Factors Associated with Physical and Social Functioning among People with Systemic Sclerosis: A Set of SPIN Cohort Cross-sectional Studies

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ABSTRACT

Background: Individuals with systemic sclerosis (SSc) face many challenges that negatively impact their physical function and ability to fulfill social roles and participate in social activities. There is limited evidence on the degree to which individuals with SSc have impaired physical function compared to the general population, how satisfied they are with their abilities to successfully undertake social roles and activities, and factors associated with physical and social function. Our objectives were to (1) compare physical function levels and satisfaction with social roles and activities in a large multinational SSc cohort to general population normative data and (2) identify factors associated with these outcomes.

Methods: Participants in the Scleroderma Patient-centered Intervention Network Cohort completed the PROMIS-29v2 Physical Function and Social Roles and Activities domain questionnaires as part of their baseline cohort assessment. Multivariable linear regressions were used to assess associations of sociodemographic, lifestyle, and physician-reported disease-related variables with physical function and ability to fulfill social roles.

Results: Among 2,385 participants with a mean age of 54.9 (standard deviation [SD] 12.6) years, 87% were female, and 83% were White. The mean physical function T-score (43.7, SD = 8.9) was approximately 2/3 of a standard deviation (SD) below the US general population (mean = 50, SD = 10), whereas the mean Satisfaction with Social Roles and Activities T-score (48.1, SD = 9.9) was 1/5 of a SD below the US general population mean. Multivariable analysis factors independently associated with physical function were older age (-0.74 points per SD years, 95% CI -0.78, -1.08), female sex (-1.35 points, -2.37, -0.34), fewer years of education (-0.41 points per SD in years, -0.75, -0.07), being single, divorced, or widowed (-0.76 points, -1.48, -0.03), smoking (-3.14 points, -4.42, -1.85), alcohol consumption (0.79 points per SD drinks per week,

0.45, 1.14), body mass index (BMI; -1.41 points per SD, -1.75, -1.07), diffuse subtype (-1.43 points, -2.23, -0.62), gastrointestinal involvement (-2.58 points, -3.53, -1.62), digital ulcers (-1.96 points, -2.94, -0.98), moderate (-1.94 points, -2.94, -0.93) and severe (-1.76 points, -3.24, -0.28) small joint contractures, moderate (-2.10 points, -3.44, -0.76) and severe (-2.54 points, -4.64, -0.44) large joint contractures, interstitial lung disease (ILD; -1.52 points, -2.27, -0.77), pulmonary arterial hypertension (PAH; -3.72 points, -4.91, -2.52), rheumatoid arthritis (RA; -2.10 points, -3.64, -0.56) and idiopathic inflammatory myositis (-2.10 points, -3.63, -0.56). Multivariate analyses factors independently associated with satisfaction with social roles and activities were years of education (0.54 points per SD, 0.14, 0.93); self-reported race or ethnicity other than White (-1.13 points, -2.18, -0.08); living in Canada (-1.33 points, -2.40, -0.26) or the United Kingdom (-2.49 points, -3.92, -1.06); BMI (-1.08 points per SD, -1.47, -0.69); gastrointestinal involvement (-3.16 points, -4.27, -2.05); digital ulcers (-1.90 points, -3.05, -0.76); moderate (-1.62 points, -2.78, -0.45) or severe (-2.26 points, -3.99, -0.52) small joint contractures; ILD (-1.11 points, -1.97, -0.25); PAH (-2.69 points, -4.08, -1.30); RA (-2.51 points, -4.28, -0.73); and Sjogren's syndrome (-2.42 points, -3.96, -0.88).

Conclusion: Physical function is impaired for many individuals with SSc. This does not appear to translate to lower satisfaction with social roles and activities. Multiple disease factors were associated with both outcomes. While many people with SSc may adapt to cope with challenges inherent in living with a chronic and burdensome disease, research is needed to better understand factors that influence physical and social function and to develop strategies that target specific factors to improve function.

RÉSUMÉ

Contexte: Les personnes atteintes de sclérodermie (SSc) sont confrontées à plusieurs défis ayant un impact négatif sur leur fonction physique et leur capacité à participer à des activités sociales. Peu de données existent sur le degré d'altération de la fonction physique des personnes atteintes de SSc par rapport à la population générale, sur leur degré de satisfaction à assumer avec succès des rôles et des activités sociales, et sur les facteurs associés à la fonction physique et sociale. Nos objectifs étaient (1) de comparer les niveaux de fonction physique et de satisfaction à l'égard des activités et des rôles sociaux dans une cohorte de personnes atteintes de SSc aux données de la population générale et (2) d'identifier les facteurs associés à ces résultats.

Méthodes: Les participants à la cohorte SPIN ont rempli les questionnaires [PROMIS-29v2 Physical Function et Social Roles and Activities domains] dans le cadre de l'évaluation de base de la cohorte. Des régressions linéaires multivariables ont été utilisées pour évaluer les associations entre les variables sociodémographiques et médicales, et le mode de vie, avec la fonction physique et la capacité à remplir des rôles sociaux.

Résultats: Parmi les 2,385 participants d'un âge moyen de 54.9 ans (écart-type [ET] 12.6), 87% étaient des femmes et 83% des Blancs. Le score-t moyen de la fonction physique (43.7, ET = 8.9) était inférieur d'environ 2/3 d'un ET, tandis que le score-t moyen de la satisfaction à l'égard des activités et des rôles sociaux (48.1, ET = 9.9) était inférieur d'1/5 d'un ET, à celui de la population générale américaine (moyenne = 50, ET = 10). Les facteurs d'analyse multivariable indépendamment associés à la fonction physique étaient l'âge (-0.74 point par année ET, intervalle de confiance de 95% -0.78, -1.08), le sexe (-1.35 point, -2.37, -0.34), les années d'études (-0.41 point par année ET, -0.75, -0.07), le statut marital (-0.76 points, -1.48, -0.03), fumer (-3.14 points, -4.42, -1.85), consommer de l'alcool (0.79 points par ET boissons par

semaine, 0.45, 1.14), l'indice de masse corporelle (IMC; -1.41 points par ET, -1.75, -1.07), le sous-type (-1.43 points, -2.23, -0.62), l'atteinte gastro-intestinale (-2.58 points, -3.53, -1.62), les ulcères digitaux (-1.96 points, -2.94, -0.98), les petites contractures modérés (-1.94 points, -2.94, -0.93) et sévères (-1.76 points, -3.24, -0.28), les contractures des grosses articulations modérés (-2.10 points, -3.44, -0.76) et sévères (-2.54 points, -4.64, -0.44), la maladie pulmonaire interstitielle (-1.52 points, -2.27, -0.77), l'hypertension pulmonaire (HP; -3.72 points, -4.91, -2.52), la polyarthrite rhumatoïde (PR; -2.10 points, -3.64, -0.56) et la myosite inflammatoire idiopathique (-2.10 points, -3.63, -0.56). Les facteurs indépendamment associés à la satisfaction à l'égard des activités et des rôles sociaux étaient les années d'études (0.54 point par ET, 0.14, 0.93); la race ou l'origine ethnique (-1.13 point, -2.18, -0.08); vivre au Canada (-1.33 point, -2.40, -0.26) ou au Royaume-Uni (-2.49 points, -3.92, -1.06); l'IMC (-1,08 point par ET, -1.47, -0.69); l'atteinte gastro-intestinale (-3.16 points, -4.27, -2.05); les ulcères digitaux (-1.90 points, -3.05, -0.76); les petites contractures modérées (-1.62 points, -2.78, -0.45) ou sévères (-2.26 points, -3.99, -0.52); la maladie pulmonaire interstitielle (-1.11 points, -1.97, -0.25); l'HP (-2.69 points, -4.08, -1.30); la PR (-2.51 points, -4.28, -0.73); et le syndrome de Sjögren (-2.42 points, -3.96, -0.88).

Conclusion: La fonction physique est altérée chez de nombreuses personnes atteintes de SSc. Cela ne semble pas se traduire par une moindre satisfaction à l'égard des activités et des rôles sociaux. Des recherches sont nécessaires pour mieux comprendre les facteurs qui influencent la fonction physique et sociale, et pour développer des stratégies ciblant des facteurs spécifiques afin d'améliorer ces fonctions.

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Manuscript #2: *Factors Associated with Satisfaction with Social Roles and Activities among People with Systemic Sclerosis: A Scleroderma Patient-centered Intervention Network (SPIN) Cohort Cross-sectional Study*

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LIST OF ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
BMI	Body Mass Index
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
ILD	Interstitial Lung Disease
mRSS	Modified Rodnan Skin Score
PAH	Pulmonary Arterial Hypertension
PCS	Physical Component Summary
PRO	Patient-Reported Outcome
PROMIS-29	Patient Reported Outcomes Information System
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
SD	Standard Deviation
SPIN	Scleroderma Patient-Centered Intervention Network
SSc	Systemic Sclerosis; Scleroderma

Chapter 1

INTRODUCTION

1.1 Systemic sclerosis

Systemic sclerosis (SSc; scleroderma) is a rare, chronic, autoimmune connective tissue disease that affects the skin and multiple organ systems, including the lungs, heart, kidneys, musculoskeletal system, and gastrointestinal tract.[1] Onset typically occurs between 30 and 50 years, and approximately 85% of people with SSc are female.[1] SSc is clinically heterogeneous, but common manifestations that lead to disability and reduce quality of life include mobility limitations, respiratory problems, fatigue, gastrointestinal symptoms, pain, itch, sleep disruptions, body image distress, uncertainty and fear of disease progression, and symptoms of depression and anxiety.[2–8] There is no cure, and a primary care goal is to reduce disability and sustain quality of life.[1]

1.2 Importance of patient-reported outcomes

Patient-reported outcomes (PROs) play a crucial role in successfully understanding how well people with medical conditions are sustaining quality of life and in developing tools to support them to do this. PROs measure different aspects of an individual's health status by obtaining answers directly from them, without interpretation by a physician or any other intermediary.[9] Examples of such outcomes include rating the severity of one's headache, or describing one's ability to carry out daily activities.[9] It is therefore important to consider PROs when investigating the best ways to help sustain an individual's quality of life, as this is essentially determined by the individuals themselves.

1.3 Current evidence on functioning in SSc

Challenges faced by people living with SSc may negatively influence their ability to perform basic, fundamental tasks of daily living and participate in social activities. Both of these play a critical role determining an individual's quality of life.[10–12] Indeed, physical and social functioning in SSc appear to be impaired. A 2009 systematic review (12 studies; 1,127 participants) estimated that the physical component summary (PCS) score of the Short Form Survey-36 among people with SSc was 38 (95% confidence interval (CI) 35–42), which is 1.2 standard deviations (SDs) below the US general population mean.[13] A 2018 systematic review of studies that compared people with SSc and healthy controls (7 studies; 795 patients and 1,154 healthy controls) reported a pooled mean PCS score of 41 (95% CI 31–53) and a pooled mean social function score of 55 (95% CI 36–75) in SSc.[14] These Short Form Survey-36 subscale scores were 15 (95% CI 11–19) and 13 (95% CI 5-21) points lower than control participants, respectively.[14]

1.4 Current evidence on factors associated with functioning in SSc

Identifying factors associated with both of these outcomes would allow researchers and clinicians to develop targeted interventions and support clinical management for individuals with SSc. Some studies have examined the association of different sociodemographic or disease-related factors to either social or physical functioning[6,15–19], however, little have done so with a sample of over 300 participants, and most focus on disease-related variables, ignoring the fact that sociodemographic and lifestyle factors may also play a role in certain outcomes.

1.5 Objectives

There is limited evidence on the degree to which individuals with SSc have impaired physical function compared to the general population, how satisfied they are with their abilities to successfully undertake social roles and activities, and what sociodemographic, lifestyle, and

disease-related factors are associated with these outcomes. Our objectives were to (1) compare physical function levels in a large multinational SSc cohort to general population normative data, (2) compare satisfaction with social roles and activities in a large multinational SSc cohort to general population normative data and (3) identify factors associated with both of these outcomes. To achieve these objectives, we conducted 2 cross-sectional studies on people with SSc from our Scleroderma Patient-centered Intervention Network Cohort.

