychosocial lens, and improvements in the screening and treatment of these symptoms in patients with SSc.

Our study identified important individual characteristics that place patients at higher risk for greater symptom burden and poorer physical function. In particular, patients in the "severe" symptom class were younger on average compared to the other classes and had a higher proportion of clinical characteristics such as digital ulcers, tendon friction rubs, small and large joint contractures, and GI symptoms of the esophagus, stomach, and intestine. These clinical characteristics can serve as potential targets for future symptom management interventions and should be carefully assessed by clinicians to identify patients at risk for greater symptom burden who may need additional intervention and/or referral.

Lastly, our study exemplified the synergistic effects of symptoms on patient outcomes, including physical function. In this study, we identified a "fatigue/sleep/pain" symptom class characterized by moderate fatigue, mild sleep

disturbance, and moderate pain. This class was associated with poorer physical

function, highlighting the multiplicative effects of fatigue, sleep disturbance, and pain

on physical function. Findings from this study underscore the need for person-centered

symptom management interventions targeting multiple concurrent symptoms such as

those included in our prespecified symptom cluster. Additionally, our findings provide

important insights into the types of symptom management interventions needed for

each distinct class. For example, patients in the "fatigue/sleep/pain" symptom class

might benefit from a cognitive behavioral intervention (Kwekkeboom et al., 2012)

whereas patients in the "severe" symptom class might need a multimodal intervention

that includes patient education, cognitive behavioral therapy, and/or pharmacological

treatment (Miaskowski, 2016).

4.4.1 Strengths and Limitations

Our study had several strengths, including: (1) a large sample that allowed for

the use of a statistically robust method for symptom cluster research (i.e., latent profile

analysis); (2) exploration of multiple covariates that have the potential to serve as

predictors for class membership and future targeted interventions; and (3) use of a

standardized measure (i.e., PROMIS-29) to allow for comparison of classes across

different populations. However, we used a convenience sample of patients who had

access to the internet and received specialized SSc care, thereby limiting the

generalizability of our findings. In addition, the patient-reported measure we used to capture the symptoms and our outcome was collected retrospectively which might have introduced recall bias. Lastly, this study used cross-sectional data which provided only a snapshot of a patient's symptoms at a single point in time. Future studies should consider the use of ecological momentary symptom assessments to capture symptom reports as close to real time as possible to provide a clearer picture of the complex symptom experiences.

4.5 Conclusion

This study identified five distinct classes of patients with SSc who shared similar symptom experiences with anxiety, depression, fatigue, sleep disturbance, and pain. Additionally, this study explored differences in individual characteristics that placed patients with SSc at higher risk for greater symptom burden and poorer physical function. Findings from this study provide important insights into the complex symptom experiences of patients with SSc that will help inform the development of symptom management interventions in this population. Future research is needed to evaluate the influence of biopsychosocial mechanisms on class membership and the stability of these distinct classes over time in patients with SSc.

5. Conclusion

The purpose of this dissertation was to advance the science of symptom self-management in patients with systemic sclerosis (SSc) by gaining a deeper understanding of the unique symptom experiences and their link to self-management outcomes. This dissertation uncovered new areas of research in SSc by evaluating the state of the science of self-management interventions, examining the relationship between pain and self-efficacy, and identifying subgroups of patients who shared similar symptom experiences. The results of this dissertation will serve as the foundation for my future research which will focus on the development and testing of symptom self-management interventions in patients with SSc. This chapter provides an overview of the key findings, strengths and limitations, and recommendations for future research and practice.

5.1 Synthesis of Key Findings

To better understand self-management in patients with SSc, we conducted a systematic review to evaluate the state of the science of self-management interventions in this population. We found significant variability in the types of self-management interventions, their components, and their impact on key self-management outcomes. Synthesis of and recommendations for the use of self-management interventions in patients with SSc was limited by the poor methodological quality of these studies.

Findings from this systematic review highlighted significant gaps in the literature, including the need for a better understanding of the link between the complex symptom experiences of patients with SSc and self-management outcomes. To address this critical gap, we sought to gain a deeper understanding of the relationship between symptoms experienced by those with SSc, individual characteristics, and self-management outcomes.

First, we explored pain, one of the most common and debilitating symptoms of SSc, and its relationship with self-efficacy for managing pain. We found that pain and self-efficacy trajectories remained stable across time, and pain was strongly and inversely related to self-efficacy for managing pain. These findings underscored the presence of chronic pain in this population and provided important insights into the longitudinal pain experiences of patients with SSc, including the important role self-efficacy may have in improving pain outcomes. In order to strengthen our understanding of the complex symptom experience, we explored pain and its synergistic effects with other symptoms frequently experienced by those with SSc. More specifically, we used a prespecified symptom cluster (i.e., anxiety, depression, fatigue, sleep disturbance, and pain) to identify subgroups of patients who shared similar symptom experiences. In particular, we identified a subgroup of patients at greatest risk for severe symptom burden and a unique subgroup of patients who experienced symptom burden from only fatigue, sleep disturbance, and pain. Interestingly, we found

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consistent salient clinical characteristics (i.e., the presence of finger ulcers, joint

contractures, and gastrointestinal symptoms) between our study exploring pain and

self-efficacy and our study identifying subgroups of patients with similar symptom

experiences. These findings underscore the importance of careful assessment of these

clinical characteristics to help identify those at risk for greater pain, more severe

symptom burden, and worse patient outcomes.

