Three-year trajectories of disability and fatigue in systemic sclerosis: a cohort study

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ABSTRACT

Objective. *Functional disability and fatigue are important consequences of systemic sclerosis (SSc), but little is known about their course over time. The aim of this study was to identify and characterise homogeneous subgroups with distinct 3-year trajectories of disability and fatigue, separately.*

Methods. *A 3-year cohort study including 215 patients with SSc was conducted. Functional disability was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI). Fatigue was assessed using the SF-36 Vitality subscale. Longitudinal trajectories were identified using latent class growth analyses (LCGA). Baseline patient characteristics were compared across classes using multivariable logistic regression.*

Results. *Two disability classes were identified: a 'low' group (n=133) with low baseline HAQ-DI scores (intercept=0.48) and slight, statistically non-significant deterioration over time (slope=0.01), and a 'high' group (n=82) with high baseline HAQ-DI scores (intercept=1.63) and also slight, statistically non-significant deterioration over time (slope=0.01). Patients in the high disability group were more likely to be female, have higher fatigue, more helplessness, and less emotion-focused coping. Two fatigue classes were identified: an 'average' group (n=99) with average baseline Vitality scores (intercept=53.9) and slight, statistically non-significant deterioration over time (slope=-0.23), and a 'high' fatigue group (n=116) with low baseline Vitality scores (intercept=39.8) and also slight, but non-significant deterioration over time (slope=-0.15). Patients in the high fatigue group were more likely to be female, report more impact of lung involvement, and less acceptance.*

Conclusion. *Functional disability and fatigue trajectories in SSc were relatively stable over a 3-year period, and differences in baseline scores, but not slopes, defined classes.*

Introduction

Systemic sclerosis (SSc, or scleroderma) is a rare chronic connective tissue disease, characterised by vascular damage and collagen deposition in the skin and internal organs (1). SSc may cause dysfunction of the lungs, heart, kidneys, gastrointestinal tract, and the musculoskeletal system. Patients experience a broad range of symptoms, with fatigue, Raynaud's phenomenon, joint pain, stiffness of hands, muscle pain and difficulty sleeping reported most frequently, impacting different aspects of life such as employment status (2-5). Clinical manifestations of SSc and progression of the disease are highly variable among patients, and can vary widely over time (6). However, little is known about the course over time of problems important to patients with SSc, such as disability and fatigue.

Two longitudinal studies have reported that, overall, disability in patients with SSc increases slighty over time (7, 8). Disease characteristics most strongly associated with the course of disability were diffuse disease subtype, breathing problems, and more skin thickening. The course of disability varied widely across individuals in these studies, however, suggesting that subgroups of patients may exist with a distinct disability progression over time, that may warrant different treatment approaches. In other rheumatic diseases, the course of disability over time was found to be associated with sociodemographic characteristics, *e.g.* age and education level; clinical variables including body mass index, pain, number of comorbidities, and fatigue; and psychosocial

characteristics such as acitivity avoidance, depressive symptoms, and perceived self-efficacy (9-11).

In addition to functional disabilities, patients with SSc have rated fatigue amongst their most prevalent symptoms, and reported that fatigue has a major impact on the ability to carry out everyday activities (4, 5, 12-15). Levels of fatigue in SSc were similar to fatigue experienced by cancer patients in active treatment and patients with other rheumatic diseases, and higher compared with the general population and cancer patients in remission (16). To date, only one study has examined the course of fatigue in patients with SSc (17) and reported that levels of fatigue fluctuated in some individuals, but that the overall cohort did not show a significant trend of change over time. In that study, fatigue severity over time was associated with pain, severity of gastrointestinal and lung involvement, and psychological variables (17). No studies, however, have examined the possibility of the existence of homogeneous subgroups with distinct trajectories of fatigue in SSc. Identifying these subgroups may help health care providers to target therapy to high-risk groups that are most likely to benefit from interventions addressing fatigue.

The aim of the present study was to examine change in disability and fatigue in patients with SSc over time, to identify homogeneous subgroups with distinct trajectories of disability and fatigue, and to assess differences in baseline demographic, disease, and psychosocial characteristics of these subgroups.

Methods

Patients and procedures

Data were collected between June 2008 and August 2013 in patients classified as having SSc according to the American College of Rheumatology criteria (18) under treatment in the Sint Maartenskliniek or Radboud University Medical Center Nijmegen, the Netherlands. At baseline, medical data were recorded by the attending rheumatologist, and patients completed sets of questionnaires every 6 months for 3 years. Exclusion criteria were a life expectancy of <1 year, acute serious complications (*e.g.* acute renal crisis), severe psychiatric comorbidity (*e.g.* severe substance abuse, psychosis or dementia), other serious comorbidities (*e.g.* cancer), and insufficient knowledge of the Dutch language. The attending rheumatologist invited eligible patients to participate during a patient's regular visit to the outpatient clinic. Patients provided informed consent, and the local medical ethics board (CMO 2008/109) approved the study.