CHAPTER 2

Manuscript 1

2.1 Factors Associated with Physical Function Among People with Systemic Sclerosis: A SPIN Cohort Cross-Sectional Study - by permission of Oxford University Press

Published paper:

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Systemic sclerosis (SSc, scleroderma) is a complex, rare, chronic autoimmune disease involving microvascular damage that is characterized by fibrosis of the skin and other organs, including the lungs, gastrointestinal tract, kidneys, and heart.[1] Challenges that negatively impact health-related quality of life include disability and diminished physical function, respiratory difficulty, gastrointestinal symptoms, fatigue, pain, sleep disruptions, body image distress, uncertainty and fear of disease progression, and symptoms of depression and anxiety.[1]

Physical function is defined as the ability to perform basic, instrumental activities of daily living,[2,3] and is a key component of quality of life.[4,5] Multiple studies have reported that physical function is robustly associated with health-related quality of life in SSc.[6-9] Physical function in SSc appears to be substantially impaired. A 2009 systematic review (12 studies; 1,127 participants) estimated that the physical component summary (PCS) score of the Short Form Survey-36 among people with SSc was 38 (95% confidence interval (CI) 35 to 42), which is 1.2 standard deviations (SDs) below the US general population mean.[10] A 2018 systematic review of studies that compared people with SSc and healthy controls (7 studies; 795 patients and 1,154 healthy controls) reported a pooled mean PCS score of 41 (95% CI 31 to 53) in SSc, which was 15 points (95% CI 11 to 19 points) lower than control participants.[11]

Identifying factors associated with physical function would help us identify targets to develop interventions and support clinical management. We identified several studies that have examined factors potentially associated with physical function in SSc,[12-16] but few studies have done so with at least 200 SSc participants. One study evaluated 578 participants from the Canadian Scleroderma Research Group Registry and found that age, modified Rodnan Skin Score (mRSS), tender joints, gastrointestinal symptoms, breathing problems, pruritus, and Raynaud's phenomenon were significantly related to SF-36 PCS scores.[12] However, many key

disease-related factors were subjectively reported by patients (e.g., number of gastrointestinal symptoms, severity of breathing problems, severity of Raynaud's phenomenon), which may have magnified associations with self-reported physical function compared to objectively assessed disease status indicators.[12] Another study evaluated 492 participants from the Leiden SSc cohort and found that pulmonary arterial hypertension, Raynaud's phenomenon, mRSS, gastrointestinal symptoms and digital ulcers were statistically significantly associated to SF-36 PCS scores.[13] However, this study did not assess associations with sociodemographic or lifestyle variables, including smoking and alcohol consumption, which may also be associated with physical function in rheumatic and musculoskeletal diseases.[17]

A better understanding of physical function in SSc and associated disease manifestations would support research on approaches to disease management to improve quality of life. Our objective was to (1) compare physical function levels in a large multinational SSc cohort to general population normative data and 2) identify sociodemographic, lifestyle and SSc disease factors associated with physical function.

METHODS

This was a cross-sectional study that evaluated baseline data from the Scleroderma Patient-centered Intervention Network (SPIN) Cohort.[18–20] It was reported based on guidance in the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[21] Methods from studies that use data from the SPIN Cohort are similar. Thus, we followed reporting guidance from the Text Recycling Research Project.[22]

Participants and Procedures

The SPIN Cohort is a convenience sample of participants from 7 countries: Australia, Canada, France, Mexico, the United Kingdom, the United States, and Spain.[18–20] Eligible

participants are recruited by the attending physician or a nurse coordinator during regular physician visits. Participants included in the SPIN Cohort must be ≥18 years of age; fluent in English, French or Spanish; and classified as having SSc based on the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[23] as verified by a SPIN site physician. After obtaining written informed consent from eligible participants, onsite staff submit an online medical data form and participants receive an automated email with instructions on how to activate their online SPIN account and complete their baseline measures. SPIN Cohort participants complete subsequent online assessments every 3 months. The SPIN Cohort study was approved by the Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal (#MP-05-2013-150) and by the ethics committees of all recruiting sites. Participant recruitment is ongoing. This study used baseline assessment data from participants enrolled in the SPIN Cohort from April 2014, the date of inception, until March 2023. SPIN Cohort participants were included in this study if they completed all Patient Reported Outcomes Information System (PROMIS-29) version 2.0 domains at their baseline assessment.

Measures

SPIN Cohort participants provided sociodemographic (race or ethnicity, education level, marital status) and lifestyle (e.g., smoking status, alcohol consumption) information and completed patient-reported outcome measures. Physicians reported participants' age; sex; height; weight; years since initial onset of non-Raynaud phenomenon symptoms; SSc subtype (limited, diffuse, sine); mRSS; presence of gastrointestinal symptoms (upper; lower; or no gastrointestinal involvement); presence of digital ulcers anywhere on the fingers; presence of tendon friction rubs (currently; in the past; never); presence of small or large joint contractures (none; mild [≤

25% range of motion limitation]; moderate to severe [> 25%]); presence of pulmonary arterial hypertension; presence of interstitial lung disease; existing history of SSc renal crisis; presence of current or past overlap syndromes (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, autoimmune thyroid disease, idiopathic inflammatory myositis, and primary biliary cirrhosis); and presence of SSc-related antibodies (antinuclear antibody, anti-centromere, anti-topoisomerase I and anti-RNA polymerase III).

Physical Function

Physical function was evaluated using the 4a Short Form of the PROMIS-29 v2.0 Physical Function domain, which assesses patient-reported health status over the past 7 days.[24] Item scores are summed to give a Physical Function domain score that is converted into a T-score normalized to the United States general population (mean = 50, SD = 10).[25] A normal level of physical functioning is represented by a T-score over 45.0, mild impairment by a T-score between 40.0 to 45.0, moderate impairment between 30.0 to 39.9 and severe impairment in physical functioning by a T-score less than 30.0.[26] The PROMIS-29v2.0 has been validated within the SPIN Cohort, with Cronbach's α ranging from 0.86 to 0.96 for all PROMIS-29v2.0 domains and good convergent validity.[27]

Pruritus

Pruritus severity was evaluated with a single item: "In the past week, how severe was your itch?", with patients using a 11-point numeric rating scale (0 = not severe at all to 11 = unbearable). Similar numerical rating scales have been shown to be valid for assessing pruritus severity.[28]

Pain

Pain intensity in the last week was assessed with the PROMIS-29v2.0 using a single-item: "In the past seven days, how would you rate your pain on average?".[29,30] This item is rated on a 10-point numerical rating scale (0 = no pain to 10 = worst imaginable pain). Single- and multi-level item measurements of pain intensity have been shown to perform equivalently in individuals with SSc.[31] Pain interference in the last week was assessed with the PROMIS-29v2.0 using 4 items, each rated on a 5-point Likert scale (1 = "Not at all" and 5 = "Very much").

Statistical Analysis

We computed descriptive statistics for all variables for the entire sample and separately for those with diffuse and limited SSc (including sine) and by sex. Unadjusted outcomes were generated with simple linear regressions used to assess bivariate associations of sociodemographic, lifestyle, and disease-related variables with physical function. Adjusted outcomes were generated with multivariable linear regression used to assess the independent association of each variable with physical function. We identified items to be included in the model *a priori* based on previous studies of factors associated with physical function and other patient-reported outcomes in SSc[12-17,32–35] and on the experience of research team members who either have or provide health care for individuals with SSc. We did not include psychosocial or functional variables that are outcomes of SSc (depression symptoms, anxiety symptoms, pain, fatigue, self-efficacy) as predictors in the main model as they are likely to have bidirectional causal associations with physical function. We did this to avoid reverse causality where outcome variables may be causally associated to predictor variables, which can lead to (1) biased model coefficients, potentially masking important associations between disease variables and physical function; (2) spuriously inflated goodness-of-fit estimates (R^2); and (3) inability to determine the relative causal influence between the variables for which reverse causation is likely.[36]

Variables included in the main analysis were age (years standardized); male sex (reference = female); years of education (years standardized); single, divorced/separated, or widowed (reference = married or living as married); non-White (reference = White); Canada, United Kingdom, France, other (Australia, Mexico, Spain) (reference = United States); smoker (reference = non-smoker); alcohol consumption (drinks per week standardized); body mass index (BMI) (standardized); years since first non-Raynaud's symptoms (years standardized); diffuse subtype (reference = limited or sine); gastrointestinal involvement (reference = no); digital ulcers (reference = no); current or past tendon friction rubs (reference = never); moderate or severe small joint contractures (reference = none or mild); moderate or severe large joint contractures (reference = none or mild); history of SSc renal crisis (reference = no); interstitial lung disease (reference = no); pulmonary arterial hypertension (reference = no); systemic lupus erythematosus (reference = no); rheumatoid arthritis (reference = no); Sjogren's syndrome (reference = no); autoimmune thyroid disease (reference = no); idiopathic inflammatory myositis (reference = no); primary biliary cirrhosis (reference = no). See Supplementary Table S1 for variable specifications.

We accounted for missing data by using multiple imputation via chained equations, using the mice package in R.[37] We generated 20 imputed datasets, using 15 cycles per dataset. Variables included in the mice procedure included: all variables in the main regression model, all variables considered in sensitivity analyses, and anxiety, depression, pain intensity and interference, fatigue, sleep, and satisfaction with social roles and activities function domain scores on the PROMIS-29v2.0.

We conducted 4 multivariable sensitivity analyses. We (1) conducted a complete case analysis of the main model; (2) added pruritus and pain to the main model since the direction of

the association of pain and pruritus with physical function was hypothesized to be predominantly from pain and pruritis towards physical function; (3) replaced disease subtype with continuous mRSS; and (4) added SSc-related antibodies (antinuclear antibodies (reference = negative); anti-centromere (reference = negative); anti-topoisomerase I (reference = negative); and anti-RNA polymerase III (reference = negative)) to the main model. See Supplementary Table S1.

We standardized continuous predictor variables after imputation and prior to entering them in the models. We reported unstandardized regression coefficients with 95% CIs and total explained variance for each model (adjusted R^2). All regression analyses were conducted in R (R version 3.6.3, RStudio Version 1.2.5042).

Patient involvement

Patient members of the SPIN Steering Committee play a role in developing SPIN research priorities, including identifying the need for the present study. Five patient members of the Steering Committee reviewed and provided comments on the study protocol and manuscript and are co-authors.

RESULTS

Our sample consisted of 2,385 participants from 53 sites with baseline PROMIS-29v2.0 Physical Function domain scores. Participants were predominantly female (N= 2,079; 87%) and White (N= 1,970; 83%). Mean (SD) age was 54.9 (12.6) years, mean (SD) education was 15.0 (3.7) years, and mean (SD) BMI was 25.3 (5.6). Most participants were from the United States (N=813; 34%), France (N=713; 30%), or Canada (N=515; 22%). Mean (SD) time in years since onset of first non-Raynaud's symptoms was 10.9 (8.8), and 904 (38%) participants had diffuse SSc. Table 1 shows participant sociodemographic and disease characteristics by sex. See Supplementary Table S2 for participant characteristics.

The mean (SD) physical function score in the full sample was 43.7 (8.9), which is considerably lower than the United States general population mean (SD) of 50 (10). Figure 1 (see also Supplementary Table S3) shows mean physical function scores by months since enrollment in the SPIN Cohort. Among all participants, 1,005 (42%) had physical function scores within normal limits (T-score > 45); 508 (21%) reported mild impairment (T-score 40 to 45), 787 (33%) moderate impairment (T-score 30 to 39.9); and 85 (4%) severe impairment (T-score < 30). By country, mean (SD) scores ranged from 41.8 (9.9) among 241 participants from the UK to 45.5 (8.4) in 101 participants from Australia, Mexico, or Spain. Participants with diffuse SSc reported somewhat lower mean (SD) physical function scores (42.0 [8.4]) than those with limited or sine SSc (44.8 [8.9]). Scores for females and males were similar. See Figures 2 and 3, and Supplementary Table S4.