Our findings raised important questions into how symptoms unfold over time,

including whether the subgroups we identified would have similar trajectories to pain

given the presence of pain as a prominent symptom in these subgroups. Additionally,

our findings provided important insights into the psychosocial factors of symptoms in

SSc (i.e., pain and self-efficacy), however, further investigation of the potential

underlying biological mechanisms of these symptoms is needed. A deeper

understanding of these biological mechanisms would allow for a more comprehensive

assessment of symptoms using a biopsychosocial lens, which could lead to improved

prevention and treatment of these symptoms in patients with SSc.

5.2 Strengths and Limitations

This dissertation had many strengths including the use of one of the largest

international cohorts of patients with SSc. While our sample was reflective of the SSc

population (predominately Caucasian females), it was a convenience sample of patients

with access to the internet and specialized care for SSc, thereby limiting the generalizability of our study findings. Our studies had large samples which allowed for robust statistical methods such as a latent profile analysis, however, the use of cross-sectional data only provided a single snapshot of the symptom experience and its retrospective nature had the potential to introduce recall bias. While we used valid and reliable patient-reported measures to capture the symptoms and outcomes, the use of existing data limited our ability to capture other essential components of the symptom experience such as symptom distress, symptom perception, and symptom meaning. Additionally, high rates of missing data limited our evaluation of changes in pain beyond three years and the time between data collection points was too infrequent to capture symptom flares previously described in qualitative studies.

5.3 Recommendations for Future Research and Practice

5.3.1 Research

Findings from this dissertation provide important insights into future research needed in SSc. First, researchers should consider the use of ecological momentary assessments to capture symptom reports in real-time and to provide a deeper understanding of symptom fluctuations experienced by patients with SSc. In addition, future research should explore the stability of the subgroups we identified using a latent transition analysis given the progressive nature of SSc. These findings would help inform intervention development and delivery, including determining the type of

intervention that would be most appropriate and the best timing for delivery of the intervention.

Second, future research should further investigate the potential biological underpinnings of pain and the symptoms included in our prespecified symptom cluster (i.e., anxiety, depression, fatigue, sleep disturbance, and pain). A better understanding of the underlying mechanisms, such as biological factors, would contribute to our understanding of the biopsychosocial mechanisms of symptoms in SSc and improve the screening and treatment of symptoms associated with negative patient outcomes. In addition, the use of objective measures such as biomarkers in combination with patient-reported measures would further our understanding of the complex and dynamic symptom experiences of those with SSc.

Third, findings from this dissertation underscore the need for targeted symptom self-management interventions in patients with SSc, including interventions that focus on multiple concurrent symptoms such as those included in our prespecified symptom cluster. For example, patients in the "fatigue/sleep/pain" symptom subgroup may benefit from a cognitive behavioral intervention (Kwekkeboom et al., 2012), whereas patients in the "severe" symptom subgroup may need a multimodal intervention (i.e., patient education, cognitive behavioral therapy, and pharmacological treatment) to successfully target multiple symptoms (Miaskowski, 2016). The subgroups we identified have been described in other chronic conditions, raising important questions into

whether interventions used in other chronic conditions to reduce symptom burden would be effective for patients with SSc. In addition, future research should consider moving to a more preventative approach in which symptom self-management interventions are initiated prior to the onset of symptoms to equip patients with the necessary skills to manage their symptoms as they occur.

5.3.2 Practice and Policy

Nurses play an essential role in systematically assessing and monitoring symptoms. This dissertation reinforces the need for increased awareness and evaluation of the complex symptoms experienced by those with SSc. The integration and/or consistent collection of patient-reported measures in the electronic health record may serve as an important step to more frequent and consistent assessment of symptoms experienced by patients with SSc. In addition, the detailed assessment of all five symptoms included in our prespecified symptom cluster at routine clinic visits will help clinicians identify those at greatest risk for severe symptom burden and those in need of additional intervention and/or referral.

5.4 Conclusions

This dissertation provides important insights into our understanding of the dynamic and complex symptom experiences of those with SSc and their association with psychosocial characteristics and self-management outcomes. Findings from this

dissertation underscore the need for the development and testing of symptom self-

management interventions in this population. Future research is needed to better

understand the complex interactions among symptoms, self-management behaviors,

and the underlying biological mechanisms that influence the symptom experiences of

SSc.

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Biography

Robyn Katherine Wojeck earned her Bachelor of Science in Nursing degree from the University of Miami in 2014, a Master of Science in Nursing from Vanderbilt University in 2015, and is currently a PhD candidate at Duke University's School of Nursing. Prior to pursing her doctoral training, Robyn worked as a family nurse practitioner in multiple Level 1 Trauma Centers, as well as a registered nurse in the Emergency Department and Intensive Care Unit. During her doctoral studies, Robyn received funding from the National Institutes of Health through a Ruth L. Kirschstein F31 National Research Service Award (NRSA) to support her dissertation research and predoctoral training. She was also selected as a Jonas Nurse Scholar and received funding from the Jonas Center for Nursing Excellence to support her leadership development. In addition, Robyn was awarded pilot funding from the Duke University School of Nursing. Robyn is an active member of Sigma Theta Tau International and has presented her research nationally and internationally. Robyn is the first author on two manuscripts (one published, one under review) and the co-author of one manuscript under review:

Wojeck, R.K., Bailey, D.E., Somers, T.J., & Knisely, M.R. (2021). Self-management interventions in systemic sclerosis: A systematic review. *Research in Nursing & Health.* https://doi.org/10.1002/nur.22118

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