Measures

• *Outcome measures*

Functional disability was measured with the Health Assessment Questionnaire - Disability Index (HAQ-DI) (19). The HAQ-DI includes 20 items covering 8 dimensions of functioning and is rated on a scale from 0 (without any difficulty) to 3 (unable tot do). For each domain the highest (worst) score is used to calculate the HAQ-DI total score, with each of the domains valued equally. Total HAQ-DI scores range from 0 (no disability) to 3 (severe disability). The HAQ-DI showed good validity and responsiveness to change in patients with SSc (8, 20, 21).

Fatigue was assessed with the 4-item Vitality subscale of the Medical Outcomes Study Short Form 36 (SF-36), assessing a patient's level of fatigue during the previous four weeks (22). Items are scored on a 5-point Likert scale (1 = all the time, 5 = none of the time). Total SF-36 Vitality scores are normalised based on US population data (M = 50, SD = 10), with higher scores indicating less fatigue. The SF-36 is a reliable and valid measure in patients with SSc (21).

• *Baseline characteristics*

Demographic variables included age, gender, marital status (married *vs.* not married), and education (≤12 years *vs.* >12 years of education).

Disease variables were provided by the attending rheumatologist and included disease subtype (limited SSc vs. diffuse SSc), disease duration (defined as the time since onset of the first non-Raynaud's symptom), antibody profile (anticentromere antibody (ACA) and antitopomerase antibody (anti-TOPO); positive vs. negative). In addition, patients rated the impact of disease symptoms (Raynaud's phenomenon, digital ulcers, gastrointestinal symptoms, breathing problems, and pain) on a 10-cm visual analogue scale (VAS) ranging from 0 "does not interfere" to 100 "very severe limitation".

Because previous research has shown that psychosocial factors were related to physical disability and fatigue cross-sectionally and over time, measures of cognitions, coping, and social support were recorded. The Illness Cognition Questionnaire (ICQ) (23) consists of 18 items that assess disease cognitions of helplessness, acceptance, and disease benefits. Participants rated their agreement with the statements on a 4-point Likert scale, ranging from 1 (not at all) to 4 (completely). Higher scores on the subscales represented higher level of agreement with a particular disease cognition. The questionnaire showed good psychometric properties in chronic diseases (23). The Coping Inventory Stressful Situations (CISS) (24) includes 48 items that assess three coping strategies including problem-focused coping, emotion-focused coping, and avoidance. Items were scored on a 5-point Likert scale, ranging from 1 (not at all) to 5 (very much). Higher scores indicate a greater use of that particular coping style. The CISS scales demonstrated good reliability and validity across samples (24, 25). The Personal Resources Questionnaire-85 Part 2 (PRQ-85) (26) includes 25 items that assess patients' perceived level of social support using a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Higer scores indicate greater availability of and satisfaction with social support. There is strong evidence for the validity and reliability (27).

Statistical analysis

• *Identification of classes*

Descriptive statistics are provided as means and standard deviations (SD) for continuous variables and percentages for categorical variables. Latent class growth analysis (LCGA) was

conducted using MPlus to identify trajectories (classes) over time for disability and fatigue separately, following the guidelines described by Jung and Wickrama (28). LCGA estimates individual differences (variability) in parameters reflecting participants' change in outcome over time. Individuals are classified into latent classes based upon similar patterns in the outcome of interest (*i.e.*, disability and fatigue, respectively). LCGA assumes no within-class variation on the growth factors. Thus, all individual longitudinal trajectories within a subgroup are considered to be homogeneous, leading to a clearer identification of classes. MPlus' full information maximum likelihood estimation for handling missing data was applied.

Following the guidelines, a single-class growth curve model was specified, as well as a three-class model. To determine the number of classes in the sample, the three-class model was compared with a two-class and four-class model. In total, the fit of four unconditional latent class models (*i.e.*, models with no covariates) were estimated, with one to four linear trajectories, for fatigue and disability seperately. The number of trajectories was determined based on fit indices, model parsimony, and clinical interpretability. The model with the best fit has the smallest Bayesian Information Criterion (BIC), and significant p-values ($p<0.05$) for the Vuong-Lo-Mendell Ruben Likelihood Ratio Test (LMR-LRT) and the Bootstrap Likelihood Ratio Test (BLRT), which indicate that a model with a *k* number of classes has a better fit than a model with *k-1* number of classes. Other model fit considerations were a higher entropy statistic (near 1.0), indicating the degree to which latent trajectories may be clearly distinguished, and higher posterior probabilities of group membership (near 1.0), indicating the degree to which individuals have been correctly classified into a class. For clinical interpretability, we also considered the number of participants (not less than 10% of total sample) of the identified classes.

After LCGA was conducted, we proceeded to fit a growth mixture model (GMM) that freely estimates the within-class variances. However, by allowing this variation in covariance matrices, the model did not reach convergence. Therefore, the results provided by the LCGA regarding the number of classes of trajectories were used in further exploratory analyses. For each individual patient in the database, the predicted class of the best fitting model (*i.e.*, with the optimal number of subgroups) was obtained.

• *Baseline characteristics of classes*

We compared baseline demographic, disease, clinical, and psychosocial characteristics between the identified classes using univariate and multivariate logistic regression analyses, for functional disability and fatigue separately. Multivariate Imputation by Chained Equation (MICE) was used to produce 20 complete datasets, using 15 cycles for each dataset (29). Results of the imputed datasets were combined following Rubin's rules (30).