In the main multivariable analysis (Table 2), among sociodemographic variables, older age (-0.74 points per SD in years, 95% CI -0.78 to -1.08); female sex (-1.35 points, 95% CI -2.37 to -0.34); fewer years of education (-0.41 points per SD in years, 95% CI -0.75 to -0.07); and being single, divorced or separated, or widowed (-0.76 points, 95% CI -1.48 to -0.03) were associated with lower physical function. Among lifestyle variables, there were significant associations with smoking (-3.14 points, 95% CI -4.42 to -1.85), alcohol consumption (0.79 points per SD in drinks per week, 95% CI 0.45 to 1.14), and BMI (-1.41 points per SD in BMI, 95% CI -1.75 to -1.07). Among disease variables, there were significant associations with diffuse subtype (-1.43 points, 95% CI -2.23 to -0.62), gastrointestinal involvement (-2.58 points, 95% CI -3.53 to -1.62), digital ulcers (-1.96 points, 95% CI -2.94 to -0.98), moderate (-1.94 points, 95% CI -2.94 to -0.93) and severe (-1.76 points, 95% CI -3.24 to -0.28) small joint contractures, moderate (-2.10 points, 95% CI -3.44 to -0.76) and severe (-2.54 points, 95% CI -4.64 to -0.44)

large joint contractures, interstitial lung disease (-1.52 points, 95% CI -2.27 to -0.77), and pulmonary arterial hypertension (-3.72 points, 95% CI -4.91 to -2.52). Among overlap syndromes, rheumatoid arthritis (-2.10 points, 95% CI -3.64 to -0.56) and idiopathic inflammatory myositis (-2.10 points, 95% CI -3.63 to -0.56) were significantly associated. Variables not significantly associated were race or ethnicity, country, years since first non-Raynaud's syndrome, presence of current or past tendon friction rubs, history of SSc renal crisis, systemic lupus erythematosus, Sjogren's syndrome, autoimmune thyroid disease, and primary biliary cirrhosis. Adjusted R^2 for the final model was 0.17.

In sensitivity analyses, complete case analysis results, which included 1,663 participants, were similar to those of main analyses (see Supplementary Table S5). When adding pruritus and pain intensity to the model, both pruritus (-0.68 points per SD in pruritus, 95% CI -1.00 to -0.37) and pain intensity (-4.55 points per SD in pain intensity, 95% CI -4.87 to -4.24) were associated with lower physical function. In the analysis that used mRSS instead of disease subtype, mRSS was significantly associated with worse physical function (-0.99 points per SD in mRSS score, 95% CI -1.41 to -0.58). Lastly, when adding SSc-related antibodies to the model, we found Anti-topoisomerase I [Scl70] (positive) to have a significant association (0.96 points, 95% CI 0.04 to 1.89). No results from other variables changed substantively in sensitivity analyses. See Supplementary Tables S6 to S8.

DISCUSSION

Among 2,385 participants with SSc from 7 countries, the mean T-score for physical function was 43.7, which is approximately 2/3 of a SD below the US general population (mean = 50, SD = 10). There were 58% of participants with mild (21%), moderate (33%), or severely impaired (4%) physical function. We found that disease variables associated with worse physical

function included diffuse SSc subtype or mRSS, gastrointestinal involvement, digital ulcers, the presence of moderate or severe small or large joint contractures, interstitial lung disease, pulmonary arterial hypertension, and the presence of overlap syndromes including rheumatoid arthritis and idiopathic inflammatory myositis. These factors may influence physical function via pain, mobility limitations, fatigue and breathlessness, or other pathways. We also found that older age; female sex; fewer years of education; being single, divorced/separated, or widowed; smoking; fewer alcoholic drinks per week; and increased BMI were associated with worse physical function.

We assessed pain separately, in a sensitivity analysis, due to overlap that may occur in measuring pain and physical function. We found that pain likely plays an important role in an individual's ability to complete physical tasks. More specifically, we found that pain was strongly negatively associated with physical function (-4.55 points per SD in pain intensity, 95% CI -4.87 to -4.24). This finding is consistent with results from a previous SPIN study on pain intensity and interference in SSc (N = 2,157), which found that 38% of participants reported moderate or severe pain intensity, and 35% reported moderate or severe pain interference with their ability to carry out daily activities.[38]

Our findings on physical function are generally consistent with two prior studies including the next largest study of people with SSc and a large study of people with other rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus.[8,39] A study of 477 Australian patients with SSc reported a mean (SD) on the PROMIS-29v1 Physical Function domain of 41.9 (8.6).[8] The study of 4,346 participants with rheumatoid arthritis and 240 with systemic lupus erythematosus reported PROMIS-29 Physical Function domain means (SD) of 42.0 (9.1) for rheumatoid arthritis, and 43.9 (9.7) for systemic lupus erythametosus.[39] No

previous study has examined the association of a large number of physician-assessed SSc disease manifestations with physical function, as we did in the present study. The long list of disease factors that we found to be associated with lower physical function highlights the many challenges faced by people with SSc. SSc is a highly heterogeneous disease, but several key factors that are commonly experienced, including diffuse disease subtype, gastrointestinal involvement, and interstitial lung disease, were robustly associated with physical function.

The adjusted R^2 for our main multivariable regression model was 0.17. This may appear low, but it is expected in samples comprised entirely of people with a chronic condition as all have the similar experience of living with the condition. High R^2 values are important in predictive modelling, but much less so when models are used for testing hypotheses about possible associations of variables of interest with critical patient-important outcomes. In this case, including in the present study, having a sufficiently large sample size to generate reasonably precise parameter estimates is a more important consideration.[36]

Management strategies and interventions to address the high level of impairment in physical function in SSc are needed. A 2019 systematic review on the effect and safety of exercise therapy in patients with SSc only found 4 randomized controlled trials (RCTs), all with small samples (maximum N per trial arm = 16), and concluded that there was sparse evidence that could not be used to draw strong conclusions on effectiveness.[40] A 2017 RCT (N = 220) compared a 1-month personalized physical therapy program involving trained physiotherapists and occupational therapist to usual care in patients with SSc and reported short-term effects on disability but minimal positive long-term outcomes.[41]

Self-management programs are commonly used to help people more effectively manage their disease in arthritis[42] and other common chronic conditions.[43] In SSc, an RCT (N = 267)

tested the effects of a self-administered internet-based self-management program in comparison to an educational booklet on improving self-efficacy for disease management but did not find the intervention to be statistically superior to control.[44] Currently, SPIN is conducting a trial to compare the SPIN-SELF program, a self-management program that provides patients with essential knowledge and coping skills to help better manage day-to-day problems in SSc, to usual care.[45] This program combines self-management modules with expert and patient instructions delivered online with support from peer-led groups.[45] Self-management programs aim to address impairments in physical function by teaching skills to better cope with pain or gastrointestinal symptoms or to partner more effectively with health care providers.

Strengths of our study include its large international sample with participants from 53 SPIN sites across 7 countries; the inclusion of a large number of sociodemographic, lifestyle, and physician-assessed disease-related factors in analyses; and the involvement of people with lived SSc experience in the project via leadership in SPIN and participation in the study. There are also limitations to consider. First, the SPIN Cohort is a convenience sample. However, a comparison with the European Scleroderma Trials and Research and Canadian Scleroderma Research Group cohorts indicated broad comparability of participant characteristics, which supports generalizability in SSc.[18] Second, participants were required to answer questions via online questionnaires, which may potentially reduce generalizability of results. Third, our study was cross-sectional, which does not allow us to infer causality based on our results.

In summary, we found that physical function in patients with SSc is substantially impaired on average and that many factors likely contribute to this. SSc disease manifestations associated with lower physical function included disease subtype and skin score, gastrointestinal involvement, digital ulcers, small or large joint contractures, interstitial lung disease, pulmonary

arterial hypertension, rheumatoid arthritis, idiopathic inflammatory myositis, as well as pruritus and pain intensity, and anti-topoisomerase I [Scl70]. Many of these had strong associations with physical function such as smoking, GI involvement, large joint contractures, pulmonary arterial hypertension, rheumatoid arthritis, and idiopathic inflammatory myositis. More studies are needed to better understand the role each of these factors play in physical function, to develop strategies that target specific factors to improve function, and to inform healthcare providers on specific actions they can take when identifying these factors. Future studies should additionally look at associations longitudinally. Meanwhile, health-care providers should work with patients to identify and address SSc-related factors that are associated with limitations in physical function and help them find ways to cope with the disease and its symptoms.

Contributions: TDS, DBR, MEC, BL, LK, MCG, AB, BDT contributed to study conceptualization; GVG, BL, MG to data curation; TDS, GVG, BL to formal analysis; TDS, MEC, LK, BDT to funding acquisition; TDS, DBR, MEC, LK, SJB, AG, KG, GG, MH, LKH, VM, MDM, LM, MR, MS, RW, BDT to investigation; TDS, DBR, MEC, BL, LK, BDT to methodology; MEC to project administration; DBR, MCG, AB, BDT to supervision; TDS, MG to visualization; TDS, BDT to writing the original draft; and all authors reviewing and editing the final draft.

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*w*ith any organisations that might have an interest in the submitted work in the previous three years. All authors declare no other relationships or activities that could appear to have influenced the submitted work.

Data Availability: De-identified individual participant data with a data dictionary and analysis codes that were used to generate the results reported in this article will be made available upon request to the corresponding author and presentation of a methodologically sound proposal that is approved by the Scleroderma Patient-centered Intervention Network Data Access and Publications Committee. Data requesters will need to sign a data transfer agreement.

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FIGURE LEGENDS

Figure 1. Forest plot including mean physical function scores in months since enrollment in the SPIN Cohort. U.S. general population mean is represented by the dotted line. Means, standard deviations, and number of participants at each assessment are shown in Supplementary Table S3.

Figure 2. Forest plot including mean physical function scores (95% CIs) by country, disease subtype, and sex. U.S. general population mean is represented by the dotted line.

Figure 3. Bar chart including proportion of participants with physical function scores by classification by country, disease subtype, and sex.

Table 1. Sample sociodemographic and disease characteristics by sex.

	Female (N = 2,079)		Male (N = 306)	
	N[a]	Mean (SD) or N (%)	N	Mean (SD) or N (%)
Age (years)	2,075	54.5 (12.7)	306	57.2 (11.8)
Education (years)	2,073	15.0 (3.7)	304	14.5 (3.9)
Marital status	2,075		306	
Married or living as married		1,415 (68%)		246 (80%)
Single, divorced/separated, widowed		660 (32%)		60 (20%)
Race or ethnicity	2,073		306	
White		1,712 (83%)		258 (84%)
Non-white		361 (17%)		48 (16%)
Country	2,077		306	
United States		704 (34%)		109 (36%)
France		607 (29%)		106 (35%)
Canada		453 (22%)		62 (20%)
United Kingdom		219 (11%)		22 (7%)
Australia, Mexico, Spain		94 (5%)		7 (2%)
Smoking status	2,076		306	
Smoker		155 (7%)		22 (7%)
Non-smoker		1,921 (93%)		284 (93%)
Alcohol consumption (drinks per week)	2,075	1.8 (3.6)	304	3.6 (6.1)
Body mass index	2,079	25.2 (5.8)	306	25.8 (4.2)
Years since first non-Raynaud's symptoms	1,903	11.1 (8.9)	287	9.4 (7.9)
Disease subtype	2,058		302	
Diffuse		759 (37%)		145 (48%)
Limited or sine[b]		1,299 (63%)		157 (52%)
mRSS	1,723	7.5 (7.9)	260	9.0 (8.6)
Gastrointestinal involvement	2,050	1,763 (86%)	303	253 (83%)
Digital ulcers	2,001	309 (15%)	286	56 (20%)
Tendon friction rubs	1,825		275	
Current		194 (11%)		38 (14%)
Past		180 (10%)		41 (15%)
Small Joint Contractures	1,962		293	
Moderate		354 (18%)		70 (24%)
Severe		147 (7%)		21 (7%)
Large Joint Contractures	1,926		285	
Moderate		170 (9%)		30 (11%)
Severe		67 (3%)		7 (2%)
History of SSc renal crisis	2,048	84 (4%)	303	17 (6%)
Interstitial lung disease	2,034	666 (33%)	301	161 (53%)
Pulmonary arterial hypertension	1,982	172 (9%)	289	35 (12%)
Pruritus	1,885	1.8 (2.7)	269	1.5 (2.3)
Pain intensity	2,079	3.7 (2.6)	306	3.2 (2.4)
Pain interference	2,078	55.7 (9.7)	306	54.5 (9.2)
Systemic lupus erythematosus	2,027	59 (3%)	296	6 (2%)
Rheumatoid arthritis	2,026	114 (6%)	296	11(4%)
Sjogren's syndrome	1,992	163 (8%)	293	163 (8%)
Autoimmune thyroid disease	1,986	137 (7%)	291	6 (2%)
Idiopathic inflammatory myositis	2,029	101 (5%)	293	20 (7%)
Primary biliary cirrhosis	2,010	43 (2%)	291	1 (0%)
Antinuclear antibodies	1,911	1,805 (94%)	283	264 (93%)
Anti-centromere	1,625	617 (38%)	236	48 (20%)
Anti-topoisomerase I [Scl70]	1,804	474 (26%)	273	81 (30%)
Anti-RNA polymerate III	1,170	212 (18%)	183	33 (18%)

[a]N for some variables < 2,385 due to missing data. [b]Includes 73 participants with sine SSc;

Table 2. Linear regression analysis of sociodemographic and disease characteristic associations with physical function.

	Physical Function Full Sample (N = 2,385)	
	Unadjusted Regression Coefficient (95% CI)[a]	**Adjusted Regression Coefficient (95% CI)[a]**
Sociodemographic variables and body mass index (BMI)		
Age (years standardized)	**-0.47 (-0.84, -0.11)**	**-0.74 (-0.78, -1.08)**
Male sex (reference = female)	0.81 (-0.26, 1.87)	**1.35 (0.34, 2.37)**
Years of education (years standardized)	**0.72 (0.36, 1.08)**	**0.41 (0.07, 0.75)**
Single, divorced/separated, or widowed (reference = married or living as married)	**-1.22 (-1.99, -0.44)**	**-0.76 (-1.48, -0.03)**
Non-White (reference = White)	**-1.30 (-2.25, -0.36)**	-0.76 (-1.67, 0.15)
Country (reference = United States)		
Canada	0.12 (-0.86, 1.09)	-0.23 (-1.15, 0.70)
United Kingdom	**-1.80 (-3.07, -0.53)**	-1.17 (-2.41, 0.07)
France	0.62 (-0.27, 1.51)	0.68 (-0.21, 1.56)
Other (Australia, Mexico, Spain)	**1.97 (0.14, 3.80)**	1.42 (-0.29, 3.13)
Lifestyle variables and body mass index (BMI)		
Smoker (reference = non-smoker)	**-1.92 (-3.28, -0.56)**	**-3.14 (-4.42, -1.85)**
Alcohol consumption (drinks per week standardized)	**1.03 (0.67, 1.39)**	**0.79 (0.45, 1.14)**
BMI (standardized)	**-1.27 (-1.63, -0.91)**	**-1.41 (-1.75, -1.07)**
Disease variables		
Years since first non-Raynaud's symptoms (years standardized)	-0.32 (-0.69, 0.05)	-0.07 (-0.44, 0.30)
Diffuse subtype (reference = limited or sine)	**-2.80 (-3.53, -2.08)**	**-1.43 (-2.23, -0.62)**
Gastrointestinal involvement (reference = no)	**-3.45 (-4.46, -2.44)**	**-2.58 (-3.53, -1.62)**
Digital ulcers (reference = no)	**-3.55 (-4.53, -2.57)**	**-1.96 (-2.94, -0.98)**
Tendon friction rubs (reference = never)		
Current	**-2.97 (-4.14, -1.81)**	-0.79 (-1.95, 0.37)
Past	**-2.41 (-3.6, -1.23)**	-0.16 (-1.39, 1.07)
Small joint contractures (reference = none or mild)		
Moderate	**-3.50 (-4.44, -2.57)**	**-1.94 (-2.94, -0.93)**
Severe	**-4.77 (-6.12, -3.41)**	**-1.76 (-3.24, -0.28)**
Large joint contractures (reference = none or mild)		
Moderate	**-4.55 (-5.83, -3.28)**	**-2.10 (-3.44, -0.76)**
Severe	**-4.36 (-6.42, -2.30)**	**-2.54 (-4.64, -0.44)**
History of SSc renal crisis (reference = no)	**-3.38 (-5.14, -1.62)**	-0.43 (-2.11, 1.24)
Interstitial lung disease (reference = no)	**-2.77 (-3.52, -2.02)**	**-1.52 (-2.27, -0.77)**
Pulmonary arterial hypertension (reference = no)	**-5.18 (-6.42, -3.95)**	**-3.72 (-4.91, -2.52)**
Overlap syndromes		
Systemic lupus erythematosus (reference = no)	**-2.49 (-4.68, -0.29)**	-1.71 (-3.77, 0.35)
Rheumatoid arthritis (reference = no)	**-4.04 (-5.63, -2.44)**	**-2.10 (-3.64, -0.56)**
Sjogren's syndrome (reference = no)	**-2.32 (-3.72, -0.92)**	-0.86 (-2.19, 0.47)
Autoimmune thyroid disease (reference = no)	-0.70 (-2.21, 0.81)	0.06 (-1.34, 1.47)
Idiopathic inflammatory myositis (reference = no)	**-3.78 (-5.40, -2.16)**	**-2.10 (-3.63, -0.56)**

Primary biliary cirrhosis (reference = no)	0.64 (-1.99, 3.28)	0.81 (-1.64, 3.26)

[a]All regression coefficients are unstandardized. Standardized predictor variables calculated by subtracting raw scores from mean and dividing by standard deviation. Bolded results are statistically significant ($P < 0.05$). Adjusted $R^2 = 0.17$.

Figure 1

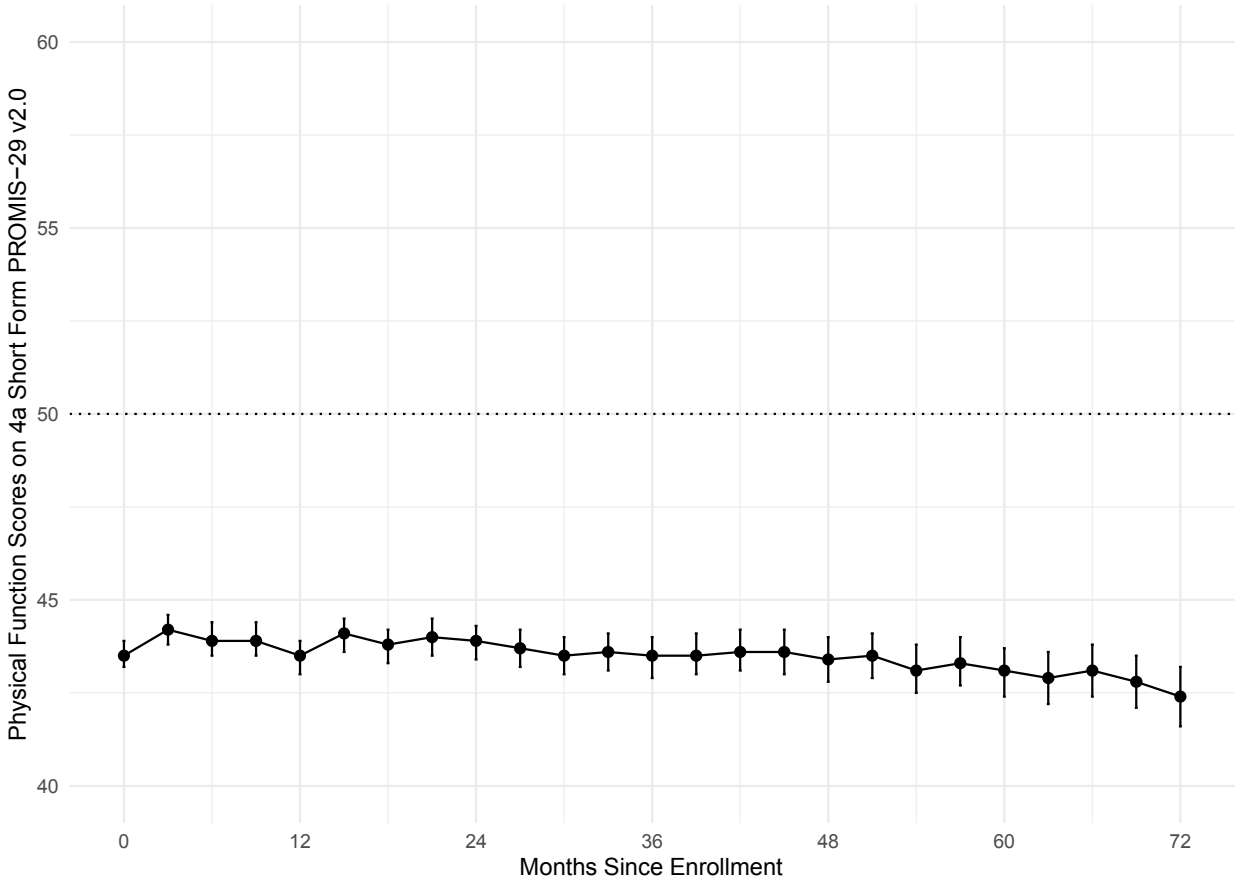

60
55
50
45
40
Physical Function Scores on 4a Short Form PROMIS−29 v2.0
0
12
24
36
48
60
72
Months Since Enrollment