First, univariate associations of baseline characteristics with the classes of disability and fatigue were calculated. Next, to understand the independent contribution of the baseline characteristics, multivariate logistic regression analyses were conducted. Because the number of variables in the regression models would lead to overfitting of the model, we were not able to enter all the variables that were univariately associated into the multivariable regression analysis. Therefore, we pre-selected characteristics before fitting the final model by dividing the variables of interest in four blocks: one block included the demographic variables (age, gender, education, employment, marital status); another block included the disease characteristics (time since onset first non-Raynaud symptom, subtype SSc, ACA, anti-TOPO); the third block included the self-reported clinical characteristics [impact of gastrointestinal involvement, lung involvement, Raynaud's phenomenon, and digital ulcers, SF-36 Vitality subscale (in the disability model), and HAQ-DI (in the fatigue model)]; and the final block included the psychosocial characteristics [ICQ helplessness and acceptance; CISS problem-focused coping, emotion-focused coping, avoidance coping; social support (PRQ-85)]. For each block, we used a backward stepwise regression (in each step, a variable was removed if $p>0.10$) to determine which variables to include in the final logistic regression model. All selected variables that were entered simultaneously in the final regression model. As pain may have substantial conceptual overlap with fatigue and disability, it was not included in the primary analyses. A sensitivity analysis was conducted to examine the association of pain with disability and fatigue, respectively. A second sensitivity analysis was conducted where we ran the final regression model with complete cases only. Finally, we assessed the frequency distributions between the classes of disability and fatigue using a chi-squared test.

LCGA was performed in Mplus7 and the logistic regression analyses in Stata 13.

Results

Sample characteristics

In total, 279 patients were invited to participate in the cohort study, of whom 215 completed the baseline questionnaire. After 3 years, 54 participants (25.1%) had dropped out (Fig. 1). At baseline, the mean age (SD) of the 215 participants was 56.4 (12.0) years, 67.9% were women, and most participants were married or cohabiting (76.3%). The mean disease duration measured from the first non-Raynaud's symptom to baseline was 9.2 (8.0) years, and 75.1% of participants had limited SSc. Baseline characteristics are presented in Table I. The total number of missing values among the 22 baseline characteristics was 50 (1.1%), corresponding to 36 participants.

Course of disability

For the complete sample, the intercept of the HAQ-DI score generated with Mplus was 0.92 (95% confidence interval [CI] 0.83 to 1.01), indicating mild to moderate disability. There was a slight increase in HAQ-DI score (more disability) over time (slope 0.02; 95% CI 0.01 to 0.03), equivalent to an

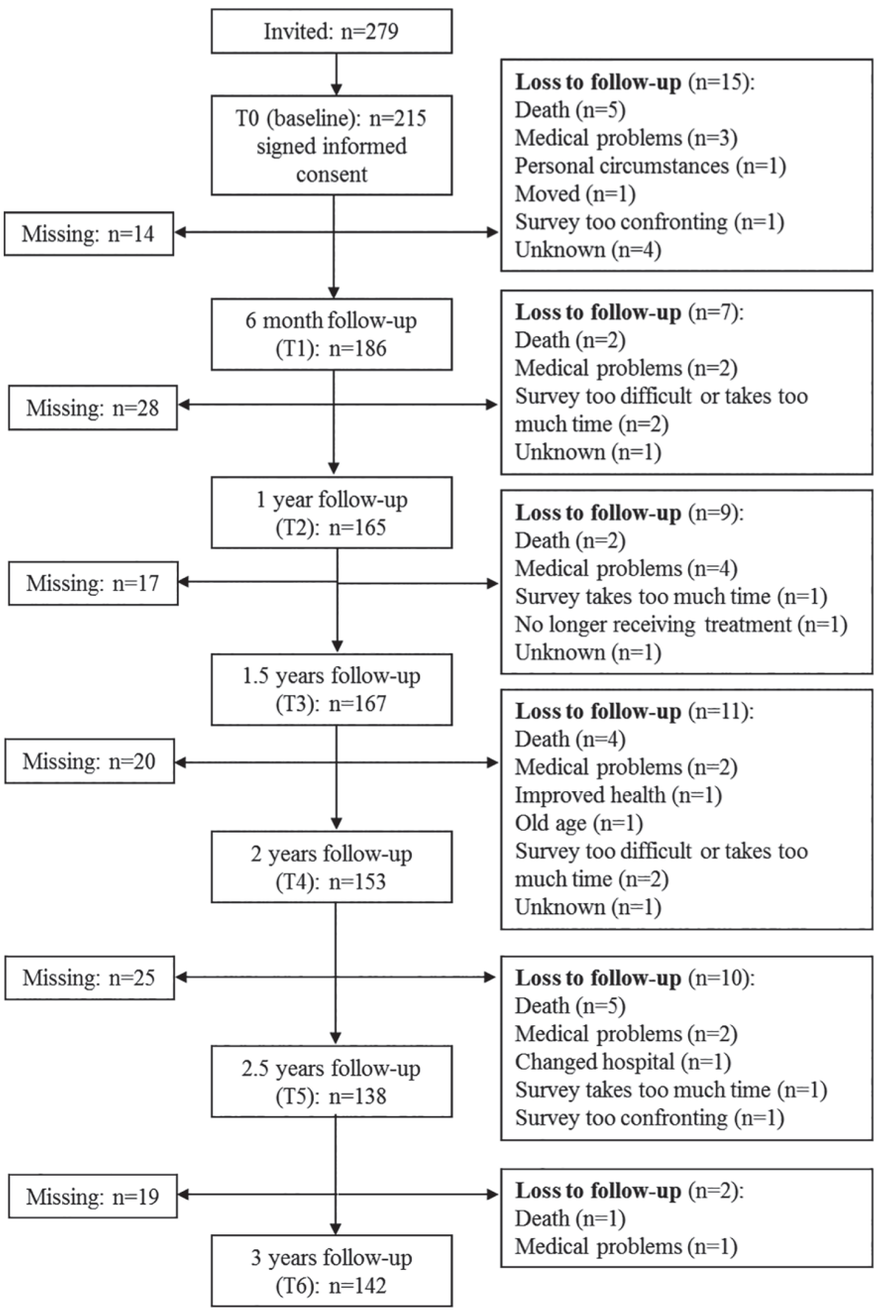

Fig. 1. Study flowchart.

average increase in HAQ-DI score of 0.04 per year, or 0.12 over 3 years. The number of participants with a missing HAQ-DI score was 1 (0.5%) at baseline, and increased to 76 (35.3%) after 3 years.

• *Identification of classes*

For disability, a two-class model was identified as most appropriate based on fit indices, internal reliability, and interpretability (Table II). In the three-class model, compared with the two-class model, the BIC was better, but the entropy was lower and the LMR-LRT was non-significant. The posterior probabilities were also better in the two-class model.

The two subgroups differed in the baseline values (intercepts) of the HAQ-DI and there were only small, statistically non-significant, changes in disability over time; both classes showed trajectories of slight worsening of disability. The first subgroup consisted of 133 participants and was defined as 'low disability', as particpants reported low baseline disability scores (intercept 0.48; 95% CI 0.38 to 0.58) and the slope was 0.01 (95% CI 0.00 to 0.02). The second subgroup was defined as 'high disability', as the 82 participants showed high baseline disability scores (intercept 1.63; 95% CI 1.45 to 1.82) and the slope was 0.01 (95% CI -0.01 to 0.03).

• *Baseline characteristics of classes*

The results of the univariate and multivariate regression analyses comparing baseline characteristsics of the participants between the two disability classes are shown in Tables I and III. Eight variables were selected to be included in the final model. Participants in the high disability class were characterised by: female gender, more fatigue, more helplessness, and less emotion-focused coping.

The results from the complete cases sensitivity analysis differed slightly from the model with imputed data, in that female gender was not a significant characteristic of the high disability subgroup. In the sensitivity analysis with pain added to the final model, results differed from the model without pain (data not shown): emotion-focused coping and pain were significant characteristics of disability classification, but not female gender, fatigue, and helplessness.

Course of fatigue

The intercept of the SF-36 Vitality score for the complete sample was 46.42 (95% CI 45.15 to 47.69), and there was a slight decrease (more fatigue) over time (slope -0.23; 95% CI -0.41 to -0.05), equivalent to an average decrease in SF-36 Vitality score of 0.46 per year, or 1.38 over 3 years. The number of participants with missing SF-36 Vitality scores was 3 (1.4%) at baseline and increased to 74 (34.4%) after 3 years.

• *Identification of classes*. For fatigue, a two-class model was identified as most appropriate (Table IV). In the three-class model, compared with the two-class model, the BIC and entropy were better, but the LMR-LRT was

Table I. Baseline characteristics of the identified subgroups of disability and fatigue.