Figure 2

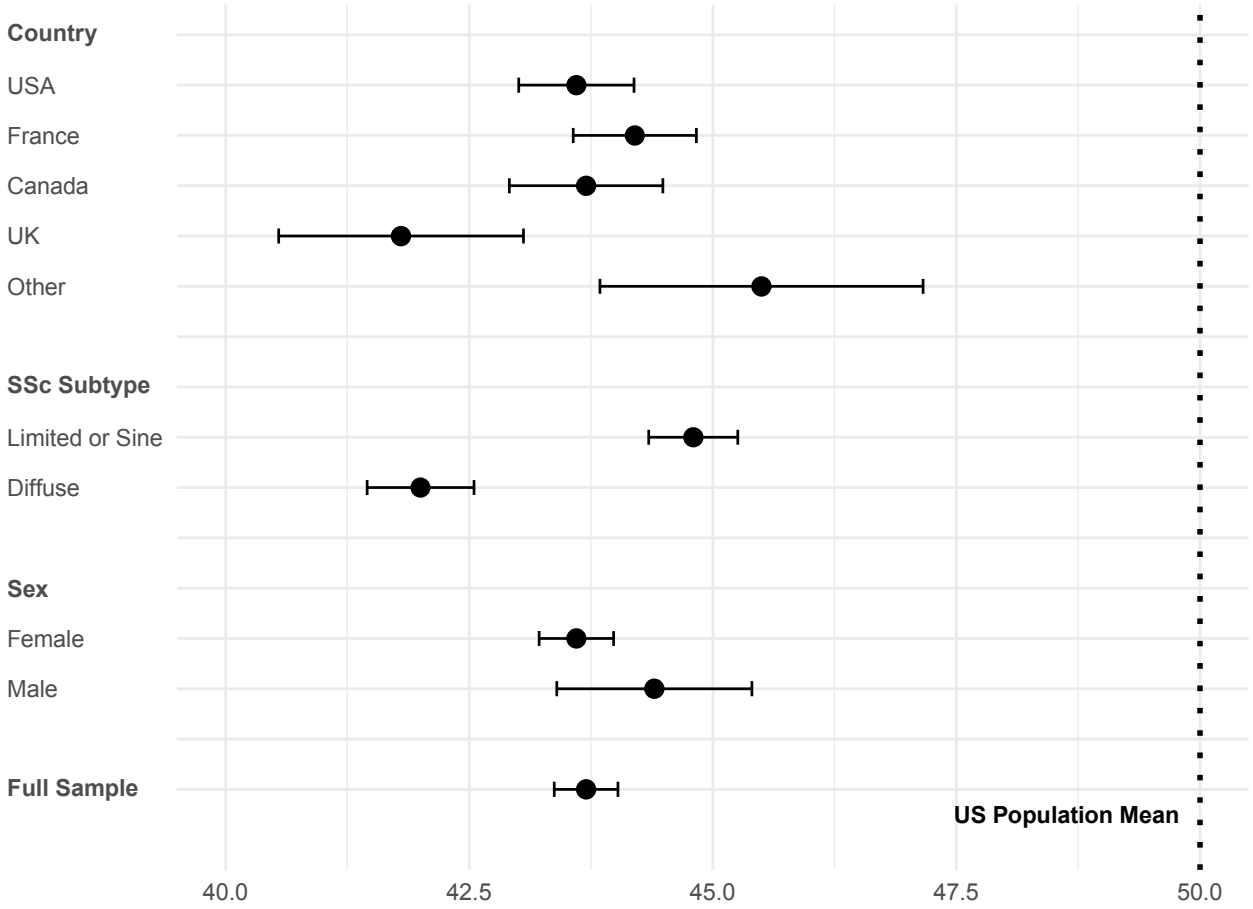
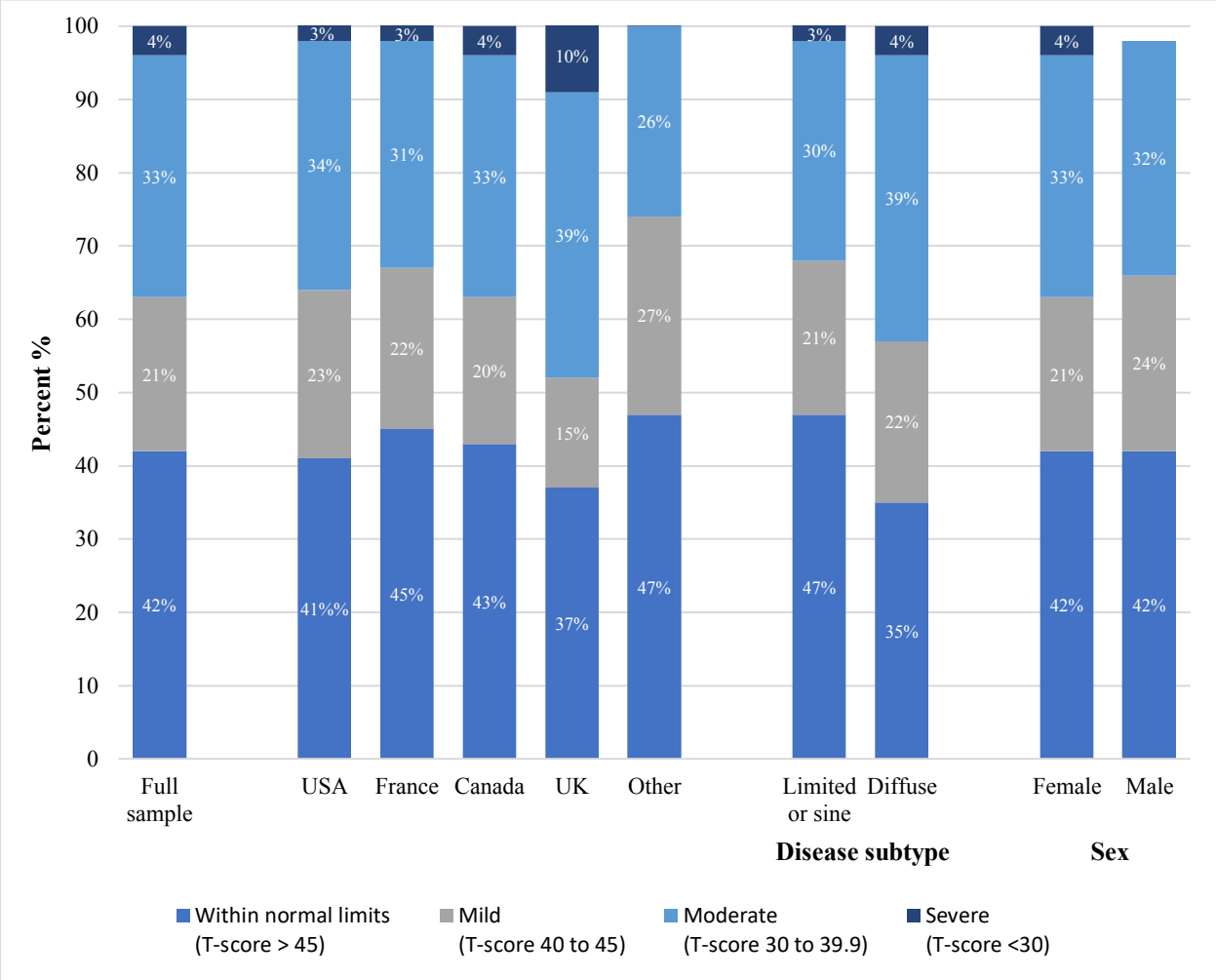

Country
USA
France
Canada
UK
Other
SSc Subtype
Limited or Sine
Diffuse
Sex
Female
Male
Full Sample
US Population Mean
40.0
42.5
45.0
47.5
50.0
4a Short Form PROMIS−29 v2.0 Mean T−Score with 95% Confidence Inter vals

Figure 3


Percent %
100
90
80
70
60
50
40
30
20
10
0
4%
33%
21%
42%
3%
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47%
3%
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4%
39%
22%
35%
4%
33%
21%
42%
32%
24%
42%
Full sample
USA
France
Canada
UK
Other
Limited or sine
Diffuse
Female
Male
Disease subtype
Sex
Within normal limits (T-score > 45)
Mild (T-score 40 to 45)
Moderate (T-score 30 to 39.9)
Severe (T-score <30)

2.2 Connecting text

Our study found that among 2,385 participants with SSc, the mean physical function T-score (SD) was 43.7 (8.9), which was approximately 2/3 of an SD below the US general population mean (SD) of 50 (10). Factors statistically significantly associated with this outcome were age, sex, years of education, marital status, smoking status, alcohol consumption, BMI, disease subtype, mRSS, gastrointestinal involvement, digital ulcers, small and large joint contractures, interstitial lung disease, pulmonary arterial hypertension, rheumatoid arthritis, idiopathic inflammatory myositis, pruritus, pain intensity, and anti-topoisomerase I [Scl70]. Our results highlight that physical function in people living with SSc seems to be substantially impaired and can be impacted by several different factors. This led us to question if impairment in physical abilities translates to a reduction in one's capacity to perform and participate in social roles and activities, and if this in turn reduces one's satisfaction with such abilities. If similar factors are found to be associated with both social and physical functioning, we can potentially identify core targets to address when developing interventions to improve the overall quality of life of people living with SSc. This information would allow us to gain a deeper understanding of how quality of life is affected in this disease, and how we can help individuals better cope with certain side effects of their disease.

Chapter 3

Manuscript 2

3.1 Factors Associated with Satisfaction with Social Roles and Activities Among People with Systemic Sclerosis: A Scleroderma Patient-centered Intervention Network (SPIN) Cohort Cross-Sectional Study

Published paper:

Dal Santo T, Rice DB, Carrier ME, et al. Factors associated with satisfaction with social roles and activities among people with systemic sclerosis: a Scleroderma Patient-centered Intervention Network (SPIN) cohort cross-sectional study. *RMD Open.* 2024;10:e003876.
doi: 10.1136/rmdopen-2023-003876

INTRODUCTION

Systemic sclerosis (SSc, scleroderma) is a chronic autoimmune disease characterized by microvascular damage and fibrosis of the skin and multiple other organs including the lungs, gastrointestinal tract, kidneys, and heart.[1] Associated challenges include pain, fatigue, disability and diminished physical function, dissatisfaction with appearance, social discomfort, fear of disease and symptom progression, and reduced mental health[1-6], all of which may negatively influence the ability to successfully fulfil social roles and participate in activities.[7]

There is limited data on how satisfied people with SSc are with their ability to successfully carry out social roles and participate in activities, but individuals with SSc may experience substantial impairment in social functioning, including limitations in the ability to work, complete personal and household responsibilities, and perform typical daily routines.[8-11] A 2018 systematic review[10] (7 studies; 795 people with SSc and 1,154 healthy controls) found a mean difference in scores on the Short Form Survey-36 social functioning subscale, which measures limitations in social activities due to physical or emotional problems, between SSc patients and healthy controls of 13 points (95% confidence interval (CI) 5 to 21 points)[10], an approximately 0.5 standardized mean difference.[12,13] Only relatively small studies with < 300 participants have examined factors associated with satisfaction with social function or participation in social roles in SSc, and these studies have included only small numbers of general SSc disease characteristics as possible factors (e.g., diffuse or limited subtype, disease duration) but not specific physician-assessed disease manifestations.[14,15]

A better understanding of satisfaction with social roles and activities among people with SSc and factors associated with satisfaction would support development of tools to improve social function and adjustment to changes in social functioning. The objectives of this study were

to (1) compare satisfaction with social roles and activities in a large multinational SSc cohort to general population normative data, and (2) identify sociodemographic, lifestyle and SSc disease factors associated with satisfaction with social roles and activities.

METHODS

This was a cross-sectional study that evaluated baseline data from the Scleroderma Patient-centered Intervention Network (SPIN) Cohort.[16-18] It was reported based on guidance in the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[19] Methods from studies that use data from the SPIN Cohort are similar. Thus, we followed reporting guidance from the Text Recycling Research Project.[20]

Participants and procedures

The SPIN Cohort is a convenience sample of participants from 7 countries: Australia, Canada, France, Mexico, the United Kingdom, the United States, and Spain.[16-18] Eligible participants are recruited by the attending physician or a nurse coordinator during regular physician visits. Participants included in the SPIN Cohort must be ≥18 years of age; fluent in English, French or Spanish; and classified as having SSc based on the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[21] as verified by a SPIN site physician. After obtaining written informed consent from eligible participants, onsite staff submit an online medical data form and participants receive an automated email with instructions on how to activate their online SPIN account and complete their baseline measures. SPIN Cohort participants are invited to complete subsequent online assessments every 3 months. The SPIN Cohort study was approved by the Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal (#MP-05-2013-150) and by the ethics committees of all recruiting sites. Participant recruitment is ongoing.

This study used baseline assessment data from participants enrolled in the SPIN Cohort from April 2014, the date of inception, until March 2023. SPIN Cohort participants were included in this study if they completed all Patient Reported Outcomes Information System (PROMIS-29) version 2.0 domains at their baseline assessment.

Measures

SPIN Cohort participants provided sociodemographic (race or ethnicity, education level, marital status) and lifestyle (e.g., smoking status, alcohol consumption) information and completed patient-reported outcome measures. Physicians reported participants' age; sex; height; weight; years since initial onset of non-Raynaud phenomenon symptoms; SSc subtype (limited, diffuse, sine); mRSS; presence of gastrointestinal symptoms (upper; lower; or no gastrointestinal involvement); presence of digital ulcers anywhere on the fingers; presence of tendon friction rubs (currently; in the past; never); presence of small or large joint contractures (none; mild [≤ 25% range of motion limitation]; moderate to severe [> 25%]); presence of pulmonary arterial hypertension; presence of interstitial lung disease; existing history of SSc renal crisis; presence of current or past overlap syndromes (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, autoimmune thyroid disease, idiopathic inflammatory myositis, and primary biliary cirrhosis); and presence of SSc-related antibodies (antinuclear antibody, anti-centromere, anti-topoisomerase I and anti-RNA polymerase III).

Satisfaction with Social Roles and Activities

Satisfaction with social roles and activities was evaluated in the SPIN Cohort using the 4a Short Form of the PROMIS-29 v2.0 Satisfaction with Social Roles and Activity domain, which assesses patient-reported health status over the past 7 days.[22] This domain measures the level of satisfaction individuals have with their ability to perform different social roles and activities such

as work inside and outside the home, personal and household responsibilities, and daily routines.[23] Satisfaction with social roles and activities is assessed with 4 items, each rated on a 5-point Likert scale. Item scores are summed to give a Satisfaction with Social Roles and Activities domain score that is converted into a T-score standardized to the United States general population (mean = 50, standard deviation (SD) = 10).[24] Normal levels of satisfaction with one's social roles and activities is represented by a T-score over 45.0, mild impairment by a T-score that ranges between 40.0 to 45.0, moderate impairment between 30.0-39.9 and severe impairment in satisfaction with social roles and activities by a T-score less than 30.0.[25] The PROMIS-29v2.0 has been validated within the SPIN Cohort, with a satisfactory Cronbach's α ranging from 0.86 to 0.96 for all PROMIS-29v2.0 domains and a good convergent validity.[26]

Pruritus

Pruritus severity was evaluated with a single item: "In the past week, how severe was your itch?", with patients using a 11-point numeric rating scale (0 = not severe at all to 11 = unbearable). Similar numerical rating scales have been shown to be valid for assessing pruritus severity.[27]

Pain

Pain intensity in the last week was assessed with the PROMIS-29v2.0 using a single-item: "In the past seven days, how would you rate your pain on average?".[28,29] This item is rated on a 10-point numerical rating scale (0 = no pain to 10 = worst imaginable pain). Single- and multi-level item measurements of pain intensity have been shown to perform equivalently in individuals with SSc.[30] Pain interference in the last week was assessed with the PROMIS-29v2.0 using 4 items, each rated on a 5-point Likert scale (1 = "Not at all" and 5 = "Very much").

Statistical Analysis

We computed descriptive statistics for all variables for the entire sample and separately for those with diffuse and limited SSc (including sine) and by sex. Unadjusted outcomes were generated with simple linear regressions used to assess bivariate associations of sociodemographic, lifestyle, and disease-related variables with satisfaction with social roles and activities. Adjusted outcomes were generated via multivariable linear regression used to assess the independent association of each variable with satisfaction with social roles and activities. We identified items to be included in the model *a priori* based on factors associated with psychosocial outcomes in SSc[4,7,31-33] and based on the experience of research team members who either have or provide health care for individuals with SSc. We did not include psychosocial or functional variables that are outcomes of SSc (depression symptoms, anxiety symptoms, pain, fatigue, self-efficacy) as predictors in the main model as they are likely to have bidirectional causal associations with social functioning. We did this to avoid reverse causality where outcome variables may be causally associated to predictor variables, which can lead to (1) biased model coefficients, potentially masking important associations between disease variables and social functioning; (2) spuriously inflated goodness-of-fit estimates (R^2); and (3) inability to determine the relative causal influence between the variables for which reverse causation is likely.[34]

Variables included in the main analysis were age (years standardized); male sex (reference = female); years of education (years standardized); single, divorced or separated, or widowed (reference = married or living as married); non-White (reference = White); Canada, United Kingdom, France, other (Australia, Mexico, Spain) (reference = United States); body mass index (BMI) (standardized); years since first non-Raynaud's symptoms (years standardized); diffuse subtype (reference = limited or sine); gastrointestinal involvement (reference = no); digital ulcers (reference = no); current or past tendon friction rubs (reference = never); moderate or severe

small joint contractures (reference = none or mild); moderate or severe large joint contractures (reference = none or mild); history of SSc renal crisis (reference = no); interstitial lung disease (reference = no); pulmonary arterial hypertension (reference = no); systemic lupus erythematosus (reference = no); rheumatoid arthritis (reference = no); Sjogren's syndrome (reference = no); autoimmune thyroid disease (reference = no); idiopathic inflammatory myositis (reference = no); primary biliary cirrhosis (reference = no). We did not include variables such as smoking status or alcohol consumption as social functioning may influence these. See online supplemental material 1 for variable specifications.

We accounted for missing data by using multiple imputation via chained equations, using the mice package in R.[35] We generated 20 imputed datasets, using 15 cycles per dataset. Variables included in the mice procedure included: all variables in the main regression model, all variables considered in sensitivity analyses, alcohol consumption and smoking status, and anxiety, depression, pain intensity and interference, fatigue, sleep, and physical function domain scores on the PROMIS-29v2.0.

We conducted 4 multivariable sensitivity analyses. We (1) conducted a complete case analysis of the main model; (2) added pruritus and pain to the main model; (3) replaced disease subtype with continuous mRSS; and (4) added SSc-related antibodies (antinuclear antibodies (reference = negative); anti-centromere (reference = negative); anti-topoisomerase I [Scl70] (reference = negative); and anti-RNA polymerase III (reference = negative)) to the main model. See online supplemental material 1.

We standardized continuous predictor variables after imputation and prior to entering them in the models. We reported unstandardized regression coefficients with 95% CIs and total

explained variance for each model (adjusted R^2). All regression analyses were conducted in R (R version 3.6.3, RStudio Version 1.2.5042).

Patient involvement

Patient members of the SPIN Steering Committee play a role in developing SPIN research priorities, including identifying the need for the present study. Five patient members of the Steering Committee reviewed and provided comments on the study protocol and manuscript and are co-authors.

RESULTS

Our sample consisted of 2,385 participants from 53 sites with baseline SPIN Cohort PROMIS-29v2.0 Satisfaction with Social Roles and Activities domain data. Participants were predominantly female (N = 2,079; 87%) and White (N= 1,970; 83%). Mean (SD) age was 54.9 (12.6) years, mean (SD) education was 15.0 (3.7) years, and mean (SD) BMI was 25.3 (5.6). Most participants were from the United States (N = 813; 34%), France (N = 713; 30%), or Canada (N = 515; 22%). Mean (SD) years since onset of first non-Raynaud's symptoms was 10.9 (8.8), and 904 (38%) participants had diffuse SSc. Table 1 shows participant sociodemographic and disease characteristics, including the number with data for each variable, for the full sample and by disease subtype. See online supplemental material 2 for participant characteristics by sex.

As shown in Table 2, the mean (SD) satisfaction with social roles and activities score in the full sample was 48.1 (9.9), which is slightly lower than the United States general population mean (SD) of 50.0 (10.0). Among all participants, 1,307 (55%) had social functioning scores within normal limits; 590 (25%) reported mildly impaired scores, 387 (16%) reported moderately impaired scores; and 101 (4%) reported severe impairment. By country, mean (SD)

scores ranged from 45.5 (10.2) among 241 participants from the United Kingdom to 50.7 (8.5) in 101 participants from Australia, Mexico, or Spain. Participants with diffuse SSc reported a lower mean (SD) of satisfaction with social roles and activities 46.8 (9.8) than those with limited or sine SSc 49.0 (9.8). Scores were similar by sex.

In the main multivariable analysis (Table 3), among sociodemographic variables, fewer years of education (-0.54 points per SD in years, 95% CI -0.93 to -0.14); self-reported race or ethnicity other than White (-1.13 points, 95% CI -2.18 to -0.08); and living in Canada (-1.33 points, 95% CI -2.40 to -0.26) or United Kingdom (-2.49 points, 95% CI -3.92 to -1.06) were associated with reduced satisfaction with social roles and activities. Higher BMI (-1.08 points per SD in BMI, 95% CI -1.47 to -0.69) was also significantly associated. Among disease variables, there were significant associations with gastrointestinal involvement (-3.16 points, 95% CI -4.27 to -2.05); digital ulcers (-1.90 points, 95% CI -3.05 to -0.76); moderate (-1.62 points, 95% CI -2.78 to -0.45) or severe (-2.26 points, 95% CI -3.99 to -0.52) small joint contractures; interstitial lung disease (-1.11 points, 95% CI -1.97 to -0.25); and pulmonary arterial hypertension (-2.69 points, 95% CI -4.08 to -1.30). Among overlap syndromes, rheumatoid arthritis (-2.51 points, 95% CI -4.28 to -0.73); and Sjogren's syndrome (-2.42 points, 95% CI -3.96 to -0.88) were significantly associated. Variables not significantly associated were age; sex; marital status; living in France, Australia, Mexico or Spain; years since first non-Raynaud's symptoms; disease subtype; presence of current or past tendon friction rubs; moderate or severe large joint contractures; history of SSc renal crisis; systemic lupus erythematosus; autoimmune thyroid disease; idiopathic inflammatory myositis; and primary biliary cirrhosis. Adjusted R^2 for the final model was 0.10.

Complete case analysis results, which included 1,664 participants, were similar to those of the main analyses (see online supplemental material 3). When adding pruritus and pain intensity to the model in a sensitivity analysis, both pruritus (-0.83 points per SD in pruritus, 95% CI -1.20 to -0.47); and pain intensity (-5.33 points per SD in pain intensity, 95% CI -5.69 to -4.98) were associated with reduced satisfaction with social roles and activities. The sensitivity analysis replacing disease subtype with mRSS found that mRSS was significantly associated with satisfaction with social roles and activities (-0.69 points per SD in mRSS score, 95% CI -1.18 to -0.21). No antibodies had a significant association. See online supplemental materials 4-6.

DISCUSSION

Among 2,385 participants with SSc from 7 countries, the mean T-score for satisfaction with social roles and activities was 48.1 (9.9), which is approximately 0.2 SD below the United States general population mean. Over half (55%) of participants reported satisfaction with social roles and activities within normal limits. We found that disease variables associated with reduced satisfaction with social roles and activities included gastrointestinal involvement, digital ulcers, the presence of moderate or severe small joint contractures, interstitial lung disease, pulmonary arterial hypertension, mRSS, pruritus, pain intensity, and the presence of overlap syndromes including rheumatoid arthritis and Sjogren's syndrome. We also found that fewer years of education, self-reported race or ethnicity other than White, living in Canada or the United Kingdom, having a higher BMI, pruritus, pain intensity, and mRSS was associated with greater impairment in satisfaction with one's social functioning. Among those with large associations, gastrointestinal involvement may reduce one's ability to carry out social roles due to symptoms such as nausea, abdominal pain, or fecal incontinence;[36] pulmonary arterial hypertension can cause breathlessness, fatigue, and dizziness, which can impact the ability to perform everyday

tasks such as traveling to work or taking care of household chores;[37,38] hand and joint involvement can decrease one's the ability to carry out many tasks necessary for work or household roles;[39] overlap syndromes, including rheumatoid arthritis or Sjogren's syndrome, present their own challenges and can exacerbate other symptom-related barriers from SSc.