	Total n=215	Subgroup 1 Low disability n=133	Subgroup 2 High disability n=82	Subgroup 1 Average fatigue n=99	Subgroup 2 High fatigue n=116
Demographics					
Age, mean (SD), years	56.4 (12.0)	55.1 (12.4)*	58.7 (11.0)	57.0 (11.5)	56.0 (12.4)
Female, n (%)	146 (67.9)	82 (61.7)*	64 (78.0)	53 (53.5)*	93 (80.2)
Higher education (> 12 years), n (%)	88 (41.1)	65 (49.2)*	23 (28.0)	45 (45.9)	43 (37.1)
Currently employed, n (%)	71 (32.9)	59 (44.1)*	12 (14.6)	40 (40.1)*	31 (26.7)
Married/ cohabiting, n (%)	164 (76.3)	107 (80.5)	57 (69.5)	80 (80.9)	84 (72.4)
Disease characteristics					
Time since onset first non-Raynaud symptom, mean (SD), years	9.2 (8.0)	9.1 (8.3)	9.3 (7.5)	8.4 (6.8)	9.8 (8.9)
Patients with limited SSc, n (%)	162 (75.1)	102 (76.4)	60 (73.0)	73 (73.6)	89 (76.4)
ACA positive, n (%)	54 (25.1)	34 (25.6)	20 (24.4)	25 (25.3)	29 (25.0)
Anti-TOPO positive, n (%)	57 (26.5)	40 (30.1)	17 (20.7)	34 (34.3)*	23 (19.8)
Clinical factors					
VAS gastrointestinal involvement, mean (SD)	18.8 (24.6)	15.1 (22.4)*	24.8 (26.8)	9.8 (16.4)*	26.4 (27.7)
VAS lung involvement, mean (SD)	26.2 (26.4)	17.8 (21.3)*	39.9 (28.2)	12.5 (15.1)*	37.9 (28.4)
VAS Raynaud's phenomenon, mean (SD)	41.2 (28.8)	37.5 (27.9)*	47.2 (29.4)	30.7 (26.7)*	50.2 (27.6)
VAS digital ulcers, mean (SD)	23.7 (29.9)	20.2 (27.4)*	29.3 (32.6)	14.2 (22.2)*	31.8 (32.9)
VAS pijn, mean (SD)	28.4 (24.7)	21.8 (21.5)*	39.2 (25.7)	19.1 (19.6)*	36.4 (25.8)
HAQ-DI, mean (SD)	0.91 (0.70)	0.47 (0.38)*	1.61 (0.51)	0.57 (0.56)*	1.19 (0.69)
SF-36 Vitality subscale, mean (SD)	46.8 (10.0)	49.8 (9.9)*	42.1 (8.4)	55.0 (7.4)*	39.9 (6.0)
Psychosocial factors					
Helplessness (ICQ), mean (SD)	12.7 (4.3)	11.6 (3.8)*	14.5 (4.5)	10.5 (3.5)*	14.5 (4.0)
Acceptance (ICQ), mean (SD)	16.4 (4.1)	16.7 (3.8)	15.8 (4.6)	18.1 (3.6)*	14.9 (4.0)
Problem-focused coping (CISS), mean (SD)	50.6 (11.0)	50.9 (10.6)	50.1 (11.6)	50.0 (11.2)	51.1 (10.8)
Emotion-focused coping (CISS), mean (SD)	34.0 (11.7)	34.7 (12.2)	32.9 (10.8)	30.2 (10.0)*	37.3 (12.1)
Avoidance coping (CISS), mean (SD)	40.4 (9.9)	40.7 (10.1)	39.9 (9.7)	40.4 (10.6)	40.4 (9.3)
Social support (PRQ-85), mean (SD)	131.5 (20.6)	135.3 (19.5)*	125.4 (21.0)	136.4 (18.2)*	127.3 (21.7)

SSc: systemic sclerosis; ACA: anticentromere anitbody; anti-TOPO: antitopomerase antibody; VAS: visual analogue scale; HAQ-DI: Health Assessment Questionnaire - Disability Index; SF-36: Short-Form 36 Health Survey; ICQ: Illness Cognition Questionnaire; CISS: Coping Inventory Stressful Situations; PRQ-85: Personal Resources Questionnaire 85. *$p<0.05$.

Table II. Fit indices, entropy and average posterior probabilities across models with different number of subgroups with distinct trajectories of disability.

No. of subgroups	BIC	LMR-LRT	BLRT	Entropy	n	Posterior probabilities	Intercept (95% CI)	Slope linear (95% CI)
2	1532.53	0.015	<0.0001	0.921	133	0.98	0.48 (0.38, 0.58)	0.01 (0.00, 0.02)
					82	0.97	1.63 (1.45, 1.82)	0.01 (-0.01, 0.03)
3	1154.35	0.31	<0.0001	0.897	59	0.95	1.84 (1.56, 2.11)	0.01 (-0.02, 0.03)
					82	0.95	0.27 (0.19, 0.36)	0.01 (-0.01, 0.02)
					74	0.95	0.91 (0.61, 1.20)	0.02 (0.00, 0.04)
4	964.13	0.16	<0.0001	0.920	73	0.97	0.25 (0.17, 0.33)	0.01 (-0.01, 0.02)
					56	0.96	1.59 (1.39, 1.79)	0.02 (0.00, 0.04)
					13	0.94	2.40 (2.15, 2.64)	0.03 (-0.04, 0.10)
					73	0.94	0.82 (0.67, 0.97)	0.02 (0.00, 0.05)

BIC: Bayesian Information Criterion; LMR-LRT: Vuong-Lo-Mendell Rubin Likelihood Ratio Test; BLRT: Bootstrap Likelihood Ratio Test; CI: confidence interval.

non-significant. The posterior probabilities were also better in the two-class model.

The two fatigue subgroups differed in their baseline values (intercepts) of the SF-36 Vitality subscale and both subgroups showed small, statistically non-significant, worsening of fatigue over time. The first subgroup consisted of 99 participants and was defined as 'average fatigue', as participants fatigue levels were virtually similar to a US norm population (intercept 53.94; 95% CI 51.44 to 56.45) and the slope was -0.23 (95% CI -0.49 to 0.04). The second subgroup was defined as 'high fatigue', as the 116 participants showed high baseline fatigue (intercept 39.81; 95% CI 38.30 to 41.32) and the slope was -0.15 (95% CI -0.47 to 0.17).

• *Baseline characteristics of classes*

The results of the univariate and multivariate regression analyses comparing

Table III. Final model of baseline characteristics associated with subgroup membership for fatigue and disability, multivariable logistic regression analysis.

	Fatigue high fatigue (n=116) *vs.* average fatigue (n=99)			Disability high disability (n=82) *vs.* low disability (n=133)		
	OR	95% CI	*p*	OR	95% CI	*p*
Demographics						
Female sex	4.59	1.87-11.30	<0.01	2.21	1.01-4.85	0.05
Higher education (> 12 years)				0.51	0.24-1.09	0.08
Currently employed	1.41	0.57-3.47	0.46	0.50	0.22-1.16	0.11
Disease characteristics						
Anti-TOPO positive	0.53	0.21-1.36	0.19			
Clinical factors						
VAS gastrointestinal involvement (0-100)	1.01	0.99-1.03	0.15			
VAS lung involvement (0-100)	1.05	1.02-1.07	<0.01	1.01	1.00-1.03	0.06
VAS Raynaud's phenomenon (0-100)	1.01	1.00-1.03	0.07			
HAQ-DI (0-3)	1.79	0.86-3.71	0.12			
SF-36 Vitality subscale (0-100)				0.94	0.90-0.99	0.02
Psychosocial factors						
Helplessness (ICQ) (6-24)	1.14	0.99-1.30	0.06	1.12	1.01-1.25	0.04
Acceptance (ICQ) (6-24)	0.84	0.74-0.95	<0.01			
Emotion-focused coping (CISS) (16-80)				0.95	0.91-0.98	<0.01
Social support (PRQ-85) (25-175)	0.99	0.97-1.01	0.26	0.98	0.97-1.00	0.07

Anti-TOPO: antitopomerase antibody; VAS: visual analogue scale; HAQ-DI: Health Assessment Questionnaire - Disability Index; SF-36: Short-Form 36 Health Survey; ICQ: Illness Cognition Questionnaire; CISS: Coping Inventory Stressful Situations; PRQ-85: Personal Resources Questionnaire 85; OR: odds ratio; CI: confidence interval.

baseline characteristsics of the participants in the two identified subgroups are shown in Tables I and III. Ten variables were selected for the final model. Participants in the high fatigue class, compared with participants in the average fatigue class, were characterised by: female gender, more impact of lung involvement, and less acceptance.

In both sensitivity analyses, adding pain to the final model and only including complete cases, results were virtually similar to those from the model without pain (data not shown).

Distribution of disability and fatigue classes

Approximately one-third (31%) of the patients could be classified to both the high disability and high fatigue groups, whereas 39 percent (n=83) of the cohort was classified to both the low disability and average fatigue groups (Table V). There was a statistically significant association between the disability subgroups and the fatigue subgroups ($p<0.01$).

Discussion

The main finding of our 3-year observational study was that disability and fatigue in SSc are relatively stable over time. Overall, both disability and fatigue deteriorated slightly over time; HAQ-DI scores increased on average with 0.04 points per year, and SF-36 Vitality scores decreased with 0.46 points per year. We identified a low and a high subgroup for disability, and an average and high subgroup for fatigue. Classes differed in baseline characteristics, but had similar trajectories over time, with small, statistically non-significant worsening of symptoms over time. Thus, differences in baseline scores, but not slopes, defined classes. Patients in the high disability group were more likely to be female, have higher fatigue, more helplessness, and less emotion-focused coping. However, when pain was entered in the model, emotion-focused coping and pain were the only significant characteristics of disability classification, indicating that pain is an important factor in relation to disability, which role needs to be further explored.

Our findings are in line with previous studies that have examined change in disability over time in patients with

Table IV. Fit indices, entropy and average posterior probabilities across models with different number of subgroups with distinct trajectories of fatigue.

No. of subgroups	BIC	LMR-LRT	BLRT	Entropy	n	Posterior probabilities	Intercept (95% CI)	Slope linear (95% CI)
2	8068.14	0.003	<0.0001	0.852	99	0.96	53.94 (51.44, 56.45)	-0.23 (-0.49, 0.04)
					116	0.96	39.81 (38.30, 41.32)	-0.15 (-0.47, 0.17)
3	7853.00	0.095	<0.0001	0.862	90	0.94	49.41 (46.57, 52.26)	-0.06 (-0.33, 0.21)
					28	0.92	62.27 (56.38, 68.16)	-0.39 (-0.81, 0.03)
					97	0.94	38.81 (37.35, 40.28)	-0.29 (-0.60, 0.02)
4	7812.30	0.051	<0.0001	0.821	16	0.93	64.73 (62.24, 67.23)	-0.22 (-0.74, 0.30)
					80	0.85	46.71 (43.75, 49.66)	0.02 (-0.34, 0.39)
					41	0.85	55.36 (53.12, 57.61)	-0.36 (-0.80, 0.08)
					78	0.95	38.07 (36.06, 40.08)	-0.30 (-0.61, 0.01)

BIC: Bayesian Information Criterion; LMR-LRT: Vuong-Lo-Mendell Rubin Likelihood Ratio Test; BLRT: Bootstrap Likelihood Ratio Test; CI: confidence interval.

Table V. Frequency distributions between the classes of disability and fatigue.