Our findings on satisfaction with ability to participate in social roles and activities are generally consistent with the next largest study of people with SSc and another large study of people with rheumatoid arthritis or systemic lupus erythematosus.[40,41] One study assessed 477 Australian patients with SSc and reported a mean (SD) on the PROMIS-29v1 social interaction domain of 46.5 (9.7).[40] The other study assessed 4,346 participants with rheumatoid arthritis and 240 with systemic lupus erythematosus, and reported PROMIS-29 satisfaction with social role T-score means (SD) of 48.9 (9.7) for rheumatoid arthritis, and 49.2 (10.0) for systemic lupus erythematosus.[41]

Our findings on satisfaction with social roles and activities, which were close to the US general population mean, differed from our findings on physical function using data from the same participants from the SPIN Cohort.[42] In that study, we found a mean T-score (SD) for the PROMIS-29v2.0 Physical Function domain of 43.7 (8.9), equivalent to approximately 2/3 of a SD below the US general population mean. The finding of substantially lower physical function but only minimally impaired satisfaction with social roles and activities may reflect the nature of each construct. The Physical Function domain is a relatively objective measure, though self-reported, of one's ability to complete concrete tasks, such as going up and down stairs, whereas the Satisfaction with Social Roles and Activities domain measures one's satisfaction with their ability to fulfill social roles and participate in activities. This is also seen in other chronic diseases, where people adapt their expectations and satisfaction with what they can do, despite

objectively decreasing abilities. This phenomenon is known as a response shift[43] and suggests that people may be coping with the changes they are experiencing by adapting their expectations and, thus, their level of satisfaction with what they are able to do despite their adverse circumstances.[44-45] The degree to which people may be able to participate in social roles and activities may be reduced but their satisfaction with their ability to participate is not.

The adjusted R^2 for the main multivariable model was 0.10. Low R^2 measures are expected in samples of people with a chronic condition as all experience similar symptoms and side effects of the condition. High R^2 values are an important consideration in predictive modelling but are not as valuable when models are used for testing hypotheses about the possible effects of variables of interest. In such cases, including in the present study, having a large enough sample size to generate reasonably precise parameter estimates is a more important consideration.[34]

More studies of this nature are needed to better understand the course of satisfaction with social roles and activities in SSc. Future studies might focus on pin-pointing characteristics of individuals who successfully cope and adapt and potential reasons as why differences occur. We found that a wide variety of factors may impact an individual's satisfaction with their social abilities, some of which are modifiable (e.g., BMI), but some of which are not (e.g., co-occurring diseases such as rheumatoid arthritis). Considering this, future studies are needed to help patients who are less satisfied with their social roles and activities cope with and accept the challenges related to living with SSc. One potential strategy may be acceptance and commitment therapy (ACT), which works on verbal behavior to influence and change one's thoughts and feelings (41). A 2016 systematic review (N = 18 studies) on the use of ACT in chronic and long-term conditions concluded that evidence is promising, albeit limited.[47]

Strengths of our study include its large international sample with participants from 53 SPIN sites across 7 countries, our analysis of a wide range of sociodemographic, lifestyle, and physician-assessed disease-related factors, and the involvement of people with lived SSc experience in the project via leadership in SPIN and participation in the study. There are some limitations that also need to be considered. First, the SPIN Cohort is a convenience sample. However, a comparison with the European Scleroderma Trials and Research and Canadian Scleroderma Research Group cohorts indicated broad comparability of participant characteristics, which supports generalizability in SSc.[17] Second, participants were required to answer questions via online questionnaires, which could potentially reduce generalizability of our results. Third, this was a cross-sectional study and we cannot infer causality based on our results. Fourth, our sample may have been older or differed in other ways compared to the US general population sample to which we compared levels of satisfaction with social roles. Fifth, we did not assess the number of organs involved or the presence of end of stage organ dysfunction.

To summarize, we assessed the association of several factors with satisfaction with social roles and activities in 2,385 patients with SSc. We found many variables statistically significantly associated, including fewer years of education, self-reported race or ethnicity other than White, living in Canada or the United Kingdom, having a higher BMI, gastrointestinal involvement, presence of digital ulcers, moderate or severe small joint contractures, interstitial lung disease, pulmonary arterial hypertension, pruritus, pain intensity, mRSS, rheumatoid arthritis, and Sjogren's syndrome. However, overall, there was only a minimal impairment in satisfaction with social roles and activities, despite evident physical limitations. This may suggest that many individuals with SSc have learned how to adapt and cope with limited

physical capacity. More research is needed to better understand strategies that may be used to support coping. For the time being, health-care providers can work to help patients adapt and cope with their current symptoms, side effects, and levels of satisfaction with their social roles and activities.

Competing Interests: *None.*

Contributorship Statement: TDS, DBR, MEC, BL, LK, MCG, AB, BDT contributed to study conceptualization; GVG, BL to data curation; TDS, GVG, BL to formal analysis; TDS, MEC, LK, BDT to funding acquisition; TDS, DBR, MEC, LK, SJB, AG, KG, GG, MH, LKH, VM, MDM, LM, MR, MS, RW, BDT to investigation; TDS, DBR, MEC, BL, LK, BDT to methodology; MEC to project administration; DBR, MCG, AB, BDT to supervision; TDS to visualization; TDS, BDT to writing the original draft; and all authors reviewing and editing the final draft.

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Data Sharing: De-identified individual participant data with a data dictionary and analysis codes that were used to generate the results reported in this article will be made available upon request to the corresponding author and presentation of a methodologically sound proposal that is approved by the Scleroderma Patient-centered Intervention Network Data Access and Publications Committee. Data requesters will need to sign a data transfer agreement.

Patient and Public Involvement: Patient members of the SPIN Steering Committee play a role in developing SPIN research priorities, including identifying the need for the present study. Five patient members of the Steering Committee reviewed and provided comments on the study protocol and manuscript and are co-authors.

Table 1. Sample sociodemographic and disease characteristic

	Full sample (N = 2,385)		Limited SSc[a] (N = 1,456)		Diffuse SSc (N = 904)	
	N[b]	Mean (SD) or N (%)	N	Mean (SD) or N (%)	N	Mean (SD) or N (%)
Age (years)	2,381	54.9 (12.6)	1,452	56.6 (12.4)	904	52.1 (12.4)
Sex	2,385		1,456		904	
Female		2,079 (87%)		1,299 (89%)		759 (84%)
Male		306 (13%)		157 (11%)		145 (16%)
Education (years)	2,377	15.0 (3.7)	1,450	14.9 (3.8)	902	15.1 (3.6)
Marital status	2,381		1,453		903	
Married or living as married		1,661 (70%)		1,035 (71%)		611 (68%)
Single, divorced/separated, widowed		720 (30%)		418 (29%)		292 (32%)
Race or ethnicity[c]	2,379		1,453		901	
White		1,970 (83%)		1,268 (87%)		684 (76%)
Non-white		409 (17%)		185 (13%)		217 (24%)
Country	2,383		1,455		903	
United States		813 (34%)		436 (30%)		370 (41%)
France		713 (30%)		470 (32%)		241 (27%)
Canada		515 (22%)		332 (23%)		173 (19%)
United Kingdom		241 (10%)		143 (10%)		94 (10%)
Australia, Mexico, Spain		101 (4%)		74 (5%)		25 (3%)
Smoking status	2,382		1,454		903	
Smoker		177 (7%)		118 (8%)		55 (6%)
Non-smoker		2,205 (93%)		1,336 (92%)		848 (94%)
Alcohol consumption (drinks per week)	2,379	2.0 (4.1)	1,453	2.1 (4.3)	901	1.8 (3.5)
Body mass index	2,385	25.3 (5.6)	1,456	25.5 (5.6)	904	24.9 (5.7)
Years since first non-Raynaud's symptoms	2,190	10.9 (8.8)	1,325	12.1 (9.3)	843	8.9 (7.4)
Disease subtype	2,360		1,456		904	
Diffuse		904 (38%)		0 (0%)		904 (100%)
Limited or sine[a]		1,456 (62%)		1,456 (100%)		0 (0%)
mRSS	1,983	7.7 (8.0)	1,213	4.2 (4.2)	754	13.4 (9.4)
Gastrointestinal involvement	2,353		1,442		891	
Yes		2,016 (85%)		1,225 (85%)		779 (87%)
No		337 (14%)		217 (15%)		112 (13%)
Digital ulcers	2,287		1,407		859	
Yes		365 (16%)		132 (9%)		228 (27%)
No		1,922 (84%)		1,275 (91%)		631 (73%)
Tendon friction rubs	2,100		1,308		775	
Current		232 (11%)		120 (9%)		110 (14%)
Past		221 (11%)		41 (3%)		178 (23%)
Never		1,647 (78%)		1,147 (88%)		487 (63%)
Small Joint Contractures	2,255		1,388		848	
None or mild		1,663 (74%)		1,176 (85%)		473 (56%)
Moderate		424 (19%)		161 (12%)		260 (31%)
Severe		168 (7%)		51 (4%)		115 (14%)
Large Joint Contractures	2,211		1,359		833	
None or mild		1,937 (88%)		1,263 (93%)		658 (79%)
Moderate		200 (9%)		65 (5%)		134 (16%)
Severe		74 (3%)		31 (2%)		41 (5%)
History of SSc renal crisis	2,351		1,442		890	
Yes		101 (4%)		24 (2%)		77 (9%)
No		2,250 (96%)		1,418 (98%)		813 (91%)
Interstitial lung disease	2,335		1,431		883	
Yes		827 (35%)		390 (27%)		432 (49%)
No		1,508 (65%)		1,041 (73%)		451 (51%)

Pulmonary arterial hypertension	2,271		1,398		852	
Yes		207 (9%)		131 (9%)		74 (9%)
No		2,064 (91%)		1,267 (91%)		778 (91%)
Pruritus	2,154	1.8 (2.6)	1,300	1.6 (2.5)	831	2.1 (2.8)
Pain intensity	2,385	3.6 (2.6)	1,456	3.5 (2.6)	904	3.8 (2.6)
Pain interference	2,384	55.5 (9.7)	1,455	54.8 (9.6)	904	56.6 (9.7)
Systemic lupus erythematosus	2,323		1,428		876	
Yes		65 (3%)		44 (3%)		20 (2%)
No		2,258 (97%)		1,384 (97%)		856 (98%)
Rheumatoid arthritis	2,322		1,426		877	
Yes		125 (5%)		64 (4%)		59 (7%)
No		2,197 (95%)		1,362 (96%)		818 (93%)
Sjogren's syndrome	2,285		1,403		863	
Yes		176 (8%)		124 (9%)		52 (6%)
No		2,109 (92%)		1,279 (91%)		811 (94%)
Autoimmune thyroid disease	2,277		1,397		861	
Yes		143 (6%)		99 (7%)		44 (5%)
No		2,134 (94%)		1,298 (93%)		817 (95%)
Idiopathic inflammatory myositis	2,322		1,430		872	
Yes		121 (5%)		60 (4%)		59 (7%)
No		2,201 (95%)		1,370 (96%)		813 (93%)
Primary biliary cirrhosis	2,301		1,413		869	
Yes		44 (2%)		38 (3%)		5 (1%)
No		2,257 (98%)		1,375 (97%)		864 (99%)
Antinuclear antibodies	2,194		1,360		818	
Positive		2,069 (94%)		1,296 (95%)		757 (93%)
Negative		125 (6%)		64 (5%)		61 (7%)
Anti-centromere	1,861		1,171		680	
Positive		665 (36%)		609 (52%)		54 (8%)
Negative		1,196 (64%)		562 (48%)		626 (92%)
Anti-topoisomerase I [Scl70]	2,077		1,267		799	
Positive		555 (27%)		243 (19%)		311 (39%)
Negative		1,522 (73%)		1,024 (81%)		488 (61%)
Anti-RNA polymerate III	1,353		808		539	
Positive		245 (18%)		49 (6%)		195 (36%)
Negative		1,108 (82%)		759 (94%)		344 (64%)

[a] Includes 73 participants with sine SSc; [b] N for some variables < 2,385 due to missing data; [c] Race or ethnicity data were self-reported in each country using standard categories used in that country. Therefore, categories differed between countries and could only be aggregated in the 2 categories reported.