	Average fatigue, n (%)	High fatigue, n (%)	Total, n (%)
Low disability, n (%)	83 (38.6)	50 (23.3)	133 (61.9)
High disability, n (%)	16 (7.4)	66 (30.7)	82 (38.1)
Total, n (%)	99 (46.0)	116 (54.0)	215 (100)

SSc (7, 8). Among 745 Canadian SSc patients, an increase in HAQ-DI score that ranged from 0.12 to 0.21 over 3 years was reported (7). The minimum clinically important difference (MCID), which defines the smallest change in a health measure's score that patients identify as important (31), for the HAQ-DI has been suggested to be up to 0.14 in patients with SSc (32, 33). Thus, the change over 3 years that we found in our cohort is in the range of a clinically meaningful change for patients with SSc.

In line with a previous study including 256 SSc patients with early SSc, fatigue levels in our study changed only slightly over time in the overall sample and in the two classes separately (17). The MCID for the SF-36 Vitality scale is unknown for SSc, but has been suggested to be 14.8 for patients with RA (34). Thus, our finding that the SF-36 Vitality score decreases by 1.38 over 3 years indicates that this change is not clinically meaningful.

Self-reported impact of lung problems was an important characteristic of the patients with high baseline fatigue in our study. This was in line with the cohort of Assessi et al., where diffuse capacity of the lung for carbon monoxide (DLco) was predictive of change in fatigue severity (17), suggesting that patients with more extensive lung involvement are more likely to experience worse fatigue.

The results of our study have implications for clinical practice. Remarkably, but in line with results of previous studies (17, 35), SSc subtype and disease duration were not identified as characteristics of the high disability and high fatigue group, whereas cognitions and coping were associated with these groups. This implies that psychosocial factors could be considered targets for treatment that focuses on reducing disability and fatigue and its impact on daily activities. Treatment should ideally be targeted to those who are most likely to benefit, thus preferably to patients experiencing both high disability and high fatigue, which is approximately one-third of the patients in our study. Further research should focus specifically on these patients and need to identify the best strategy to target these consequences of SSc. An important research question might be, whether it is more effective to provide an intervention that targets both disability and fatigue at the same time or whether addressing the most bothersome symptom would also result in improvements of the other symptom.

The main limitation of our study relates to the relatively small sample size. As a consequence of this, we were not able to conduct GMM analyses. GMM is a more flexible approach compared to LCGA and allows assessment of parameters that can vary both within and between classes. Furthermore, there may have been different reasons for drop out in our study, and in some instances, the missingness itself may be informative, such as when patients drop out as a consequence of disease worsening or death (36). We were not able to account for this informative dropout due to the small sample size. As a consequence, the deterioration over time may be underestimated, because the remaining cohort may appear to be doing better over time simply because the sicker patients have dropped out or were not included in the study during recruitment. Although medical treatments including immunosuppressants, corticosteroids as well as some clinical variables such as the presence of arthritis, pulmonary arterial hypertension or ulcers can influence the course of disability and fatigue, data on these variables were not available from the cohort. Our cohort was a convenience sample of patients in two centers specialised in SSc treatment, and there was no information available about the received treatments during the 3-year follow-up.

In conclusion, functional disability and fatigue trajectories in SSc were relatively stable over a 3-year period, and differences in baseline scores, but not slopes, defined classes. More than half of the patients with SSc in our sample are relatively little affected by disability in daily functioning, whereas the vast majority of patients report to be consistently impacted by fatigue. In addition, our findings imply that psychosocial factors such as coping and cognitions could be considered as targets for treatment in particular in those patients who experience both high disability and high levels of fatigue.

References

1. KATSUMOTO TR, WHITFIELD ML, CONNOLLY MK: The pathogenesis of systemic sclerosis. *Annu Rev Pathol* 2011; 6: 509-37.
2. MORRISROE K, HUQ M, STEVENS W *et al.*: Determinants of unemployment amongst Australian systemic sclerosis patients: results from a multicentre cohort study. *Clin Exp Rheumatol* 2016; 34 (Suppl. 100): S79-84.
3. DECUMAN S, SMITH V, GRYPDONCK M, DE KEYSER F, VERHAEGHE S: Factors influencing the occupational trajectory of patients with systemic sclerosis: a qualitative study. *Clin Exp Rheumatol* 2015; 33 (Suppl. 91): S26-30.
4. BASSEL M, HUDSON M, TAILLEFER SS, SCHIEIR O, BARON M, THOMBS BD: Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian national survey. *Rheumatology* 2011; 50: 762-7.
5. WILLEMS LM, KWAKKENBOS L, LEITE CC *et al.*: Frequency and impact of disease symptoms experienced by patients with systemic sclerosis from five European countries. *Clin Exp Rheumatol* 2014; 32 (Suppl. 86): S88-93.
6. GU YS, KONG J, CHEEMA GS, KEEN CL, WICK G, GERSHWIN ME: The immunobiology of systemic sclerosis. *Semin Arthritis Rheum* 2008; 38: 132-60.
7. SCHNITZER M, HUDSON M, BARON M, STEELE R, CANADIAN SCLERODERMA RESEARCH GROUP: Disability in systemic sclerosis - a longitudinal observational study. *J Rheumatol* 2011; 38: 685-92.
8. STEEN VD, MEDSGER TA JR: The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997; 40: 1984-91.
9. HOLLA JF, VAN DER LEEDEN M, HEYMANS MW *et al.*: Three trajectories of activity limitations in early symptomatic knee osteoarthritis: a 5-year follow-up study. *Ann Rheum Dis* 2014; 73: 1369-75.
10. HERMSEN LA, SMALBRUGGE M, VAN DER WOUDEN JC, LEONE SS, DEKKER J, VAN DER HORST HE: Trajectories of physical func-