Table 2. Satisfaction with social roles and activities by country, disease subtype, and sex

	T-score mean	Within normal limits (T-score > 45)	Mild (T-score 40 to 45)	Moderate (T-score 30 to 39.9)	Severe (T-score < 30)
Full sample (N = 2,385)	48.1 (9.9)	1,307 (55%)	590 (25%)	387 (16%)	101 (4%)
Country					
USA (N = 813)	48.8 (9.7)	466 (57%)	191 (24%)	136 (17%)	20 (3%)
France (N = 713)	48.0 (9.9)	395 (55%)	177 (25%)	105 (15%)	36 (5%)
Canada (N = 515)	47.8 (9.9)	274 (53%)	134 (26%)	81 (16%)	26 (5%)
UK (N = 241)	45.5 (10.2)	101 (42%)	65 (27%)	57 (24%)	18 (8%)
Other[a] (N = 101)	50.7 (8.5)	71 (70%)	21 (21%)	8 (8%)	1 (1%)
SSc Subtype					
Limited or sine[b] (N = 1,456)	49.0 (9.8)	858 (59%)	343 (24%)	212 (15%)	43 (3%)
Diffuse (N = 904)	46.8 (9.8)	440 (49%)	243 (27%)	167 (19%)	54 (6%)
Sex					
Female (N = 2,079)	48.0 (9.8)	1,134 (55%)	518 (25%)	338 (16%)	89 (4%)
Male (N = 306)	48.6 (10.1)	173 (57%)	72 (24%)	49 (16%)	12 (4%)

[a]Includes 40 participants in Australia, 21 in Mexico, and 40 in Spain; [b] Includes 73 participants with sine SSc

Table 3. Linear regression analysis of sociodemographic and disease characteristic associations with satisfaction with social roles and activities

	Satisfaction with Social Roles and Activities Full Sample (N = 2,385)	
	Unadjusted Regression Coefficient (95% CI)[a]	**Adjusted Regression Coefficient (95% CI)[a]**
Sociodemographic variables and body mass index (BMI)		
Age (years standardized)	0.15 (-0.25, 0.54)	0.08 (-0.34, 0.49)
Male sex (reference = female)	0.55 (-0.63, 1.74)	1.04 (-0.12, 2.21)
Years of education (years standardized)	**0.70 (0.31, 1.10)**	**0.54 (0.14, 0.93)**
Single, divorced/separated, or widowed (reference = married or living as married)	**-0.90 (-1.76, -0.03)**	-0.53 (-1.37, 0.31)
Non-White (reference = White)	**-1.45 (-2.50, -0.40)**	**-1.13 (-2.18, -0.08)**
Country (reference = United States)		
Canada	-0.99 (-2.08, 0.09)	**-1.33 (-2.40, -0.26)**
United Kingdom	**-3.33 (-4.74, -1.92)**	**-2.49 (-3.92, -1.06)**
France	-0.80 (-1.78, 0.19)	-0.87 (-1.89, 0.15)
Other (Australia, Mexico, Spain)	1.92 (-0.11, 3.95)	1.53 (-0.45, 3.51)
BMI (standardized)	**-0.89 (-1.28, -0.49)**	**-1.08 (-1.47, -0.69)**
Disease variables		
Years since first non-Raynaud's symptoms (years standardized)	0.13 (-0.28, 0.55)	0.33 (-0.11, 0.77)
Diffuse subtype (reference = limited or sine)	**-2.17 (-2.99 -1.36)**	-0.60 (-1.54, 0.35)
Gastrointestinal involvement (reference = no)	**-3.73 (-4.86, -2.61)**	**-3.16 (-4.27, -2.05)**
Digital ulcers (reference = no)	**-3.33 (-4.43, -2.23)**	**-1.90 (-3.05, -0.76)**
Tendon friction rubs (reference = never)		
Current	**-2.36 (-3.69, -1.03)**	-0.26 (-1.64, 1.12)
Past	**-2.04 (-3.41, -0.67)**	-0.30 (-1.77, 1.17)
Small joint contractures (reference = none or mild)		
Moderate	**-3.02 (-4.07, -1.98)**	**-1.62 (-2.78, -0.45)**
Severe	**-4.45 (-5.97, -2.93)**	**-2.26 (-3.99, -0.52)**
Large joint contractures (reference = none or mild)		
Moderate	**-4.01 (-5.44, -2.57)**	-1.43 (-2.99, 0.13)
Severe	**-3.03 (-5.28, -0.77)**	-1.31 (-3.71, 1.08)
History of SSc renal crisis (reference = no)	**-3.48 (-5.43, -1.53)**	-1.40 (-3.34, 0.55)
Interstitial lung disease (reference = no)	**-2.24 (-3.07, -1.40)**	**-1.11 (-1.97, -0.25)**
Pulmonary arterial hypertension (reference = no)	**-3.48 (-4.87, -2.09)**	**-2.69 (-4.08, -1.30)**
Overlap syndromes		
Systemic lupus erythematosus (reference = no)	-1.80 (-4.20, 0.60)	-0.27 (-2.63, 2.09)
Rheumatoid arthritis (reference = no)	**-3.98 (-5.74, -2.21)**	**-2.51 (-4.28, -0.73)**
Sjogren's syndrome (reference = no)	**-3.68 (-5.22, -2.13)**	**-2.42 (-3.96, -0.88)**
Autoimmune thyroid disease (reference = no)	-1.08 (-2.73, 0.57)	-0.11 (-1.70, 1.49)
Idiopathic inflammatory myositis (reference = no)	**-3.64 (-5.44, -1.84)**	-1.67 (-3.46, 0.11)
Primary biliary cirrhosis (reference = no)	-0.68 (-3.63, 2.27)	-0.96 (-3.80, 1.88)

[a]All regression coefficients are unstandardized. Standardized predictor variables calculated by subtracting raw scores from mean and dividing by standard deviation. Bolded results are statistically significant ($P < 0.05$). Adjusted $R^2 = 0.10$.

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Chapter 4

GENERAL DISCUSSION

4.1 Summary of findings

We conducted a set of 2 cross-sectional studies including 2,385 participants with SSc from 7 countries. In summary, the mean T-score (SD) for physical function was 43.7 (8.9) and the mean T-score (SD) for satisfaction with social roles and activities was 48.1 (9.9). These were approximately 2/3 and 1/5 of an SD below the US general population (mean = 50, SD = 10), respectively. Although only 42% of individuals had physical function scores within normal limits, this proportion increased to 55% of participants for satisfaction with social roles and activities. Disease variables associated with both patient-reported outcomes included mRSS, gastrointestinal involvement, digital ulcers, moderate or severe small joint contractures, interstitial lung disease, pulmonary arterial hypertension, pruritus, pain intensity, and the presence of the overlap syndrome rheumatoid arthritis. We also found that fewer years of education, and an increased BMI were associated with worsening of both physical function and satisfaction with social roles and activities. The adjusted R^2s for the main multivariable regressions models were below 0.2. Low R^2 values are expected in samples with chronic diseases as most individuals have similar experiences and deal with similar factors. Our studies sought to identify associated factors with physical and social functioning in individuals with SSc, not to predict any individual's scores in these outcomes, which would be related to R^2.

Our findings on mean physical function and satisfaction with social roles and activities scores are generally consistent with data reported in previous studies with similar samples. However, our results on satisfaction with social roles and activities differ substantially from our results on physical function. Our findings suggest that a limitation in physical abilities, which can

evidently lead to a reduction in one's level of social participation, does not necessarily translate to a reduction in one's satisfaction with their level of social participation. One potential explanation for this can be that individuals living with SSc may develop coping strategies related to adapting their expectations for what they can or cannot do, potentially lowering their personal standard for involvement in social tasks, and therefore maintaining their satisfaction levels based on these new standards. This phenomenon is known as a response-shift, and has been seen in other chronic diseases.[20] Another explanation for this can be that these individuals are demonstrating resilience. Similar to a response shift, resilience can be defined as a process where individuals positively adapt to adversity.[21,22] Some individuals may adapt better than others to SSc and the obstacles that come with it, causing their satisfaction levels to remain stable or decrease minimally.

In addition to differences in the overall scores for both PROs, there were also some difference in the factors found to be associated with them. For example, we found that age, sex, disease subtype, the presence of large joint contractures, and idiopathic inflammatory myositis were statistically significantly associated with physical functioning but not with satisfaction with social roles and activities. In conjunction with the idea of a response-shift, perhaps these factors can worsen one's physical function but do not affect one's satisfaction with their social abilities. For example, it is very likely that as individuals living with SSc get older, their functional abilities decrease significantly. However, their expectations of themselves as a social entities might decrease, therefore leaving their satisfaction with their social roles and activities unaffected. On the other hand, some disease factors may have strictly physical outcomes, and do not have an impact on the way one's abilities are perceived. For example, although sex can be largely associated with physical function, perhaps males and females have similar expectations for themselves socially, therefore removing the association of sex to one's satisfaction with social

activities. Factors found to be associated with satisfaction with social roles and activities but not physical function included self-reported race or ethnicity, and country of residence. One possible explanation for this difference is that SSc symptoms remain similar across the globe and likely have similar impacts on one's physical functioning. However, social demands or expectations may differ by country or ethnicity, thereby having an impact on one's satisfaction with social roles and activities.

Management strategies and interventions are needed to address the high level of impairment in physical function, and the possible impairment in satisfaction with social roles and activities. Considering there are many disease-related factors associated with both outcomes, and that factors can vary from one person to the next, interventions aimed at helping individuals cope with these factors may be more beneficial than attempting to reduce their presence. Self-management programs can be a promising solution. Such programs, such as SPIN-SELF, a program SPIN is currently testing in a clinical trial, focus on helping individuals effectively manage their disease, and related symptoms.[23] SPIN-SELF's program has 9 modules, including some focused on coping with pain, finger ulcers, gastrointestinal symptoms, and itch. Focusing on improving the management of these disease-related factors, which have all been found to be associated with decreased physical functioning and satisfaction with social roles and activities, can potentially have large impacts on improving these PROs. Despite limited evidence on efficacy, other promising strategies can include ACT or interventions focused on promoting resilience.[24,25]

4.2 Limitations

Our studies have limitations to consider. First, the SPIN Cohort is a convenience sample, and participants were required to answer questions via online questionnaires. These may potentially reduce the generalizability of our results. Second, our studies were cross-sectional and

did not allow us to infer causality of our results. Future research should focus on assessing these associations longitudinally, in hopes of finding specific trends in the presence of certain factors and their effects on patient-reported outcomes. Third, we did not control for disease progression. Individuals enter our cohort at different stages of their diagnosis, and it is possible that results may differ depending on how long an individual has had the disease, the amount of symptoms present at the time of enrolment, or how they view/deal with their symptoms at the time. Fourth, we did not assess whether those who reported highly impaired physical functioning also reported highly impaired satisfaction with social roles and activities. It is unlikely, however, that all participants who scored high on satisfaction with social roles and activities did not have impaired physical functioning. Fifth, we did not assess outcomes by subgroups such as age, sex, or disease duration. These may potentially have an impact on both physical function and satisfaction with social roles and activities scores.

4.3 Conclusions

To conclude, our objectives were to compare physical function and satisfaction with social roles and activities levels in a large multinational SSc cohort to general population normative data and identify factors associated with both outcomes. We achieved these objectives by conducting 2 cross-sectional studies that assessed the association of several sociodemographic, lifestyle, and disease-related factors with physical functioning and satisfaction with social roles and activities in 2,385 individuals living with SSc. Our findings emphasize the fact that physical impairment is high in SSc, but this does not necessarily translate to a decrease in one's satisfaction with their degree of social participation. Our studies highlight the importance of considering PROs when assessing the well-being of individuals. Interventions are needed to help improve physical function in individuals with SSc in hopes of additionally

improving their overall quality of life. Longitudinal studies assessing the association of disease-related factors with physical function and satisfaction with social roles and activities can provide important information on factors to target when developing such interventions. In the meantime, healthcare providers need to work with patients to identify present factors and help them adapt with their current symptoms.

4.4 References

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