tioning and their prognostic indicators: a prospective cohort study in older adults with joint pain and comorbidity. *Maturitas* 2014; 78: 316-22.
11. PISTERS MF, VEENHOF C, VAN DIJK GM, HEYMANS MW, TWISK JW, DEKKER J: The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. *Osteoarthritis Cartilage* 2012; 20: 503-10.
12. SUAREZ-ALMAZOR ME, KALLEN MA, ROUNDTREE AK, MAYES M: Disease and symptom burden in systemic sclerosis: a patient perspective. *J Rheumatol* 2007; 34: 1718-26.
13. JOACHIM G, ACORN S: Life with a rare chronic disease: the scleroderma experience. *J Adv Nurs* 2003; 42: 598-606.
14. SANDUSKY SB, MCGUIRE L, SMITH MT, WIGLEY FM, HAYTHORNTHWAITE JA: Fatigue: an overlooked determinant of physical function in scleroderma. *Rheumatology* 2009; 48: 165-9.
15. VAN LANKVELD WG, VONK MC, TEUNISSEN H, VAN DEN HOOGEN FH: Appearance self-esteem in systemic sclerosis--subjective experience of skin deformity and its relationship with physician-assessed skin involvement, disease status and psychological variables. *Rheumatology* 2007; 46: 872-6.
16. THOMBS BD, BASSEL M, MCGUIRE L, SMITH MT, HUDSON M, HAYTHORNTHWAITE JA: A systematic comparison of fatigue levels in systemic sclerosis with general population, cancer and rheumatic disease samples. *Rheumatology* 2008; 47: 1559-63.
17. ASSASSI S, LEYVA AL, MAYES MD *et al.*: Predictors of fatigue severity in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. *PLoS One* 2011; 6: e26061.
18. SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTICS AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
19. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcomes in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
20. POOLE JL, STEEN VD: The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. *Arthritis Care Res* 1991; 4: 27-31.
21. KHANNA D, FURST DE, CLEMENTS PJ *et al.*: Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. *J Rheumatol* 2005; 32: 832-40.
22. WARE JE JR, SHERBOURNE CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
23. EVERS AW, KRAAIMAAT FW, VAN LANKVELD W, JONGEN PJ, JACOBS JW, BIJLSMA JW: Beyond unfavorable thinking: the illness cognition questionnaire for chronic diseases. *J Consult Clin Psychol* 2001; 69: 1026-36.
24. ENDLER NS, PARKER JDA, DE RIDDER DTD, VAN HECK GL: Coping Inventory for Stressful Situations: CISS Handleiding. Swets Test Publishers; 2004.
25. MCWILLIAMS LA, COX BJ, ENNS MW: Use of the Coping Inventory for Stressful Situations in a clinically depressed sample: factor structure, personality correlates, and predictionof distress. *J Clin Psychol* 2003; 59: 423-37.
26. BRANDT PA, WEINERT C: The PRQ – a social support measure. *Nurs Res* 1981; 30: 277-80.
27. WEINERT C: A social support measure: PRQ85. *Nurs Res* 1987; 36: 273-7.
28. JUNG T, WICKRAMA KAS: An introduction to latent class growth analysis and growth mixture modeling. *Soc Pers Psychol Compass* 2008; 2: 302-17.
29. AZUR MJ, STUART EA, FRANGAKIS C, LEAF PJ: Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011; 20: 40-9.
30. WOOD AM, WHITE IR, ROYSTON P: How should variable selection be performed with multiply imputed data? *Stat Med* 2008; 27: 3227-46.
31. JAESCHKE R, SINGER J, GUYATT GH: Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10: 407-15.
32. KHANNA D, FURST DE, HAYS RD *et al.*: Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. *Ann Rheum Dis* 2006; 65: 1325-9.
33. SEKHON S, POPE J, CANADIAN SCLERODERMA RESEARCH GROUP, BARON M: The minimally important difference in clinical practice for patient-centered outcomes including health assessment questionnaire, fatigue, pain, sleep, global visual analog scale, and SF-36 in scleroderma. *J Rheumatol* 2010; 37: 591-8.
34. POUCHOT J, KHERANI RB, BRANT R *et al.*: Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. *J Clin Epidemiol* 2008; 61: 705-13.
35. THOMBS BD, HUDSON M, BASSEL M *et al.*: Sociodemographic, disease, and symptom correlates of fatigue in systemic sclerosis: evidence from a sample of 659 Canadian Scleroderma Research Group Registry patients. *Arthritis Rheum* 2009; 61: 966-73.
36. DIGGLE P, KENWARD MG: Informative drop-out in longitudinal data analysis. *Applied Statistics* 1994; 43: 49-93.